

DESCRIPTION

TITLE OF INVENTION

SEVEN-MEMBERED RING COMPOUND AND PHARMACEUTICAL USE
5 THEREFOR

TECHNICAL FIELD

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The present invention relates to a 7-membered ring
10 compound having a chymase inhibitory activity and useful
as a pharmaceutical for the prevention and/or treatment
of diseases, in which chymase is involved, such as
bronchial asthma, chronic obstructive pulmonary disease,
urticaria, atopic dermatitis, allergic conjunctivitis,
15 rhinitis, rheumatoid arthritis, food allergies, colitis,
allergic enteritis, mastocytosis, scleroderma, heart
failure, cardiac hypertrophy, hypertension, arrhythmia,
atherosclerosis, abdominal aortic aneurysm, myocardial
infarction, restenosis after PTCA, restenosis after
20 bypass graft surgery, ischemic peripheral circulatory
disorders, hyperaldosteronism, diabetes, diabetic
retinopathy, diabetic nephropathy, nephritis,
glomerulosclerosis, renal insufficiency, solid tumor,
fibrosis, postoperative adhesion, cicatrix, glaucoma, and
25 ocular hypertension.

BACKGROUND ART

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Chymase is stored as an ingredient in granules of
mast cells (MC), which are one of the inflammatory cells
30 closely related to inflammation, and is widely present
mainly in the tissue such as skin, heart, vascular walls,
intestines etc. (see Non-Patent Document 1). Human
chymase is known as an enzyme for specifically producing
angiotensin II (i.e., Ang II) from angiotensin I (i.e.,
35 Ang I) independently from angiotensin converting enzyme.
There is a report that, in human cardiac tissue, 80% of
the production of angiotensin II is derived from by

chymase (see Non-Patent Document 2). Ang II is known to be closely related to regulation of the blood pressure, diuretic regulation, and hypertrophy and remodeling of the cardiovascular system, that is, the migration and proliferation of smooth muscle cells etc. and the growth of the extracellular matrix in the cardiovascular system tissue. From these findings, it is suggested that chymase is closely related to cardiovascular lesions through production of Ang II. In addition to production of Ang II, it is reported that chymase has the following actions based on its protease activity:

- 1) degradation of the extracellular matrix (see Non-Patent Document 3) and production of collagen (see Non-Patent Document 4);
- 2) activation of matrix metalloprotease (see Non-Patent Document 5 and Non-Patent Document 6).
- 3) processing and activation of cytokine, for example, release of latent TGF β 1 from extracellular matrix (see Non-Patent Document 7), activation of latent TGF β 1 to active TGF β 1 (see Non-Patent Document 8) and activation of IL-1 β (see Non-Patent Document 9);
- 4) activation of stem cell factor (SCF) which induces differentiation and proliferation of MCs (see Non-Patent Document 10);
- 5) degradation of apolipoprotein B in LDL (see Non-Patent Document 11) and degradation of apolipoprotein A in HDL (see Non-Patent Document 12); and
- 6) conversion of big endothelin to a bioactive peptide comprised of 31 amino acid residues (ET(1-31)) (see Non-Patent Document 14).

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Further, it is reported that chymase stimulates rat peritoneal mast cells to induce degranulation (see Non-Patent Document 15) and that administration of human chymase intraperitoneally to mice or subcutaneously to guinea pigs induces infiltration of eosinophil and other

leukocytes (see Non-Patent Document 16), and causes continuous increase of vascular permeability not through the action of histamine (see Non-Patent Document 17). These various reports relating to the action of chymase suggest that chymase plays an important role in the processes of tissue inflammation, repair, and healing, and in allergic conditions. It is believed that in these processes, the excessive reaction of chymase is involved in various diseases.

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From the above-mentioned findings, a chymase inhibitor can be expected to be useful as a pharmaceutical for the prevention or treatment of, for example, bronchial asthma, chronic obstructive pulmonary disease, urticaria, atopic dermatitis, allergic conjunctivitis, rhinitis, rheumatoid arthritis, food allergies, colitis, allergic enteritis, mastocytosis, scleroderma, heart failure, cardiac hypertrophy, hypertension, arrhythmia, atherosclerosis, abdominal aortic aneurysm, myocardial infarction, restenosis after PTCA, restenosis after bypass graft surgery, ischemic peripheral circulatory disorders, hyperaldosteronism, diabetes, diabetic retinopathy, diabetic nephropathy, nephritis, glomerulosclerosis, renal insufficiency, solid tumor, fibrosis, postoperative adhesion, cicatrix, glaucoma, and ocular hypertension.

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On the other hand, small molecule chymase inhibitors are already shown in books (see Non-Patent Document 18) or review articles (see Non-Patent Documents 19, 20, and 21). The efficacy of several inhibitors among these in animal disease models has been reported.

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Heart failure: see Non-Patent Document 22,

Myocardial infarction: see Non-Patent Document 23 and see Non-Patent Document 24,

Arrhythmia; see Non-Patent Document 25,

Abdominal aortic aneurysm: see Non-Patent Document 26 and Non-Patent Document 27,

Vascular restenosis: see Non-Patent Document 28,

Lipid accumulation in the aorta: see Non-Patent Document 29,

Diabetes: see Non-Patent Document 30,

Nephritis: see Non-Patent Document 31,

Fibrosis: see Non-Patent Document 32 and Non-Patent Document 33,

Post-operative adhesion: see Non-Patent Document 34,

Glaucoma: see Patent Document 1,

Hypereosinophilia: see Patent Document 2,

Atopic dermatitis: see Non-Patent Document 35,

Pruritus: see Non-Patent Document 36,

Asthma: see Non-Patent Document 37,

Enteritis: see Non-Patent Document 38.

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Further, recently, in addition to the chymase inhibitors described in the above books and reviews, imidazoledinedione derivatives (see Patent Document 3), phosphonic acid and phosphinic acid derivatives (see Patent Document 4, Patent Document 5, and Patent Document 6), benzothiophene sulfonamide derivatives (see Patent Document 7 and Patent Document 8), imidazole, thiazolimine, and oxazolimine derivatives (see Patent Document 9 and Patent Document 10), triazolidine derivatives (see Patent Document 11), pyridone derivatives (see Patent Document 12), indole derivatives (see Patent Document 13 and Patent Document 14), ring-fused pyrrole derivatives (see Patent Document 15), imidazopyridine derivatives (see Patent Document 16), benzimidazolone derivatives (see Patent Document 17), quinazolininedione derivatives (see Patent Document 18), phthalazinone derivatives (see Patent Document 20), azabenzimidazolone derivatives (see Patent Document 21), and azaquinazolininedione derivatives (see Patent Document 22) are disclosed as novel chymase inhibitors. However,

there are no examples of practical application of the above chymase inhibitors as pharmaceuticals.

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Further, 1,4-diazepan-2,5-dione derivatives are disclosed in documents as chymase inhibitors similar in structure to the present invention (see Patent Document 19), but these compounds and the compounds of the present invention are different in structure.

10 CITATIONS LIST

Patent Documents

0009

Patent Document 1: Japanese Patent Publication (A)
No. 2004-131442

15 Patent Document 2: U.S. 2002-187989

Patent Document 3: U.S. 2004-110811

Patent Document 4: U.S. 2004-82544

Patent Document 5: U.S. 2005-176769

Patent Document 6: U.S. 2008-96844

20 Patent Document 7: E.P. 1486464

Patent Document 8: WO08-084004

Patent Document 9: WO04-07464

Patent Document 10: U.S. 2007-105908

25 Patent Document 11: Japanese Patent Publication (A)
No. 2003-342265

Patent Document 12: Japanese Patent Publication (A)
No. 2004-67584

Patent Document 13: U.S. 2007-129421

Patent Document 14: U.S. 2008-96953

30 Patent Document 15: U.S. 2007-142452

Patent Document 16: WO08-045688

Patent Document 17: WO08-147697

Patent Document 18: WO09-023655

Patent Document 19: U.S. 2009-111796

35 Patent Document 20: WO2010-019417

Patent Document 21: WO2010-030500

Patent Document 22: WO2010-088195

Non-Patent Document

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Non-Patent Document 1: Mast Cell Proteases in
Immunology and Biology; Caughey, G.H., Ed; Marcel Dekker,
5 Inc.: New York, 1995

Non-Patent Document 2: J Biol Chem., 1990, 265 (36),
22348

Non-Patent Document 3: J. Biol. Chem., 1981, 256
(1), 471

10 Non-Patent Document 4: J. Biol. Chem., 1997, 272
(11), 7127

Non-Patent Document 5: J. Biol. Chem., 1994, 269
(27), 18134

15 Non-Patent Document 6: J Biol Chem., 2005, 280 (10),
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Non-Patent Document 7: J. Biol. Chem., 1995, 270
(9), 4689

Non-Patent Document 8: FASEB J., 2001, 15 (8), 1377

20 Non-Patent Document 9: J. Exp. Med., 1991, 174 (4),
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Non-Patent Document 10: Proc. Natl. Acad. Sci. USA.,
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Non-Patent Document 11: J. Biol. Chem., 1986, 261
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25 Non-Patent Document 12: J. Clin. Invest., 1996, 97
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Non-Patent Document 13: J. Immunol., 1997, 159 (4),
1987

30 Non-Patent Document 14: J. Pharmacol. Exp. Ther.,
2009, 328 (2), 540

Non-Patent Document 15: J. Immunol., 1986, 136 (10),
3812

Non-Patent Document 16: Br. J. Pharmacol., 1998, 125
(7), 1491

35 Non-Patent Document 17: Eur. J. Pharmacol., 1998,
352 (1), 91

Non-Patent Document 18: Protease Inhibitors; Barrett

- et al., Eds; Elsevier Science B.V.: Amsterdam, 1986
Non-Patent Document 19: Curr. Pharm. Des., 1998, 4
(6), 439
Non-Patent Document 20: Exp. Opin. Ther. Patents,
5 2001, 11, 1423
Non-Patent Document 21: Idrugs, 2002, 5 (12), 1141
Non-Patent Document 22: Circulation, 2003, 107 (20),
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Non-Patent Document 23: Life Sci., 2002, 71 (4),
10 437-46
Non-Patent Document 24: J. Pharmacol. Sci., 2004, 94
(4), 443
Non-Patent Document 25: J. Pharmacol. Exp. Ther.,
2004, 309 (2), 490
15 Non-Patent Document 26: Hypertens Res., 2007, 30
(4), 349
Non-Patent Document 27: Atherosclerosis, 2009, 204
(2), 359
Non-Patent Document 28: J. Pharmacol. Exp., Ther.
20 2003, 304 (2), 841
Non-Patent Document 29: Cardiovasc Res., 2002, 55
(4), 870
Non-Patent Document 30: J. Pharmacol Sci., 2009, 110
(4), 459
25 Non-Patent Document 31: J. Pharmacol. Sci., 2009,
111 (1), 82
Non-Patent Document 32: Eur. J. Pharmacol., 2003,
478 (2-3), 179
Non-Patent Document 33: Eur. J. Pharmacol., 2004,
30 493 (1-3), 173
Non-Patent Document 34: Eur. J. Pharmacol., 2004,
484 (2-3), 357
Non-Patent Document 35: J. Invest. Dermatol., 2007,
127 (4), 971
35 Non-Patent Document 36: Eur. J. Pharmacol., 2008,
601 (1-3), 186
Non-Patent Document 37: Am. J. Respir. Crit. Care

Med, 2009 Oct 29

Non-Patent Document 38: J. Pharmacol. Exp. Ther.,
2008, 324 (2), 422

5 SUMMARY OF INVENTION

Problems to Be Solved by Present Invention

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As explained above, at present, several types of
small molecule chymase inhibitors have been disclosed.
10 However, up until now, no chymase inhibitors have been
provided for clinical applications. The object of the
present invention is to provide a novel chymase inhibitor
leading to the prevention or treatment of diseases, in
which chymase is involved, such as bronchial asthma,
15 chronic obstructive pulmonary disease, urticaria, atopic
dermatitis, allergic conjunctivitis, rhinitis, rheumatoid
arthritis, food allergies, colitis, allergic enteritis,
mastocytosis, scleroderma, heart failure, cardiac
hypertrophy, hypertension, arrhythmia, atherosclerosis,
20 abdominal aortic aneurysm, myocardial infarction,
restenosis after PTCA, restenosis after bypass graft
surgery, ischemic peripheral circulatory disorders,
hyperaldosteronism, diabetes, diabetic retinopathy,
diabetic nephropathy, nephritis, glomerulosclerosis,
25 renal insufficiency, solid tumor, fibrosis, postoperative
adhesion, cicatrix, glaucoma, and ocular hypertension.

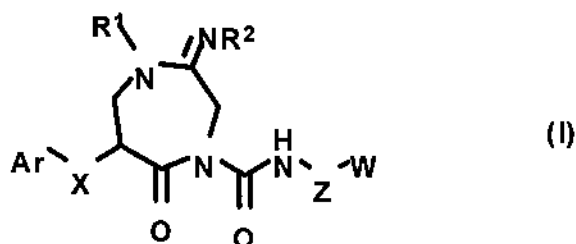
Means for Solving Problem

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30 To solve the above problem, the present invention
provides a compound, or a salt or solvate thereof, having
the following formula (I) characterized in chemical
structure by having a 7-membered ring skeleton:

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wherein Ar indicates (1) a C₆ to C₁₄ aromatic
 5 hydrocarbon group, (2) a 5- to 8-membered aromatic
 heterocyclic group including 1 to 4 hetero atoms selected
 from a nitrogen atom, sulfur atom, and oxygen atom, other
 than a carbon atom or (3) a bicyclic or tricyclic
 aromatic group formed by condensation of the above
 10 aromatic heterocyclic group and a C₆ to C₁₄ aromatic
 hydrocarbon ring,

wherein the above groups (1) to (3) of Ar are
 unsubstituted, or substituted with 1 to 5 groups selected
 from the group consisting of
 15 (i) a halogen atom,
 (ii) nitro,
 (iii) cyano,
 (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1
 to 3 halogen atoms,
 20 (v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1
 to 3 halogen atoms,
 (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1
 to 3 halogen atoms,
 (vii) C₃ to C₆ cycloalkyl,
 25 (viii) hydroxyl,
 (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1
 to 3 groups selected from a halogen atom, mono- or di-C₁
 to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆
 alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl,
 30 mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl,
 carboxyl, and C₁ to C₆ alkoxy carbonyl, or substituted with

- 1 to 13 deuterium atoms,
(x) C₁ to C₅ alkylenedioxy,
(xi) C₁ to C₆ alkylthio unsubstituted, or substituted with
1 to 3 groups selected from a halogen atom, mono- or di-C₁
5 to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆
alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl,
mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl,
carboxyl, and C₁ to C₆ alkoxycarbonyl, or substituted with
1 to 13 deuterium atoms,
10 (xii) amino,
(xiii) mono-C₁ to C₆ alkylamino,
(xiv) di-C₁ to C₆ alkylamino,
(xv) 5- to 6-membered cyclic amino,
(xvi) C₁ to C₆ alkylcarbonyl,
15 (xvii) carboxyl,
(xviii) C₁ to C₆ alkoxycarbonyl,
(xix) carbamoyl,
(xx) thiocarbamoyl,
(xxi) mono-C₁ to C₆ alkylcarbamoyl,
20 (xxii) di-C₁ to C₆ alkylcarbamoyl,
(xxiii) 5- to 6-membered cyclic aminocarbonyl,
(xxiv) sulfo,
(xxv) C₁ to C₆ alkylsulfonyl,
(xxvi) C₁ to C₆ alkoxycarbonylamino,
25 (xxvii) C₁ to C₆ alkylcarbonylamino,
(xxviii) mono- or di-C₁ to C₆ alkylaminocarbonylamino,
(xxix) aminosulfonyl, and
(xxx) mono- or di-C₁ to C₆ alkylaminosulfonyl, or
substituted with
30 (xxxi) 1 to 9 deuterium atoms,
X indicates (1) a connecting bond, (2) linear or branched
C₁ to C₆ alkylene unsubstituted, or substituted with 1 to
12 deuterium atoms, (3) an oxygen atom, (4) NR³, where R³
indicates a hydrogen atom or a C₁ to C₆ alkyl group, or
35 (5) -S(O)_m-, where m indicates an integer of 0 to 2,
Z indicates (1) a connecting bond or (2) CR⁴R⁵, where R⁴
and R⁵ are, independently,

- (A) a hydrogen atom,
(B) a deuterium atom,
(C) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) 5
carboxyl, (ii) C₁ to C₆ alkoxy carbonyl, (iii) phenyl, (iv) hydroxyl, (v) C₁ to C₆ alkoxy, (vi) a halogen atom, and
(vii) C₃ to C₆ cycloalkyl, or substituted with (viii) 1 to 13 deuterium atoms,
(D) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 10
1 to 5 groups selected from the group consisting of (i) a halogen atom and (ii) an alkyl group unsubstituted, or substituted with 1 to 3 halogen atoms or substituted with
(iii) 1 to 11 deuterium atoms,
(E) COOR⁶ wherein R⁶ indicates a hydrogen atom or C₁ to C₆ 15
alkyl, or
(F) CONR⁷R⁸ wherein R⁷ and R⁸ are, independently,
 (a) hydrogen atom,
 (b) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a 20
halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) carboxyl, (iv) C₁ to C₆ alkoxy carbonyl, (v) C₁ to C₆ alkyl carbonyl, (vi) carbamoyl, (vii) mono-C₁ to C₆ alkyl carbamoyl, (viii) di-C₁ to C₆ alkyl carbamoyl, (ix) C₆ to C₁₂ aryl and (x) C₁ to C₁₀ heteroaryl,
 (c) C₆ to C₁₄ aromatic hydrocarbon group, 25
 (d) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom, or
 (e) a bicyclic or tricyclic aromatic group formed by 30
condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring,
 wherein each of the groups (c) to (e) is
unsubstituted, or substituted with 1 to 5 groups selected 35
from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (v) C₂ to C₆

alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vii) C₃ to C₆ cycloalkyl, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (x) C₁ to C₅ alkylenedioxy, (xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 halogen atoms, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkylcarbonyl, (xvii) carboxyl, (xviii) C₁ to C₆ alkoxy carbonyl, (xix) carbamoyl, (xx) thiocarbamoyl, (xxi) mono-C₁ to C₆ alkylcarbamoyl, (xxii) di-C₁ to C₆ alkylcarbamoyl, (xxiii) C₆ to C₁₀ arylcarbamoyl, (xxiv) C₁ to C₁₀ heteroarylcarbamoyl, (xxv) sulfo, (xxvi) C₁ to C₆ alkylsulfonyl, (xxvii) aminosulfonyl, and (xxviii) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxix) 1 to 9 deuterium atoms,

W indicates (1) a hydrogen atom, (2) a C₆ to C₁₄ aromatic hydrocarbon group, (3) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom, and an oxygen atom, other than a carbon atom, (4) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring, or (5) deuterium atom,

where each of the groups (2) to (4) of the above W is unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, amino, C₁ to C₆ alkoxy carbonyl, C₁ to C₆ alkoxy carbonylamino and carboxyl, (v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vii) C₃ to C₆ cycloalkyl, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 groups selected from a halogen

atom, hydroxyl, C₁ to C₆ alkoxy, amino and mono- or di-C₁ to C₆ alkylamino, (x) C₁ to C₅ alkylenedioxy, (xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, hydroxyl, C₁ to C₆ alkoxy, amino, and mono- or di-C₁ to C₆ alkylamino, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkyl-carbonyl, (xvii) carboxyl, (xviii) C₁ to C₆ alkoxycarbonyl unsubstituted, or substituted with a halogen atom, (xix) C₇ to C₁₆ aralkyloxycarbonyl unsubstituted, or substituted with a halogen atom, (xx) carbamoyl, (xxi) mono-C₁ to C₆ alkylcarbamoyl unsubstituted, or substituted with 1 to 3 groups which are selected from a halogen atom, hydroxyl, carboxyl, C₁ to C₆ alkoxy, amino, and mono- or di-C₁ to C₆ alkylamino, (xxii) di-C₁ to C₆ alkylcarbamoyl unsubstituted, or substituted with hydroxyl, (xxiii) 5- to 6-membered cyclic aminocarbonyl unsubstituted, or substituted with C₁ to C₆ alkoxycarbonyl, (xxiv) C₆ to C₁₀ arylcarbamoyl, (xxv) C₁ to C₁₀ heteroarylcarbamoyl, (xxvi) C₇ to C₁₆ aralkylcarbamoyl, (xxvii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl, (xxviii) N-C₁ to C₆ alkyl-N-C₆ to C₁₂ arylcarbamoyl, (xxix) C₃ to C₆ cycloalkylcarbamoyl, (xxx) sulfo, (xxxi) C₁ to C₆ alkylsulfonyl, (xxxii) C₁ to C₆ alkylsulfonylamino, (xxxiii) C₆ to C₁₂ arylsulfonylamino unsubstituted, or substituted with C₁ to C₆ alkyl, (xxxiv) C₁ to C₁₀ heteroarylsulfonylamino, (xxxv) C₁ to C₆ alkoxycarbonylamino, (xxxvi) C₁ to C₆ alkylcarbonylamino, (xxxvii) mono- or di-C₁ to C₆ alkylaminocarbonylamino, (xxxviii) C₆ to C₁₂ aryl, (xxxix) C₁ to C₁₀ heteroaryl, (xl) C₆ to C₁₀ aryloxy, (xli) C₁ to C₁₀ heteroaryloxy, (xlii) C₇ to C₁₆ aralkyloxy, (xliii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkyloxy, (xliv) aminosulfonyl, (xlv) mono- or di-C₁ to C₆ alkylaminosulfonyl, (xlvi) C₇ to C₁₆ aralkyloxycarbamoyl, and (xlvii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkyloxycarbamoyl, or substituted with (xlviii) 1 to 9 deuterium atoms,

R¹ indicates

- (1) a hydrogen atom,
- (2) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or
5 substituted with (iii) 1 to 13 deuterium atoms,
- (3) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 11 deuterium atoms,
- (4) C₂ to C₆ alkynyl unsubstituted, or substituted with 1
10 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl or, substituted with (iii) 1 to 9 deuterium atoms, or
- (5) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 11 deuterium atoms,

15 R² indicates (1) OR⁹ or (2) NR¹⁰R¹¹

where R⁹, R¹⁰, and R¹¹ respectively independently indicate

- (A) a hydrogen atom,
- (B) C₁ to C₆ alkyl,
- (C) C₂ to C₆ alkenyl,
- 20 (D) C₂ to C₆ alkynyl,
- (E) C₃ to C₆ cycloalkyl
- (F) C₆ to C₁₄ aromatic hydrocarbon group,
- (G) a 5- to 8-membered aromatic heterocyclic group
including 1 to 4 hetero atoms selected from a nitrogen
25 atom, sulfur atom and oxygen atom, other than a carbon atom, or
- (H) a bicyclic or tricyclic aromatic group formed by
condensation of the above aromatic heterocyclic group and
a C₆ to C₁₄ aromatic hydrocarbon ring,

30 where each of the groups of the above (B) to (E) is unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms,
35 (v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆ alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, (x) C₁ to C₆ alkoxycarbonyl, (xi) C₁ to C₆

alkylcarbonyl, (xii) carbamoyl, (xiii) mono-C₁ to C₆ alkylcarbamoyl, (xiv) di-C₁ to C₆ alkylcarbamoyl, (xv) C₆ to C₁₂ aryl, and (xvi) C₁ to C₁₀ heteroaryl, or substituted with (xvii) 1 to 13 deuterium atoms,

- 5 further, each of the groups of the above (F) to (H) is unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms,
- 10 (v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, (xii)
- 15 C₁ to C₆ alkylcarbonyl, (xiii) carboxyl, (xiv) C₁ to C₆ alkoxy carbonyl, (xv) carbamoyl, (xvi) mono-C₁ to C₆ alkylcarbamoyl, (xvii) di-C₁ to C₆ alkylcarbamoyl, (xviii) C₁ to C₆ alkylsulfonyl, (xix) aminosulfonyl, and (xx) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted
- 20 with (xxi) 1 to 9 deuterium atoms, or
R¹ and R² may form 5- or 6-member heterocyclic ring together with the atoms they are bonded with, where the above 5-or 6-member heterocyclic ring is unsubstituted or substituted with 1 to 3 groups selected
- 25 from
- (A) a halogen atom
 - (B) oxo
 - (C) hydroxyl
 - (D) C₁ to C₆ alkyl,
 - 30 (E) C₂ to C₆ alkenyl,
 - (F) C₂ to C₆ alkynyl,
 - (G) C₃ to C₆ cycloalkyl
 - (H) C₆ to C₁₄ aromatic hydrocarbon group,
 - (I) a 5- to 8-membered aromatic heterocyclic group
- 35 including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom, and

(J) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring, or substituted with (K) 1 to 6 deuterium atoms,

5 where each of the groups of the above (D) to (G) is unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms,
10 (v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆ alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, (x) C₁ to C₆ alkoxycarbonyl, (xi) C₁ to C₆ alkylcarbonyl, (xii) carbamoyl, (xiii) mono-C₁ to C₆ alkylcarbamoyl, (xiv) di-C₁ to C₆ alkylcarbamoyl, (xv) C₆ to C₁₂ aryl, and (xvi) C₁ to C₁₀ heteroaryl, or substituted
15 with (xvii) 1 to 13 deuterium atoms, each of the groups of the above (H) to (J) is unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen
20 atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms,
25 (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, (xii) C₁ to C₆ alkylcarbonyl, (xiii) carboxyl, (xiv) C₁ to C₆ alkoxycarbonyl, (xv) carbamoyl, (xvi) mono-C₁ to C₆ alkylcarbamoyl, (xvii) di-C₁ to C₆ alkylcarbamoyl, (xviii)
30 C₁ to C₆ alkylsulfonyl, (xix) aminosulfonyl, and (xx) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxi) 1 to 9 deuterium atoms.

0015

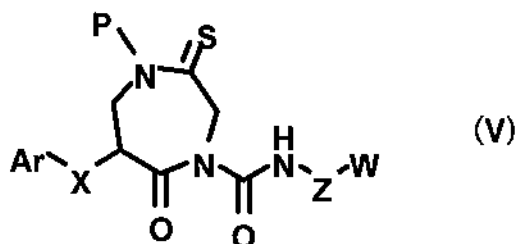
Further, the present invention provides a compound
35 having the formula (I) or a salt or solvates thereof, a pharmaceutical composition comprising the compound having the formula (I) or a pharmaceutically acceptable salt or

solvates thereof as an active ingredient, and a chymase inhibitor containing a compound having the formula (I).

0016

Furthermore, the present invention provides a method
5 for producing a compound having the above formula (I) or a salt or solvate thereof and an intermediate compound, which is useful for the producing of a compound (I), or a salt thereof having the formula (V):

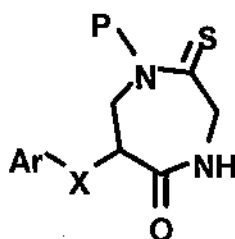
0017



0018

where Ar, W, X and Z are as defined above, P is a
protective group of allyl, allyloxycarbonyl, 9-
15 fluorenylmethylcarbonyl, C₁ to C₆ alkyloxycarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C₁ to C₆ alkylcarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C₇ to C₁₆ aralkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₅ to C₁₆
20 arylcarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₇ to C₁₆ aralkyloxycarbonyl unsubstituted, or substituted with 1 to 3 of (i) a
25 halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₅ to C₁₆ arylsulfonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro or R¹ (R¹ is as defined above),
30 or the formula (XIII):

0019



(XIII)

0020

where Ar, X, and P are as defined above.

5

0021

When the compounds, or a salt thereof or solvate thereof, having the formulae (I), (V), or (XIII) have asymmetric carbon atoms in their structures, their optically active substances and their mixtures are also included in the scope of the present invention. When they have two or more asymmetric carbon, the diastereomer mixtures are also included in the scope of the present invention. Further, when the compounds, or a salt or solvate thereof, having the formulae (I), (V), or (XIII) have double bonds in their structures, all of the cis-forms, trans-forms, and their mixtures are also included in the scope of the present invention. Further, possible resonance types and tautomers of the compounds having the formulae (I), (V), or (XIII) are also included in the scope of the present invention.

20

0022

Further, the compounds having the formulae (I), (V), or (XIII) or a salt thereof may be brought into contact with a solvent such as water, methanol, ethanol, 1-propanol, 2-propanol, formic acid, ethyl formate, acetic acid, methyl acetate, ethyl acetate, propyl acetate and isobutyl acetate or mixed solvent including these solvents, or recrystallized from these solvents etc. so as to form their solvates. These solvates are also included in the scope of the present invention.

30

0023

Further, the compounds having the above formulae

(I), (V), or (VIII) or salt or solvate thereof may contain unnatural ratios of isotopes of above 1 of the atoms forming the compounds. As the atomic isotope, for example, deuterium (^2H), tritium (^3H), iodine-125 (^{125}I), carbon-14 (^{14}C), etc. may be mentioned. Further, the compounds may be radioactively labeled by, for example, tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C), or other radioactive isotopes. Radioactively labeled compounds are useful as pharmaceutical for treatment or prevention of disease, research reagents, for example, assay reagents, and diagnostic agents, for example, in vivo image diagnostic agents. All isotope variants of the compounds of the present invention are included in the scope of the present invention, without regard as to radioactivity.

Advantageous Effects of Invention

0024

The compound having formula (I) of the present invention has a chymase inhibitory activity, is superior in stability in blood plasma and in vivo pharmacokinetics and is useful as a pharmaceutical for the prevention or treatment of diseases such as bronchial asthma, chronic obstructive pulmonary disease, urticaria, atopic dermatitis, allergic conjunctivitis, rhinitis, rheumatoid arthritis, food allergies, colitis, allergic enteritis, mastocytosis, scleroderma, heart failure, cardiac hypertrophy, hypertension, arrhythmia, atherosclerosis, abdominal aortic aneurysm, myocardial infarction, restenosis after PTCA, restenosis after bypass graft surgery, ischemic peripheral circulatory disorders, hyperaldosteronism, diabetes, diabetic retinopathy, diabetic nephropathy, nephritis, glomerulosclerosis, renal insufficiency, solid tumor, fibrosis, postoperative adhesion, cicatrix, glaucoma, and ocular hypertension.

DESCRIPTION OF EMBODIMENTS

0025

In the description, the terms "alkyl", "alkenyl", "alkynyl" and "alkoxy" include both linear and branched forms.

5 0026

1. Explanation of Compounds Having Formula (I)

10 In the above-mentioned formula (I), as examples of the "C₆ to C₁₄ aromatic hydrocarbon group" expressed by Ar, a monocyclic or polycyclic aromatic hydrocarbon group, more specifically, phenyl, biphenyl, naphthyl, indenyl, anthryl, phenanthryl (preferably, phenyl, biphenyl, naphthyl, etc., particularly preferably phenyl etc.), or other 6- to 14-membered monocyclic or polycyclic aromatic hydrocarbon group etc. may be
15 mentioned.

0027

20 Further, as examples of the "5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom" expressed by Ar, for example, a monocyclic group including 1 or more (e.g., 1 to 4, preferably 1 to 3) hetero atoms which preferably consist of 1 or 2 species of hetero atoms selected from, other than a carbon atom, a nitrogen atom, oxygen atom, and sulfur atom, or its condensed aromatic heterocyclic
25 group, more specifically, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyradinyl, pyrimidinyl, pyridazinyl, naphthylidiny, purinyl, and
30 other aromatic heterocyclic groups (preferably pyridyl, thienyl, and furyl) etc. may be mentioned.

0028

35 Further, as the "bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" represented by Ar, benzothienyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl,

benzotriazolyl, benzothiazolyl, benzisothiazolyl,
benzoxazolyl, benzisoxazolyl, benzodioxolyl, quinolyl,
isoquinolyl, quinoxaliny, phthalaziny (preferably,
benzothienyl, benzofuryl, benzodioxolyl, and quinolyl),
5 etc. may be mentioned.

0029

Among these, as examples of the above-mentioned (1)
aromatic hydrocarbon group, (2) aromatic heterocyclic
group, or (3) bicyclic or tricyclic aromatic group formed
10 by condensation of the above aromatic heterocyclic group
and a C₆ to C₁₄ aromatic hydrocarbon ring represented by
Ar, phenyl and naphthyl are particularly preferred.

0030

Next, the substituent groups (i) to (xxxi) of the
15 groups represented by Ar in the above-mentioned formula
(I) are shown together with specific examples:

(i) a halogen atom (for example, fluorine, chlorine,
bromine, and iodine may be mentioned.)

(ii) nitro

20 (iii) cyano

(iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1
to 3 halogen atoms (as the halogen atom, fluorine,
chlorine, bromine, and iodine may be mentioned, and as
the C₁ to C₆ alkyl, methyl, ethyl, n-propyl, i-propyl, n-
25 butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl,
etc. may be mentioned. As specific examples, methyl,
fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl, dichloromethyl, trichloromethyl, ethyl,
2,2,2-trifluoroethyl, n-propyl, i-propyl, n-butyl, i-
30 butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc.
(preferably methyl, ethyl, and trifluoromethyl, etc.) may
be mentioned.),

0031

(v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1
35 to 3 halogen atoms (as the halogen atom, fluorine,
chlorine, bromine, and iodine may be mentioned, and as
the C₂ to C₆ alkenyl, for example, vinyl, propenyl,

isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-yl, etc. may be mentioned.)

(vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms (as the halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, and as the C₂ to C₆ alkynyl, for example, 2-butyne-1-yl, 4-pentyne-1-yl, 5-hexyne-1-yl, etc. may be mentioned.),

(vii) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

0032

(viii) hydroxyl

(ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, mono- or di-C₁ to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆ alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl, mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl, carboxyl, and C₁ to C₆ alkoxycarbonyl, or substituted with 1 to 13 deuterium atoms

(as the C₁ to C₆ alkoxy, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, n-hexyloxy, etc. may be mentioned. As the substituent of alkoxy group, fluorine, chlorine, bromine, iodine, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-benzylcarbamoyl, N-(2-picolyl)carbamoyl, methoxycarbonyl, t-butoxycarbonyl, carboxyl and deuterium atoms, etc. may be mentioned. As specific examples, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, trifluoromethyloxy, trichloromethyloxy, methoxymethyloxy, ethoxymethyloxy, N-methyl-carbamoylmethyloxy, N,N-dimethylcarbamoylmethyloxy, N-benzylcarbamoylmethyloxy, N-(2-picolyl)-carbamoylmethyloxy, methoxycarbonylmethyloxy, t-butoxycarbonylmethyloxy and carboxylmethyloxy, etc. (preferably methoxy, ethoxy, N-methylcarbamoylmethyloxy, N-benzylcarbamoylmethyloxy, N-

(2-picolyl)-carbamoylmethyloxy, methoxycarbonylmethyloxy, t-butoxycarbonylmethyloxy, carboxylmethyloxy, [$^2\text{H}_3$]methoxy, [$^2\text{H}_5$]ethoxy, [$^2\text{H}_7$]n-propoxy and [$^2\text{H}_7$]i-propoxy may be mentioned.)

5 0033

(x) C_1 to C_5 alkylenedioxy (for example, methylenedioxy and ethylenedioxy, etc. may be mentioned.),
(xi) C_1 to C_6 alkylthio unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, mono- or di- C_1 to C_6 alkylamino, C_1 to C_6 alkoxy, mono- or di- C_1 to C_6 alkylcarbamoyl, mono- or di- C_7 to C_{16} aralkylcarbamoyl, mono- or di- C_1 to C_{10} heteroaryl- C_1 to C_6 alkylcarbamoyl, carboxyl, and C_1 to C_6 alkoxycarbonyl, or substituted with 1 to 13 deuterium atoms (as the C_1 to C_6 alkylthio, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, n-pentylthio, n-hexylthio, etc. may be mentioned, as examples of substituent groups of C_1 to C_6 alkylthio, fluorine, chlorine, bromine, iodine, N-methylamino, N,N-dimethylamino, methoxy, ethoxy, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-benzylcarbamoyl, N-(2-picolyl)-carbamoyl, methoxycarbonyl, t-butoxycarbonyl, carboxyl and deuterium atoms, etc. may be mentioned. As specific examples, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, t-butylthio, trifluoromethylthio, trichloromethylthio, methoxymethylthio, ethoxymethylthio, N-methylcarbamoylmethylthio, N-benzylcarbamoylmethylthio, N-(2-picolyl)-carbamoylmethylthio, methoxycarbonylmethylthio, t-butoxycarbonylmethylthio, carboxylmethylthio, [$^2\text{H}_3$]methylthio, [$^2\text{H}_5$]ethylthio, [$^2\text{H}_7$]n-propylthio and [$^2\text{H}_7$]i-propylthio, etc. may be mentioned.)

 0034

35 (xii) amino

(xiii) mono- C_1 to C_6 alkylamino (for example, N-methylamino etc. may be mentioned.)

(xiv) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino, etc. may be mentioned.)

(xv) 5- to 6-membered cyclic amino (for example, morpholino, piperidino, piperazino, etc. may be mentioned.)

(xvi) C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, etc. may be mentioned.)

(xvii) carboxyl

(xviii) C₁ to C₆ alkoxy carbonyl (for example, methoxycarbonyl, ethoxycarbonyl, etc. may be mentioned.)

0035

(xix) carbamoyl

(xx) thiocarbamoyl

(xxi) mono-C₁ to C₆ alkylcarbamoyl (for example, N-methylcarbamoyl, N-ethylcarbamoyl, etc. may be mentioned.)

(xxii) di-C₁ to C₆ alkylcarbamoyl (for example, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc. may be mentioned.)

(xxiii) 5- to 6-membered cyclic aminocarbonyl (for example, morpholinocarbonyl, piperidinocarbonyl, piperadinocarbonyl, etc. may be mentioned.)

0036

(xxiv) sulfo

(xxv) C₁ to C₆ alkylsulfonyl (for example, methanesulfonyl etc. may be mentioned.)

(xxvi) C₁ to C₆ alkoxy carbonylamino (for example, methoxycarbonylamino, ethoxycarbonylamino, etc. may be mentioned.)

(xxvii) C₁ to C₆ alkylcarbonylamino (for example, acetoamide group etc. may be mentioned.)

(xxviii) mono- or di-C₁ to C₆ alkylaminocarbonylamino (for example, N-methylaminocarbonylamino etc. may be mentioned.)

(xxix) aminosulfonyl

(xxx) mono- or di-C₁ to C₆ alkylaminosulfonyl (for

example, N-methylaminosulfonyl etc. may be mentioned.)

and

(xxxi) deuterium atoms.

0037

5 Among the substituent groups for the groups
expressed by the above Ar, (i) a halogen atom, (ii)
nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or
substituted with 1 to 3 halogen atoms, (viii) hydroxyl,
(ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1
10 to 3 groups selected from a halogen atom, mono- or di-C₁
to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆
alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl,
mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl,
carboxyl, and C₁ to C₆ alkoxycarbonyl, or substituted with
15 1 to 13 deuterium atoms, and (xxxi) deuterium atoms etc.
are particularly preferable.

0038

In the above formula (I), X indicates (1) a
connecting bond, (2) linear or branched C₁ to C₆ alkylene
20 unsubstituted, or substituted with 1 to 12 deuterium
atoms, (3) an oxygen atom, (4) NR³, where, R³ indicates a
hydrogen atom or C₁ to C₆ alkyl group, or (5) -S(O)_m-,
where, m indicates an integer of 0 to 2.

0039

25 As specific examples of the "linear or branched C₁ to
C₆ alkylene" expressed by X, methylene, 1,1-ethylene, 1,2-
ethylene, 1,1-propylene, etc. may be mentioned. Further,
as specific examples of the "NR³, where R³ indicates a
hydrogen atom or C₁ to C₆ alkyl group" expressed by X, -
30 NH-, -NMe-, -NEt-, -Nⁿ Pr-, -Nⁱ Pr-, etc. may be mentioned.
As X, a methylene group is particularly preferable.

0040

Next, in the above-mentioned formula (I), the (A) to
(F), which the R⁴ and R⁵ of "CR⁴R⁵" expressed by Z
35 independently indicate, are shown below along with
specific examples:

0041

(A) a hydrogen atom

(B) deuterium atoms

(C) C₁ to C₆ alkyl unsubstituted, or substituted with
1 to 5 groups selected from the group consisting of (i)
5 carboxyl, (ii) C₁ to C₆ alkoxy carbonyl, (iii) phenyl, (iv)
hydroxyl, (v) C₁ to C₆ alkoxy, (vi) a halogen atom, and
(vii) C₃ to C₆ cycloalkyl, or substituted with (viii) 1 to
13 deuterium atoms (as examples of C₁ to C₆ alkyl, methyl,
ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-
10 butyl, n-pentyl, n-hexyl, etc. may be mentioned. As
examples of the substituent groups of C₁ to C₆ alkyl,
carboxyl, methoxy carbonyl, ethoxy carbonyl, n-
propoxy carbonyl, i-propoxy carbonyl, n-butoxy carbonyl, i-
butoxy carbonyl, s-butoxy carbonyl, t-butoxy carbonyl,
15 phenyl, hydroxyl, methoxy, ethoxy, n-propoxy, i-propoxy,
n-butoxy, i-butoxy, t-butoxy, fluorine, chlorine,
bromine, iodine, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, deuterium atoms, etc. may be mentioned.)

(D) C₃ to C₆ cycloalkyl unsubstituted, or substituted
20 with 1 to 5 groups selected from the group consisting of
(i) a halogen atom and (ii) an alkyl group unsubstituted,
or substituted with 1 to 3 halogen atoms or substituted
with (iii) 1 to 11 deuterium atoms (as examples of C₃ to
C₆ cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl,
25 cyclohexyl, etc. may be mentioned. As examples of the
substituent group, fluorine, chlorine, bromine, iodine,
methyl, ethyl, trifluoromethyl, [²H₃]methyl etc. may be
mentioned.)

(E) COOR⁶ (R⁶ indicates a hydrogen atom or C₁ to C₆
30 alkyl) (as specific examples, carboxyl, methoxy carbonyl,
ethoxy carbonyl, n-propoxy carbonyl, i-propoxy carbonyl, n-
butoxy carbonyl, i-butoxy carbonyl, s-butoxy carbonyl, t-
butoxy carbonyl, etc. may be mentioned.)

(F) CONR⁷R⁸ (where specific examples of (a) to (e)
35 which R⁷ and R⁸ show independently are as follows)

(a) a hydrogen atom

(b) C₁ to C₆ alkyl unsubstituted, or substituted

with 1 to 3 groups selected from the group consisting of
(i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii)
carboxyl, (iv) C₁ to C₆ alkoxy carbonyl, (v) C₁ to C₆
alkyl carbonyl, (vi) carbamoyl, (vii) mono-C₁ to C₆
5 alkyl carbamoyl, (viii) di-C₁ to C₆ alkyl carbamoyl, (ix) C₆
to C₁₂ aryl, and (x) C₁ to C₁₀ heteroaryl (as specific
examples of C₁ to C₆ alkyl groups, methyl, ethyl, n-
propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-
pentyl, n-hexyl, etc. may be mentioned. Here, as examples
10 of the substituent groups (i) to (x) of the C₁ to C₆ alkyl
groups,

(i) a halogen atom (for example, fluorine,
chlorine, bromine, and iodine may be mentioned.)

(ii) C₃ to C₆ cycloalkyl (for example,
15 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc.
may be mentioned.)

(iii) carboxyl

(iv) C₁ to C₆ alkoxy carbonyl (for example,
methoxy carbonyl and ethoxy carbonyl, etc. may be
20 mentioned.)

(v) C₁ to C₆ alkyl carbonyl (for example, acetyl,
propionyl, butyryl, isobutyryl, pivaloyl, etc. may be
mentioned.)

(vi) carbamoyl

(vii) mono-C₁ to C₆ alkyl carbamoyl (for example,
25 N-methyl carbamoyl, N-ethyl carbamoyl, etc. may be
mentioned.)

(viii) di-C₁ to C₆ alkyl carbamoyl (for example,
N,N-dimethyl carbamoyl, N,N-diethyl carbamoyl, etc. may be
30 mentioned.)

(ix) C₆ to C₁₂ aryl (for example, phenyl, tolyl,
xylyl, biphenyl, naphthyl and indenyl, etc. may be
mentioned.)

(x) C₁ to C₁₀ heteroaryl (for example, thienyl,
35 furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl,
tetrazolyl, thiazolyl, isothiazolyl, oxazolyl,
isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl,

benzothienyl, benzofuryl, indolyl, isoindolyl,
benzimidazolyl, benzopyrazolyl, benzotriazolyl,
benzothiazolyl, benzisothiazolyl, benzoxazolyl,
benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyll,
5 phthalazinyl, naphthylidinyll and purinyl, etc.) may be
mentioned.)

0042

(c) C₆ to C₁₄ aromatic hydrocarbon group
(specific examples same as "C₆ to C₁₄ aromatic hydrocarbon
10 group" in Ar explained above. As preferable example,
phenyl may be mentioned.)

0043

(d) a 5- to 8-membered aromatic heterocyclic
group including 1 to 4 hetero atoms selected from a
15 nitrogen atom, sulfur atom, and oxygen atom, other than a
carbon atom, (specific examples are same as " a 5- to 8-
membered aromatic heterocyclic group including 1 to 4
hetero atoms selected from a nitrogen atom, sulfur atom,
and oxygen atom, other than a carbon atom" in Ar
20 explained above. As preferable example, pyridyl, thienyl,
furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl and
tetrazolyl, etc. may be mentioned.)

0044

(e) bicyclic or tricyclic aromatic group
25 formed by condensation of the above aromatic heterocyclic
group of the above (d) and a C₆ to C₁₄ aromatic
hydrocarbon ring (specific examples are same as "bicyclic
or tricyclic aromatic group formed by condensation of the
above aromatic heterocyclic group and a C₆ to C₁₄ aromatic
30 hydrocarbon group" in Ar explained above. As preferable
examples, benzothienyl, benzofuryl, indolyl,
benzimidazolyl, benzopyrazolyl, and benzotriazolyl may be
mentioned.)

0045

35 Specific examples of the substituent groups (i) to
(xxviii) which said groups (c) to (e) may have are shown
next.

0046

(i) a halogen atom (for example, fluorine, chlorine, bromine, and iodine may be mentioned.)

(ii) nitro

5 (iii) cyano

(iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms selected from fluorine, chlorine, bromine, and iodine (for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, etc.) may be mentioned, as specific examples, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, ethyl, 2,2,2-trifluoroethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc. (preferably methyl, ethyl and trifluoromethyl, etc.) may be mentioned.)

(v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms selected from fluorine, chlorine, bromine, and iodine (for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-yl, etc.) may be mentioned.)

(vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms selected from fluorine, chlorine, bromine, and iodine (for example, 2-butyne-1-yl, 4-pentyne-1-yl and 5-hexyne-1-yl, etc.) may be mentioned.)

(vii) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

35 (viii) hydroxyl

(ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example,

methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, trifluoromethyloxy and trichloromethyloxy, etc. may be mentioned.)

5 (x) C₁ to C₅ alkylenedioxy (for example, methylenedioxy and ethylenedioxy, etc. may be mentioned.)

(xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, n-pentylthio, n-hexylthio, trifluoromethylthio and trichloromethylthio, etc. may be mentioned.)

(xii) amino

(xiii) mono-C₁ to C₆ alkylamino (for example, N-methylamino, etc. may be mentioned.)

15 (xiv) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino, etc. may be mentioned.)

(xv) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperazino, etc. may be mentioned.)

20 (xvi) C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be mentioned.)

(xvii) carboxyl

25 (xviii) C₁ to C₆ alkoxy carbonyl (for example, methoxycarbonyl and ethoxycarbonyl, etc. may be mentioned.)

(xix) carbamoyl

(xx) thiocarbamoyl

30 (xxi) mono-C₁ to C₆ alkylcarbamoyl (for example, N-methylcarbamoyl and N-ethylcarbamoyl, etc. may be mentioned.)

(xxii) di-C₁ to C₆ alkylcarbamoyl (for example, N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl, etc. may be mentioned.)

35 (xxiii) C₆ to C₁₀ arylcarbamoyl (for example, N-phenylcarbamoyl etc. may be mentioned.)

(xxiv) C₁ to C₁₀ heteroarylcarbamoyl (for

example, N-pyridylcarbamoyl etc. may be mentioned.)

(xxv) sulfo

(xxvi) C₁ to C₆ alkylsulfonyl (for example, methanesulfonyl etc. may be mentioned.)

5 (xxvii) aminosulfonyl

(xxviii) mono- or di-C₁ to C₆ alkylaminosulfonyl (for example, N-methylaminosulfonyl etc. may be mentioned.), and

(xxix) deuterium atoms.

10 0047

As examples of the "C₆ to C₁₄ aromatic hydrocarbon group", "a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom", and "a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" expressed by W, ones the same as the examples of the "C₆ to C₁₄ aromatic hydrocarbon group", "a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom", and "a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" represented by Ar explained above may be mentioned.

0048

As examples of the "C₆ to C₁₄ aromatic hydrocarbon group", "5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom", and "a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" expressed by W, in particular, phenyl, pyridyl, thienyl, furyl, thiazolyl, oxazolyl, and isooxazolyl are preferable.

0049

Next, the substituent groups (i) to (xlviii) of the "C₆ to C₁₄ aromatic hydrocarbon group", "5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom", and "bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" expressed by W in the above formula (I) will be shown together with specific examples.

10 0050

(i) a halogen atom (for example, fluorine, chlorine, bromine, and iodine may be mentioned.)

(ii) nitro

(iii) cyano

15 (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 groups which are selected from the group consisting of a halogen atom, amino, C₁ to C₆ alkoxy carbonyl, C₁ to C₆ alkoxy carbonylamino and carboxyl (as C₁ to C₆ alkyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, etc. may be mentioned, as substituent groups of C₁ to C₆ alkyl, fluorine, chlorine, bromine, iodine, amino, methoxy carbonyl, ethoxy carbonyl, methoxy carbonylamino, ethoxy carbonylamino, t-butoxy carbonylamino, and carboxyl
20 may be mentioned, as specific examples, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, carboxylmethyl, ethyl, 2,2,2-trifluoroethyl, aminoethyl, methoxy carbonylethyl, t-butoxy carbonylaminoethyl,
25 carboxylethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc. (preferably methyl, ethyl, trifluoromethyl, methoxy carbonylethyl, aminoethyl and carboxylmethyl, etc.) may be mentioned.)

30 (v) C₂ to C₆ alkenyl which unsubstituted, or
35 substituted with 1 to 3 halogen atoms (as halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₂ to C₆ alkenyl, for example, vinyl, propenyl,

isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-yl, etc. may be mentioned.)

(vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms, (as halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₂ to C₆ alkynyl, for example, 2-butyne-1-yl, 4-pentyne-1-yl and 5-hexyne-1-yl, etc. may be mentioned.)

(vii) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

(viii) hydroxyl

(ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 groups which are selected from a halogen atom, hydroxyl, C₁ to C₆ alkoxy, and amino, and mono- or di-C₁ to C₆ alkylamino (as C₁ to C₆ alkoxy, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy and n-hexyloxy, etc. may be mentioned. As substituent groups of C₁ to C₆ alkoxy, fluorine, chlorine, bromine, iodine, hydroxyl, amino, N-methylamino, N,N-dimethylamino, methoxy and ethoxy, etc. may be mentioned. As specific examples, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, trifluoromethyloxy, trichloromethyloxy, methoxymethyloxy and ethoxymethyloxy, etc. (preferably methoxy and ethoxy) may be mentioned.)

(x) C₁ to C₅ alkylenedioxy (for example, methylenedioxy and ethylenedioxy, etc. may be mentioned.)

(xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 groups which are selected from a halogen atom, hydroxyl, C₁ to C₆ alkoxy and amino, and mono- or di-C₁ to C₆ alkylamino (as C₁ to C₆ alkylthio, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, n-pentylthio and n-hexylthio, etc. may be mentioned. As substituent groups of C₁ to C₆ alkylthio, fluorine, chlorine, bromine, iodine, hydroxyl, amino, N-methylamino, N,N-dimethylamino, methoxy and ethoxy, etc.

may be mentioned. As specific examples, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, t-butylthio, trifluoromethylthio, trichloromethylthio, methoxymethylthio and
5 ethoxymethylthio, etc. may be mentioned.)

(xii) amino

(xiii) mono- C_1 to C_6 alkylamino (for example, N-methylamino etc. may be mentioned.)

(xiv) di- C_1 to C_6 alkylamino (for example, N,N-
10 dimethylamino etc. may be mentioned.)

(xv) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperadino, etc. may be mentioned.)

(xvi) C_1 to C_6 alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be
15 mentioned.)

(xvii) carboxyl

(xviii) C_1 to C_6 alkoxy carbonyl unsubstituted, or substituted with a halogen atom (for example, methoxycarbonyl and ethoxycarbonyl etc. may be
20 mentioned.)

(xix) C_7 to C_{16} aralkyloxycarbonyl unsubstituted, or substituted with a halogen atom (for example, benzyloxycarbonyl etc. may be mentioned.)

25 (xx) carbamoyl

(xxi) mono- C_1 to C_6 alkylcarbamoyl unsubstituted, or substituted with 1 to 3 groups which are selected from a halogen atom, hydroxyl, carboxyl, C_1 to C_6 alkoxy, amino, and mono- or di- C_1 to C_6 alkylamino (as mono- C_1 to C_6 alkylcarbamoyl, for example, N-methylcarbamoyl and N-ethylcarbamoyl, etc. may be mentioned. As substituent
30 groups of mono- C_1 to C_6 alkyl-carbamoyl, fluorine, chlorine, bromine, iodine, hydroxyl, carboxyl, methoxy, ethoxy, amino, N-methylamino and N,N-dimethylamino, etc. may be mentioned.)
35

(xxii) di- C_1 to C_6 alkylcarbamoyl unsubstituted, or substituted with hydroxyl (for example, N,N-

dimethylcarbamoyl, N,N-diethylcarbamoyl and N-hydroxyethyl-N-methylcarbamoyl, etc. may be mentioned.)

(xxiii) 5- to 6-membered cyclic aminocarbonyl unsubstituted, or substituted with C₁ to C₆ alkoxy carbonyl (for example, morpholinocarbonyl, piperidinocarbonyl, piperadinocarbonyl and t-butoxycarbonylpiperadinocarbonyl, etc. may be mentioned.)

(xxiv) C₆ to C₁₀ arylcarbamoyl (for example, N-phenylcarbamoyl etc. may be mentioned.)

(xxv) C₁ to C₁₀ heteroarylcarbamoyl (for example, N-pyridylcarbamoyl etc. may be mentioned.)

(xxvi) C₇ to C₁₆ aralkylcarbamoyl (for example, N-benzylaminocarbonyl etc. may be mentioned.)

(xxvii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl (for example, N-pyridylmethylcarbamoyl and N-pyridylethylcarbamoyl, etc. may be mentioned.)

(xxviii) N-C₁ to C₆ alkyl-N-C₆ to C₁₂ arylcarbamoyl (for example, N-methyl-N-phenylcarbamoyl etc. may be mentioned.)

(xxix) C₃ to C₆ cycloalkylcarbamoyl (for example, N-cyclopropylcarbamoyl and N-cyclohexylcarbamoyl, etc. may be mentioned.)

(xxx) sulfo

(xxxi) C₁ to C₆ alkylsulfonyl (for example, methanesulfonyl etc. may be mentioned.)

(xxxii) C₁ to C₆ alkylsulfonylamino (for example, methanesulfonylamino etc. may be mentioned.)

(xxxiii) C₆ to C₁₂ arylsulfonylamino unsubstituted, or substituted with C₁ to C₆ alkyl (for example, benzenesulfonylamino and methylbenzenesulfonylamino, etc. may be mentioned.)

(xxxiv) C₁ to C₁₀ heteroarylsulfonylamino (for example, pyridylsulfonylamino etc. may be mentioned.)

(xxxv) C₁ to C₆ alkoxy carbonylamino (for example, methoxycarbonylamino, ethoxycarbonylamino and t-butoxycarbonylamino, etc. may be mentioned.)

(xxxvi) C₁ to C₆ alkylcarbonylamino (for example,

acetoamide etc. may be mentioned.)

(xxxvii) mono- or di- C_1 to C_6 alkylaminocarbonylamino (for example, N-methylaminocarbonylamino and N-ethylaminocarbonylamino, etc. may be mentioned.)

5 (xxxviii) C_6 to C_{12} aryl (for example, phenyl etc. may be mentioned.)

(xxxix) C_1 to C_{10} heteroaryl (C_1 to C_{10} heteroaryl including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom (for example, pyridyl, pyrazolyl and imidazolyl, etc.) may be mentioned.)

10 (xl) C_6 to C_{10} aryloxy (for example, phenoxy etc. may be mentioned.)

(xli) C_1 to C_{10} heteroaryloxy (C_1 to C_{10} heteroaryloxy including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom (for example, pyridyloxy, pyrazolyloxy and imidazolyloxy, etc.) may be mentioned.)

(xlii) C_7 to C_{16} aralkyloxy (for example, benzyloxy etc. may be mentioned.)

20 (xliii) C_1 to C_{10} heteroaryl- C_1 to C_6 alkyloxy (C_1 to C_{10} heteroaryl- C_1 to C_6 alkyloxy including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom (for example, pyridylmethyloxy, pyrazolylmethyloxy and imidazolylmethyloxy, etc.) may be mentioned.)

25 (xliv) aminosulfonyl

(xlv) mono- or di- C_1 to C_6 alkylaminosulfonyl (for example, N-methylaminosulfonyl etc. may be mentioned.)

30 (xlvi) C_7 to C_{16} aralkyloxycarbamoyl (for example, N-benzyloxycarbamoyl etc. may be mentioned.)

(xlvii) C_1 to C_{10} heteroaryl- C_1 to C_6 alkyloxycarbamoyl (C_1 to C_{10} heteroaryl- C_1 to C_6 alkyloxycarbamoyl including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom (for example, N-pyridylmethyloxycarbamoyl, N-pyrazolylmethyloxycarbamoyl and N-imidazolylmethyloxycarbamoyl, etc.) may be mentioned.)

35

(xlvi) deuterium atoms.

0051

As examples of the substituent groups of the "C₆ to C₁₄ aromatic hydrocarbon group", "5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom", and "bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" expressed by W, in particular (i) a halogen atom, (ii) nitro, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 groups which are selected from the group consisting of a halogen atom, amino, C₁ to C₆ alkoxy carbonyl, C₁ to C₆ alkoxy carbonylamino, and carboxyl, (viii) hydroxyl, (xii) amino, (xvii) carboxyl, and (xlvi) deuterium atoms are preferable.

0052

The groups of (1) to (5) which are expressed by R¹ in the above formula (I) are shown below together with specific examples:

- (1) a hydrogen atom,
- (2) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 13 deuterium atoms (as a halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₃ to C₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned, as C₁ to C₆ alkyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc. may be mentioned. As specific examples, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, cyclopropylmethyl, cyclopentylmethyl, [²H₃]methyl and [²H₅]ethyl, etc. may be mentioned.)
- (3) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or

substituted with (iii) 1 to 11 deuterium atoms, (as a halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₃ to C₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned, as C₂ to C₆ alkenyl, for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-yl, etc. may be mentioned.)

(4) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 9 deuterium atoms (as a halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₃ to C₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned, as C₂ to C₆ alkynyl, for example, 2-butyne-1-yl, 4-pentyne-1-yl and 5-hexyne-1-yl, etc. may be mentioned.)

(5) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 11 deuterium atoms, (as a halogen atom, fluorine, chlorine, bromine, and iodine may be mentioned, as C₃ to C₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

0053

As examples of the group expressed by R¹, a hydrogen atom and methyl are preferable.

0054

In the above formula (I), the groups of (A) to (H) which the R⁹, R¹⁰, and R¹¹ of the "OR⁹" and "NR¹⁰R¹¹" expressed by R² independently indicate will be shown below together with specific examples.

- (A) a hydrogen atom
- (B) C₁ to C₆ alkyl (for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc. may be mentioned.)
- (C) C₂ to C₆ alkenyl (for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-

yl, etc. may be mentioned.)

(D) C₂ to C₆ alkynyl (for example, 2-butyne-1-yl, 4-pentyne-1-yl and 5-hexyne-1-yl, etc. may be mentioned.)

5 (E) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

10 (F) C₆ to C₁₄ aromatic hydrocarbon group (specific examples are the same as "C₆ to C₁₄ aromatic hydrocarbon group" in Ar explained above. As preferable examples, phenyl may be mentioned.)

15 (G) 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom (specific examples are the same as "5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom" in Ar explained above. As preferable examples, pyridyl may be mentioned.)

20 (H) bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring (specific examples are the same as "bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" in Ar explained above. As preferable examples, benzothienyl, benzofuryl, and indolyl may be mentioned.)

0055

30 As examples of the groups which the R⁹, R¹⁰ and R¹¹ of the "OR⁹" and "NR¹⁰R¹¹" expressed by R² indicate, a hydrogen atom, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, propenyl, cyclopropyl, cyclopentyl, phenyl and pyridyl are preferable.

0056

35 Next, specific examples of the substituent groups (i) to (xvii) which may optionally be possessed by the groups of (B) to (E) respectively independently shown by R⁹, R¹⁰, and R¹¹ of the "OR⁹" and "NR¹⁰R¹¹" expressed by R²

in the above formula (I), will now be shown.

(i) a halogen atom (for example, fluorine, chlorine, bromine, and iodine may be mentioned.)

5 (ii) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

(iii) hydroxyl

10 (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methoxy, ethoxy, n-propoxy, i-propoxy and trifluoromethyloxy, etc. may be mentioned.)

(v) amino

(vi) mono-C₁ to C₆ alkylamino (for example, N-methylamino etc. may be mentioned.)

15 (vii) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino etc. may be mentioned.)

(viii) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperadino, etc. may be mentioned.)

20 (ix) carboxyl

(x) C₁ to C₆ alkoxy-carbonyl (for example, methoxycarbonyl and ethoxycarbonyl, etc. may be mentioned.)

25 (xi) C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be mentioned.)

(xii) carbamoyl

(xiii) mono-C₁ to C₆ alkylcarbamoyl (for example, N-methylcarbamoyl and N-ethylcarbamoyl, etc. may be mentioned.)

30 (xiv) di-C₁ to C₆ alkylcarbamoyl (for example, N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl, etc. may be mentioned.)

(xv) C₆ to C₁₂ aryl (for example, phenyl, naphthyl and biphenyl, etc. may be mentioned.)

35 (xvi) C₁ to C₁₀ heteroaryl (for example, pyridyl, thienyl and furyl, etc. may be mentioned.)

(xvii) deuterium atoms.

0057

Among these, (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, and (xvii) deuterium atoms are preferable.

0058

Specific examples of the substituent groups (i) to (xxi) which may optionally be possessed by the groups of (F) to (H) respectively independently shown by R⁹, R¹⁰, and R¹¹ of the "OR⁹" and "NR¹⁰R¹¹" expressed by R² in the above formula (I), will now be shown.

- (i) a halogen atom (for example, fluorine, chlorine, bromine, and iodine may be mentioned.)
- (ii) nitro
- (iii) cyano
- (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methyl, trifluoromethyl, ethyl, n-propyl and i-propyl, etc. may be mentioned.)
- (v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)
- (vi) hydroxyl
- (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methoxy, ethoxy, n-propoxy, i-propoxy and trifluoromethyloxy, etc. may be mentioned.)
- (viii) amino
- (ix) mono-C₁ to C₆ alkylamino (for example, N-methylamino etc. may be mentioned.)
- (x) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino etc. may be mentioned.)
- (xi) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperadino, etc. may be mentioned.)
- (xii) C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be

mentioned.)

(xiii) carboxyl

(xiv) C₁ to C₆ alkoxy carbonyl (for example, methoxy carbonyl and ethoxy carbonyl, etc. may be

5 mentioned.)

(xv) carbamoyl

(xvi) mono-C₁ to C₆ alkyl carbamoyl (for example, N-methyl carbamoyl and N-ethyl carbamoyl, etc. may be mentioned.)

10 (xvii) di-C₁ to C₆ alkyl carbamoyl (for example, N,N-dimethyl carbamoyl and N,N-diethyl carbamoyl, etc. may be mentioned.)

(xviii) C₁ to C₆ alkyl sulfonyl (for example, methanesulfonyl etc. may be mentioned.)

15 (xix) aminosulfonyl

(xx) mono- or di-C₁ to C₆ alkyl aminosulfonyl (for example, N-methyl aminosulfonyl etc. may be mentioned.)

(xxi) deuterium atoms

0059

20 Among these, (i) a halogen atom, (iii) cyano, (vi) hydroxyl, (xxi) deuterium atoms are preferred.

0060

In the above formula (I), as the 5-or 6-member heterocyclic groups which are formed by R¹ and R² together
25 with the atoms they are bonded with, for example, imidazole, triazole, tetrazole, oxadiazole, thiadiazole, pyrimidine, triazine, oxadiazine, thiadiazine, and other aromatic heterocyclic groups or their saturated or partially saturated heterocyclic groups may be mentioned,
30 more specifically, imidazole, imidazoline, 1,2,4-triazole, 1,2,4-triazoline, tetrazole, 1,2,4-oxadiazoline, 1,2,4-thiadiazoline, dihydropyrimidine, tetrahydropyrimidine, dihydro-1,2,4-triazine, tetrahydro-1,2,4-triazine, dihydro-1,2,4-oxadiazine, tetrahydro-
35 1,2,4-oxadiazine, dihydro-1,2,4-thiadiazine, tetrahydro-1,2,4-thiadiazine (preferably imidazole, 1,2,4-triazole, 1,2,4-triazoline, 1,2,4-oxadiazoline, and tetrahydro-

1,2,4-oxadiazine) may be mentioned.

0061

5 In the above formula (I), the substituent groups (A) to (K), which may be optionally possessed by the 5-or 6-member heterocyclic groups formed by R¹ and R² together with the atoms they are bonded with, will be shown below, together with specific examples thereof:

- (A) a halogen atom (for example, fluorine, chlorine, bromine and iodine may be mentioned.)
- 10 (B) oxo
- (C) hydroxyl
- (D) C₁ to C₆ alkyl (for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl, etc. may be mentioned.)
- 15 (E) C₂ to C₆ alkenyl (for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl and 5-hexen-1-yl, etc. may be mentioned.)
- (F) C₂ to C₆ alkynyl (for example, 2-butyn-1-yl, 4-pentyn-1-yl and 5-hexyn-1-yl, etc. may be mentioned.)
- 20 (G) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)
- (H) C₆ to C₁₄ aromatic hydrocarbon group (specific examples are the same as "C₆ to C₁₄ aromatic hydrocarbon group" in Ar explained above. As preferable examples, phenyl may be mentioned.)
- 25 (I) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom (specific examples are the same as "a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom" in Ar explained above. As preferable example, pyridyl may be mentioned.)
- 30 (J) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and
- 35

a C₆ to C₁₄ aromatic hydrocarbon ring (specific examples are the same as "a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon group" in Ar explained above. As preferable examples, benzothienyl, benzofuryl and indolyl may be mentioned.)

(K) deuterium atoms.

0062

Among these, (A) a halogen atom, (B) oxo, (C) hydroxyl, (D) C₁ to C₆ alkyl, and (K) deuterium atoms are preferred.

0063

In the above formula (I), specific examples of the substituent groups (i) to (xvii) which the groups of the 1 to 3 substituent groups (D) to (G), which may be optionally possessed by the 5-or 6-member heterocyclic groups formed by R¹ and R² together with the atoms they are bonded with, may be optionally substituted with, will now be shown.

(i) a halogen atom (for example, fluorine, chlorine, bromine and iodine may be mentioned.)

(ii) C₃ to C₆ cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

(iii) hydroxyl

(iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methoxy, ethoxy, n-propoxy, i-propoxy and trifluoromethyloxy, etc. may be mentioned.)

(v) amino

(vi) mono-C₁ to C₆ alkylamino (for example, N-methylamino etc. may be mentioned.)

(vii) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino etc. may be mentioned.)

(viii) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperadino, etc. may be mentioned.)

(ix) carboxyl

(x) C₁ to C₆ alkoxy carbonyl (for example, methoxycarbonyl and ethoxycarbonyl, etc. may be mentioned.)

5 (xi) C₁ to C₆ alkyl carbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be mentioned.)

(xii) carbamoyl

10 (xiii) mono-C₁ to C₆ alkyl carbamoyl (for example, N-methylcarbamoyl and N-ethylcarbamoyl, etc. may be mentioned.)

(xiv) di-C₁ to C₆ alkyl carbamoyl (for example, N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl, etc. may be mentioned.)

15 (xv) C₆ to C₁₂ aryl and (for example, phenyl, naphthyl and biphenyl, etc. may be mentioned.)

(xvi) C₁ to C₁₀ heteroaryl (for example, pyridyl, thienyl and furyl, etc. may be mentioned.)

(xvii) deuterium atoms.

0064

20 In the above formula (I), specific examples of the substituent groups (i) to (xxi) which the groups of the 1 to 3 substituent groups (H) to (J), which may be optionally possessed by the 5-or 6-member heterocyclic groups formed by R¹ and R² together with the atoms they are bonded with, will now be shown.

25 (i). a halogen atom (for example, fluorine, chlorine, bromine, and iodine may be mentioned.)

(ii) nitro

(iii) cyano

30 (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methyl, trifluoromethyl, ethyl, n-propyl and i-propyl, etc. may be mentioned.)

(v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, etc. may be mentioned.)

35

(vi) hydroxyl

- (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methoxy, ethoxy, n-propoxy, i-propoxy and trifluoromethyloxy, etc. may be mentioned.)
- 5 (viii) amino
- (ix) mono-C₁ to C₆ alkylamino (for example, N-methylamino etc. may be mentioned.)
- (x) di-C₁ to C₆ alkylamino (for example, N,N-dimethylamino etc. may be mentioned.)
- 10 (xi) 5- to 6-membered cyclic amino (for example, morpholino, piperidino and piperadino, etc. may be mentioned.)
- (xii) C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl, butyryl, isobutyryl and pivaloyl, etc. may be
- 15 mentioned.)
- (xiii) carboxyl
- (xiv) C₁ to C₆ alkoxy carbonyl (for example, methoxycarbonyl and ethoxycarbonyl, etc. may be mentioned.)
- 20 (xv) carbamoyl
- (xvi) mono-C₁ to C₆ alkylcarbamoyl (for example, N-methylcarbamoyl and N-ethylcarbamoyl, etc. may be mentioned.)
- (xvii) di-C₁ to C₆ alkylcarbamoyl (for example, N,N-
- 25 dimethylcarbamoyl and N,N-diethylcarbamoyl, etc. may be mentioned.)
- (xviii) C₁ to C₆ alkylsulfonyl (for example, methanesulfonyl etc. may be mentioned.)
- (xix) aminosulfonyl
- 30 (xx) mono- or di-C₁ to C₆ alkylaminosulfonyl (for example, N-methylaminosulfonyl etc. may be mentioned.)
- (xxi) deuterium atoms.

0065

35 As preferable examples of the compounds having the above formula (I), the following may be mentioned.

0066

1. The compound, or a salt or solvate thereof, wherein,

in the formula (I), X is linear or branched C₁ to C₆ alkylene, and Ar is a C₆ to C₁₄ aromatic hydrocarbon group.

0067

- 5 2. A compound, or a salt or solvate thereof, where, in the formula (I), Ar is a phenyl group, of which Ar group may be optionally unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms or with 1 to 13 deuterium atoms, and (xxxi) deuterium atoms.

0068

- 15 3. A compound, or a salt or a solvate thereof, where, in the formula (I), W is (1) a C₆ to C₁₄ aromatic hydrocarbon group or (2) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom.

0069

- 25 4. The compound, or a salt, or a solvate thereof, as indicated in the above 3, where, in the formula (I), Z is (1) a connecting bond or (2) CR⁴R⁵ where, R⁴ and R⁵ are, respectively independently,
(A) a hydrogen atom,
(B) deuterium atoms
(C) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) carboxyl, (ii) C₁ to C₆ alkoxycarbonyl, (iii) phenyl, (iv) hydroxyl, (v) C₁ to C₆ alkoxy, (vi) a halogen atom, and (vii) C₃ to C₆ cycloalkyl or substituted with (viii) 1 to 13 deuterium atoms, or
(D) C₃ to C₆ cycloalkyl unsubstituted, or substituted
35 with 1 to 5 groups selected from the group consisting of (i) a halogen atom and (ii) an alkyl group unsubstituted, or substituted with 1 to 3 halogen atoms, or substituted

with (iii) 1 to 11 deuterium atoms.

0070

- 5 5. A compound, or a salt or a solvate thereof, where,
in the formula (I), W is a hydrogen atom or a deuterium
atom.

0071

- 10 6. A compound, or a salt or solvate thereof, as
indicated in the above 5, where, in the formula (I), Z is
(1) a connecting bond or (2) CR^4R^5 where, R^4 and R^5 are,
respectively independently,
(A) a hydrogen atom,
(B) deuterium atoms
(C) C_1 to C_6 alkyl unsubstituted, or substituted with 1
to 5 groups selected from the group consisting of (i)
15 carboxyl, (ii) C_1 to C_6 alkoxy carbonyl, (iii) phenyl, (iv)
hydroxyl, (v) C_1 to C_6 alkoxy, (vi) a halogen atom, and
(vii) C_3 to C_6 cycloalkyl, or substituted with (viii) 1 to
13 deuterium atoms,
(D) C_3 to C_6 cycloalkyl unsubstituted, or substituted
20 with 1 to 5 groups selected from the group consisting of
(i) a halogen atom and (ii) an alkyl group unsubstituted,
or substituted with 1 to 3 halogen atoms, or substituted
with (iii) 1 to 11 deuterium atoms,
(E) $COOR^6$ where R^6 indicates a hydrogen atom or C_1 to C_6
25 alkyl, or
(F) $CONR^7R^8$ where R^7 and R^8 independently are,
(a) a hydrogen atom,
(b) C_1 to C_6 alkyl unsubstituted, or substituted
with 1 to 3 groups selected from the group consisting of
30 (i) a halogen atom, (ii) C_3 to C_6 cycloalkyl, (iii)
carboxyl, (iv) C_1 to C_6 alkoxy carbonyl, (v) C_1 to C_6
alkyl carbonyl, (vi) carbamoyl, (vii) mono- C_1 to C_6
alkyl carbamoyl, (viii) di- C_1 to C_6 alkyl carbamoyl, (ix) C_6
to C_{12} aryl, and (x) C_1 to C_{10} heteroaryl,
35 (c) C_6 to C_{14} aromatic hydrocarbon cyclic group, or
(d) a 5- to 8-membered aromatic heterocyclic group
including 1 to 4 hetero atoms selected from a nitrogen

atom, sulfur atom, and oxygen atom, other than a carbon atom,

where the above groups (c) to (d) may be optionally substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkylcarbonyl, (xvii) carboxyl, (xxvii) aminosulfonyl and (xxviii) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxix) 1 to 9 deuterium atoms.

0072

7. A compound, or a salt or a solvate thereof, as indicated in the above 1 to 6, where, in the formula (I), R¹ is (1) a hydrogen atom or (2) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 13 deuterium atoms, and R² indicates (1) OR⁹ or (2) NR¹⁰R¹¹

where R⁹, R¹⁰, and R¹¹ independently are

- (A) a hydrogen atom,
- (B) C₁ to C₆ alkyl,
- (C) C₂ to C₆ alkenyl,
- (E) C₃ to C₆ cycloalkyl,
- (F) C₆ to C₁₄ aromatic hydrocarbon group, or
- (G) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom and oxygen atom, other than a carbon atom,

where each group of the above (B) to (E) may be optionally substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms,

(v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆ alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, and (xv) C₆ to C₁₂ aryl or substituted with (xviii) 1 to 13 deuterium atoms,

5 further, each group of the above (F) to (G) may be optionally substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, 10 or substituted with 1 to 3 halogen atoms, (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, and (xiii) carboxyl, or substituted with (xxi) 1 to 9 deuterium atoms.

0073

15 8. A compound, or a salt, or a solvate thereof, as indicated in the above 1 to 6, wherein, in the formula (I), the heterocyclic group which is formed by R¹ and R² together with the atoms they are bonded with is (1)imidazole, (2) triazole, (3) oxadiazole, or (4) 20 oxadiazine, or partially saturated heterocyclic rings of the same, where (1) to (4) may be optionally substituted with 1 to 3 groups selected from the group consisting of (A) a halogen atom, (B) oxo, 25 (C) hydroxyl, (D) C₁ to C₆ alkyl and (K) deuterium atoms.

0074

9. A compound, or a salt, or a solvate thereof, as set 30 forth in the above 1, wherein the compound is

- (1) 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(pyridin-2-yloxy)imino]-1,4-diazepan-1-yl]carbonyl)amino]propyl]benzoic acid,
(2) 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]butyl]benzoic acid, 35
(3) 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-

- methoxybenzyl)-7-oxo-3-[(2,2,2-trifluoroethoxy)imino]-
1,4-diazepan-1-yl}carbonyl)amino] butyl} benzoic acid,
(4) 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-
methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-
5 diazepan-1-yl}carbonyl)amino]ethyl} benzoic acid,
(5) 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-
methoxybenzyl)-3-(methoxyimino)-4-methyl-7-oxo-1,4-
diazepan-1-yl}carbonyl)amino]butyl} benzoic acid,
(6) (4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-
10 [(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-
yl}carbonyl)amino] ethyl}phenyl)acetic acid,
(7) 2-amino-4-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-
[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-
yl}carbonyl)amino]methyl} benzoic acid,
15 (8) (4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-
oxo-3-(phenoxyimino)-1,4-diazepan-1-
yl}carbonyl)amino]propyl}phenyl)acetic acid,
(9) 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-
methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-
20 yl}carbonyl)amino]propyl}benzoic acid, or
(10) 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-
methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-
yl}carbonyl)amino]butyl}benzoic acid.

0075

- 25 The compound having the formula (I) may be formed a
pharmaceutically acceptable salt, if necessary. When it
has an amine or other basic group as a substituent group,
for example, salts with hydrochloric acid, hydrobromic
acid, sulfuric acid, phosphoric acid, and other mineral
30 acids, salts with formic acid, acetic acid, fumaric acid,
maleic acid, oxalic acid, citric acid, malic acid,
tartaric acid, asparatic acid, glutamic acid, and other
organic carboxylic acids or salts with methanesulfonic
acid, benzenesulfonic acid, p-toluenesulfonic acid,
35 hydroxybenzenesulfonic acid, and other sulfonic acids,
etc. may be mentioned. When the compound having the
formula (I) has a carboxylic acid or other acid group as

a substituent group, for example, sodium, potassium, or other alkali metal salt, calcium, magnesium or other alkali earth metal salt, a salt with or ammonia, triethylamine, or ethylenediamine, propanediamine, pyrrolidine, piperidine, piperadine, pyridine, lysine, choline, ethanolamine, N,N-dimethylethanolamine, 4-hydroxypiperidine, glucosamine, N-methylglucamine, or other organic bases may be mentioned.

0076

The compound having the formula (I) or a salt thereof may be a nonsolvate or a solvate with water, methanol, ethanol, 1-propanol, 2-propanol, formic acid, ethyl formate, acetic acid, methyl acetate, ethyl acetate, propyl acetate and isobutyl acetate, etc.

0077

2. Explanation of Methods of Production of Compound Having Formula (I) or Salt or Solvate Thereof

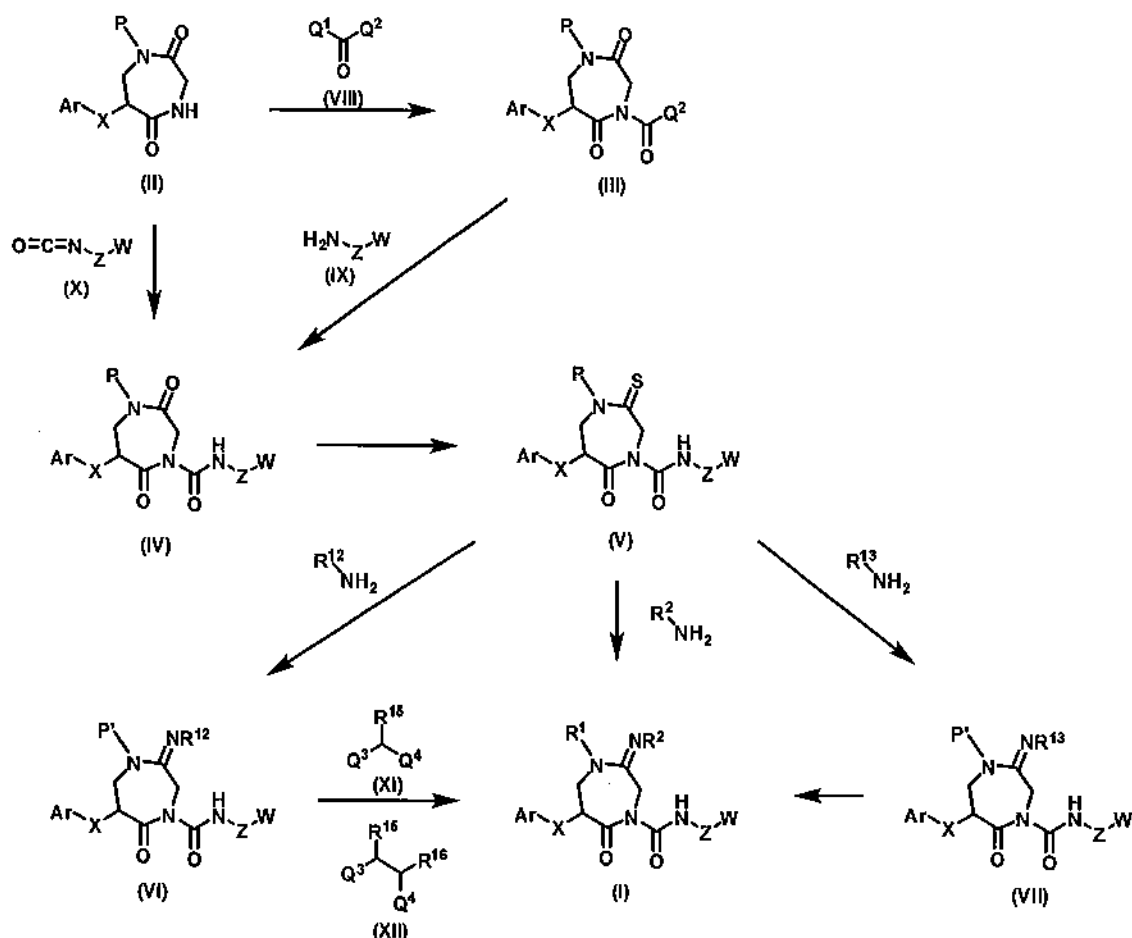
Below, methods of production the compound having the formula (I) or a salt or solvates thereof will be explained. The compound having the formula (I) or salt thereof can be produced by either or both of the two methods of production (A) and (B) explained below.

0078

Method of Production (A)

The compound having the formula (I) or a salt or solvate thereof may be synthesized by the method shown by the following scheme, for example:

0079



0080

where Ar, W, X, Z, R^1 and R^2 are the same as defined above, R^{12} indicates (1) OH or (2) NHR^{11} where R^{11} is the same as defined above, R^{13} indicates (1) OR^{14} , (2) $NR^{11}R^{14}$ where R^{11} is the same as defined above, R^{14} indicates formyl, a C_1 to C_6 alkylcarbonyl, C_2 to C_6 alkenylcarbonyl, C_2 to C_6 alkynylcarbonyl, C_3 to C_6 cycloalkylcarbonyl, C_6 to C_{14} arylcarbonyl, C_1 to C_{10} heteroarylcarbonyl, or C_1 to C_6 alkoxy carbonyl, or (3) C_2 to C_6 alkyl group substituted with two C_1 to C_6 alkoxy's, R^{15} and R^{16} independently indicate a hydrogen atom or oxo, P indicates a protective group such as allyl, allyloxycarbonyl, 9-fluorenylmethylcarbonyl, C_1 to C_6 alkyloxycarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C_1 to C_6 alkylcarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C_7 to C_{16} aralkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C_1 to

C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₅ to C₁₆ arylcarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₇ to C₁₆ aralkyloxycarbonyl
5 unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, or C₅ to C₁₆ arylsulfonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro or
10 indicates R¹ (R¹ is the same as defined above), P' indicates a hydrogen atom or P (P is the same as defined above), Q¹ and Q² independently indicate a halogen atom or C₆ to C₁₀ aryloxy unsubstituted, or substituted with 1 to 3 halogen atoms or nitro, Q³ and Q⁴ independently indicate
15 a halogen atom, C₆ to C₁₀ arylsulfonyloxy group unsubstituted, or substituted with 1 to 3 halogen atoms, C₁ to C₄ alkylsulfonyloxy group unsubstituted, or substituted with 1 to 3 halogen atoms, or C₆ to C₁₀ aryloxy 1 to 3 halogen atoms or nitro.

20 0081

As the C₂ to C₆ alkyl group substituted with two C₁ to C₆ alkoxy's expressed by R¹³, for example, an aminoacetoaldehydedimethylacetal etc. may be used.

0082

25 As the group expressed by R¹⁴, for example, formyl, C₁ to C₆ alkylcarbonyl (for example, acetyl, propionyl and trifluoroacetyl, etc.), C₂ to C₆ alkenylcarbonyl (for example, acryloyl etc.), C₂ to C₆ alkynylcarbonyl (for example, propioloyl etc.), C₃ to C₆ cycloalkylcarbonyl
30 (for example, cyclopropylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl, etc.), C₆ to C₁₄ arylcarbonyl (for example, benzoyl and naphtholyl, etc.), C₁ to C₁₀ heteroarylcarbonyl (for example, pyridylcarbonyl and imidazolylcarbonyl, etc.), C₁ to C₆ alkoxy carbonyl (for
35 example, methoxycarbonyl), etc. may be used.

0083

As the "protective group" represented by P, for

example, allyl, allyloxycarbonyl, 9-fluorenylmethylcarbonyl, linear or branched C₁ to C₆ alkyloxycarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, t-butoxycarbonyl etc.),
5 linear or branched C₁ to C₆ alkylcarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, trifluoroacetyl etc.), C₇ to C₁₆ aralkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy or (iv) nitro (for
10 example, benzyl, p-methoxybenzyl, 2,4-dimethoxybenzyl and 2,4,6-trimethoxybenzyl, etc.), C₅ to C₁₆ arylcarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro (for example, benzoyl and p-nitrobenzoyl),
15 C₇ to C₁₆ aralkyloxycarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro (for example, benzyloxycarbonyl etc.), C₅ to C₁₆ arylsulfonyl unsubstituted, or substituted with 1 to 3 of (i) a
20 halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro (for example, p-toluenesulfonyl etc.), etc. may be used.

0084

As the substituent groups expressed by Q¹ and Q², a
25 halogen atom (for example, chlorine or bromine), C₆ to C₁₀ aryloxy unsubstituted, or substituted with 1 to 3 of a halogen atom or nitro (for example, phenyloxy, p-nitrophenyloxy, p-chlorophenyloxy and 2-chlorophenyloxy, etc.), etc. may be used. As the substituent groups
30 expressed by Q³ and Q⁴, a halogen atom (for example, chlorine or bromine), C₆ to C₁₀ arylsulfonyloxy unsubstituted, or substituted with 1 to 3 halogen atoms (for example, benzenesulfonyloxy and p-toluenesulfonyloxy, etc.), C₁ to C₄ alkylsulfonyloxy
35 unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methanesulfonyloxy and trifluoromethanesulfonyloxy, etc.), or C₆ to C₁₀ aryloxy

unsubstituted, or substituted with 1 to 3 of a halogen atom or nitro (for example, phenyloxy, p-nitrophenyloxy, p-chlorophenyloxy and 2-chlorophenyloxy, etc.), etc. may be used.

5 0085

The compound (II), compound (III), compound (IV), compound (V), compound (VI), compound (VII), compound (VIII), compound (IX), compound (X), compound (XI) and compound (XII) may also be salts. Specific examples of
10 preferred salts are the same as the illustrations of salts of the compound having the formula (I).

0086

Next, the above reaction scheme which shows the production method (A) will be explained.

15 0087

First, for example, according to the method described in WO06-059801, the compound (II) and the compound (VIII) may be reacted to convert them to the compound (III), then the compound (IX) reacted with to
20 obtain the compound (IV). Further, the compound (IV) may, for example, be also obtained by the reaction of the compound (II) with the compound (X) according to the method described in WO07-139230. In the compound (IV), a compound where P is a hydrogen atom may be obtained by
25 removing the protective group P from the compound (IV) or may be obtained by the deprotection of protective group P of the compound (III), followed by the reaction with the compound (IX).

0088

30 Next, the compound (IV) can be processed by a known method using, for example, a general thiocarbonylation reagent (Lawesson's reagent and Belleau's reagent, etc.) to obtain the compound (V). Further, in the compound (V), a compound where P is a hydrogen atom can be obtained by
35 a thionation reaction of the compound (IV) where P is a hydrogen atom.

0089

In the compound (I), a compound where R^2 is (1) OR^9 and (2) $NR^{10}R^{11}$ can be obtained by, for example, the reaction of compound (V) in the presence of a metal catalyst (for example, mercury acetate and silver acetate, etc.), with R^2-NH_2 (where R^2 is (1) OR^9 or (2) $NR^{10}R^{11}$) or a salt thereof, and optionally performing a deprotection reaction. The deprotection reaction when P is a protective group may be performed before the reaction of the compound (V) and R^2-NH_2 or may be performed after it. When using a salt of R^2-NH_2 , for example, the reaction may be performed in the presence of a base such as triethylamine etc.

0090

In the compound (I), a compound where R^1 and R^2 form a 5- or 6-membered heterocyclic ring together with the atoms they are bonded with may be obtained by, for example, the reaction of the compound (V) in the presence of a metal catalyst (for example, mercury acetate and silver acetate, etc.), with $R^{12}-NH_2$ (where R^{12} is (1) OH or (2) NHR^{11}) or a salt thereof to obtain the compound (VI), and subsequent cyclization by the reaction with the compound (XI) or the compound (XII), and optionally performing a deprotection reaction. The deprotection reaction when P' is a protective group may be performed before the reaction of the compound (V) and $R^{12}-NH_2$ or may be performed after it. When using a salt of $R^{12}-NH_2$, for example, the reaction for conversion to the compound (VI) may be performed in the presence of a base such as triethylamine etc. Further, the cyclization reaction of the compound (VI) with the compound (XI) or the compound (XII) may be performed all together in the same system, or performed step by step, that is, the intermediate which is obtained by the reaction of the compound (VI) and the compound (XI) or the compound (XII) is isolated and subsequently a cyclization reaction is performed.

0091

Further, in the compound (I), a compound where R^1 and

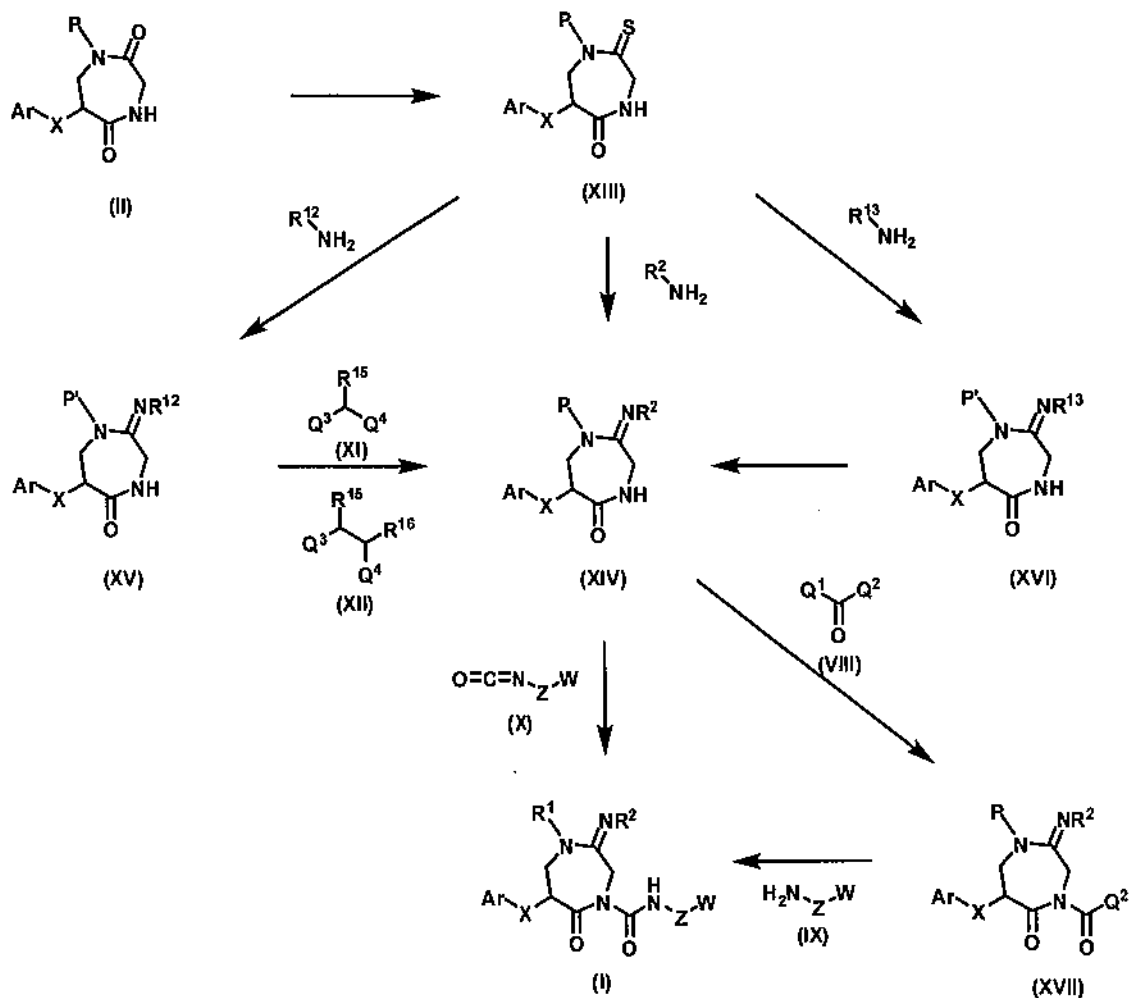
R^2 form a 5- or 6-membered heterocyclic ring together with the atoms they are bonded with may be obtained, for example, by the reaction of the compound (V) in the presence of a metal catalyst (for example, mercury acetate and silver acetate, etc.), with $R^{13}-NH_2$ (where R^{13} is (1) OR^{14} , (2) $NR^{11}R^{14}$ (R^{11} and R^{14} are the same as defined above) or (3) a C_2 to C_6 alkyl group substituted with two C_1 to C_6 alkoxy's) or a salt thereof to obtain the compound (VII), and subsequent cyclization reaction in the presence or absence of an acid catalyst (for example, pyridinium p-toluenesulfonic acid etc.) from the compound (VII), and optionally performing a deprotection reaction. The deprotection reaction when P' is a protective group may be performed before the reaction of the compound (V) and $R^{13}-NH_2$ or may be performed after it. When using a salt of $R^{13}-NH_2$, for example, the reaction for conversion to the compound (VII) may be performed in the presence such as a base of triethylamine etc. Further, the cyclization reaction of the compound (VII) may be performed all together in the same system of the reaction of the compound (V) with the compound (VII), or the compound (VII) may be isolated and a cyclization reaction performed step by step.

0092

25 Method of Production (B)

The compound having the formula (I) or a salt or solvate thereof may be synthesized by the method shown by the following scheme, for example:

0093



0094

where Ar, W, X, Z, R^1 , R^2 , R^{12} , R^{13} , R^{15} , R^{16} , P, P',
 5 Q^1 , Q^2 , Q^3 , and Q^4 are the same as defined above.

0095

The compound (II), compound (XIII), compound (XIV),
 compound (XV), compound (XVI), compound (XVII), compound
 (VIII), compound (IX), compound (X), compound (XI), and
 10 compound (XII) may also be in the form of salts. Specific
 examples of preferred salts are the same as the
 illustrations of salts of the compound having the formula
 (I).

0096

15 First, from the compound (II), the compound (XIII)
 may be obtained by a known method using, for example, a
 general thiocarbonylation reagent (Lawesson's reagent and

Belleau's reagent, etc.)

0097

5 In the compound (XIV), a compound where R^2 is (1) OR^9 and (2) $NR^{10}R^{11}$ where R^9 , R^{10} , and R^{11} are the same as defined above, may be obtained by, for example, the reaction of the compound (XIII) obtained above in the presence of a metal catalyst (for example, mercury acetate and silver acetate etc.), with R^2-NH_2 or a salt thereof.

10 0098

Further, in the compound (XIV), a compound where R^2 and P (where P indicates R^1 : R^1 and R^2 are the same as defined above) form a 5- or 6-membered heterocyclic ring together with the atoms they are bonded with may be
15 obtained by, for example, the reaction of the compound (XIII) obtained above in the presence of a metal catalyst (for example, mercury acetate and silver acetate, etc.), with $R^{12}-NH_2$ where R^{12} is (1) OH and (2) NHR^{11} or a salt thereof to obtain the compound (XV), and subsequent
20 cyclization by the reaction with the compound (XI) or the compound (XII).

0099

Furthermore, in the compound (XIV), a compound where R^2 and P (where P indicates R^1 : R^1 and R^2 are the same as
25 defined above) form a 5- or 6-membered heterocyclic ring together with the atoms they are bonded with may be obtained by for example, the reaction of the compound (XIII) obtained above, in the presence of a metal catalyst (for example, mercury acetate and silver
30 acetate, etc.), with $R^{13}-NH_2$ (where R^{13} is (1) OR^{14} , (2) $NR^{11}R^{14}$ (R^{11} and R^{14} are the same as defined above), or (3) a C_2 to C_6 alkyl group substituted with two C_1 to C_6 alkoxy's) or salt thereof to obtain the compound (XVI), and subsequent cyclization reaction from the compound
35 (XVI) in the presence or absence of an acid catalyst (for example, pyridinum p-toluenesulfonic acid etc.).

0100

From the compound (XIV) obtained above, the compound (I) may be obtained by reaction with the compound (X) according to the method described in, for example, WO07-139230, and optionally performing a deprotection reaction. Further, from the compound (XIV), the compound (I) may be obtained by reaction with the compound (VIII) according to the method described in, for example, WO06-059801 to convert it to the compound (XVII), then performing a reaction with the compound (IX), and optionally performing a deprotection reaction.

0101

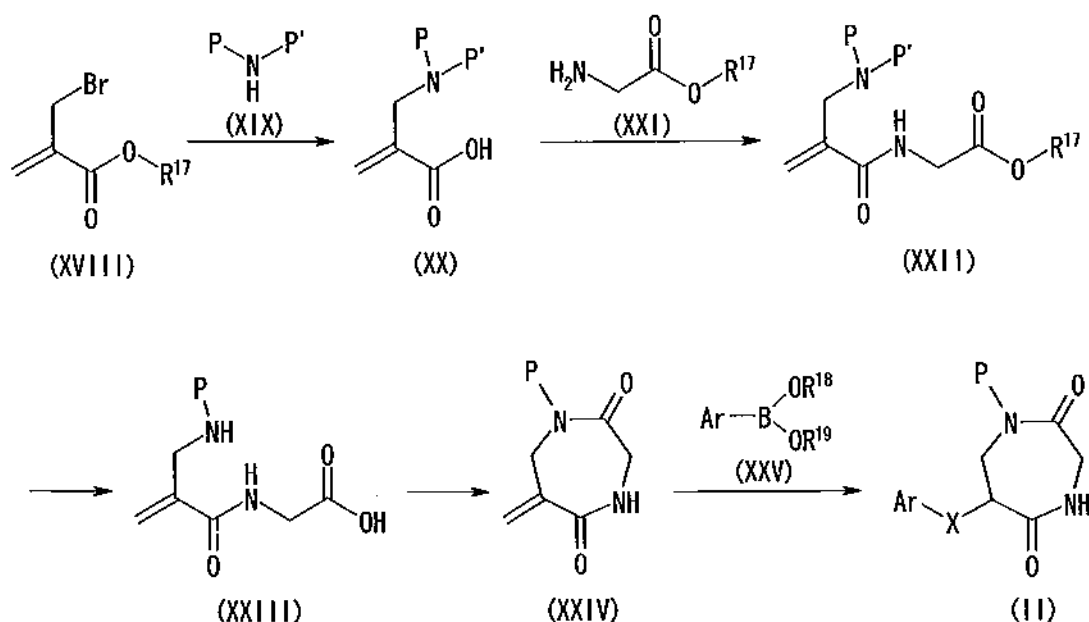
It is possible, when needed, to convert the functional groups after the reaction of the above (A) or (B) to produce the compound (I) converted in functional groups by 1 to 5 steps of an ordinary method, such as a deprotection reaction when the compound (I) of the present invention produced by the method of (A) or (B) has a protective group, the hydrogenation reaction when it has a carbon-carbon double bond or triple bond, the reduction reaction when it has a nitro group, the esterification reaction and amidation reaction when it has a carboxylic acid, the hydrolysis reaction when it has an ester group, the (i) alkylation reaction, (ii) acylation reaction, and (iii) sulfonylation reaction when it has an amino group or hydroxyl group, and the (i) alkylation reaction, (ii) acylation reaction, and (iii) sulfonylation reaction when it has a primary or secondary amide group.

0102

In the above production method (A) or (B), the compound (II) used as a starting material, or the compounds (IX) and (X) used as reactants can be obtained, for example, by the method described in WO06-059801 or WO07-139230. Further, the compounds (IX) and (X) used may be commercially available products or known compounds.

Further, in the compound (II), the compound where X indicates methylene may be synthesized by the method

shown by, for example, the scheme:



where Ar, P, and P' are the same as defined above,
 5 R¹⁷ indicates (1) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms (for example, methyl, ethyl and trichloroethyl, etc.) or (2) C₇ to C₁₆ aralkyl unsubstituted, or substituted with 1 to 3 of (i) C₁ to C₆ alkoxy or (ii) nitro (for example, benzyl and 4-methoxybenzyl, etc.), R¹⁸ and R¹⁹ independently indicate
 10 (i) a hydrogen atom or (ii) C₁ to C₆ alkyl, where R¹⁸ and R¹⁹ may form a 5- or 6-member ring together with the atoms with which they are bonded. Here, X indicates methylene.

That is, the commercially available or known
 15 compound (XVIII) and compound (XIX) may be reacted and in accordance with need a deprotection reaction performed so as to obtain the compound (XX). Next, compound (XXII) may be obtained by the condensation reaction of the compound (XX) with a glycine derivative (XXI) or a salt thereof
 20 by, for example, using a general condensation agent (for example, DCC etc.) or other known method. From the obtained compound (XXII), for example, a hydrolysis reaction using sodium hydroxide etc. or another known method may be used to remove the protective groups to
 25 obtain the compound (XXIII). When necessary at this time,

before or after the hydrolysis reaction, or before and after the hydrolysis reaction, for example, the P' protective groups may be removed in accordance with a known method using an acid and base, etc., but when P' is a hydrogen atom, this deprotection is not necessarily required. Next, from the obtained compound (XXIII), for example, a condensation reaction using a general condensation agent (for example, DCC etc.) or other known method may be followed to cyclization to obtain the compound (XXIV). Further, the obtained compound (XXIV) and a boronic acid derivative (XXV) may be reacted by a coupling reaction using, for example, a transition metal catalyst which has rhodium and palladium, etc. as the center metal, to obtain the compound (II).

0103

The R^2-NH_2 , $R^{12}-NH_2$, and $R^{13}-NH_2$ (or their salts) which are used as reaction agents in the above method of production (A) or (B) may be obtained, for example, according to the method described in the J. Med. Chem., 2005, 48, 1576, etc. Further, the R^2-NH_2 , $R^{12}-NH_2$, and $R^{13}-NH_2$ (or their salts) used may be commercially available products or known compounds.

0104

Further, the compounds (XI) and (XII) used may be commercially available products or known compounds, or compounds obtained by known methods.

0105

In a compound (I) or a salt or solvate thereof of the present invention and the synthetic intermediates for production of the compound (I), a compound including deuterium in the substituent group can be synthesized by the method of the above (A) or (B) by using suitably deuterated starting materials and reaction agents. The deuterated starting materials and reaction agents used may be commercially available products or known ones. Furthermore, in the compound (I) or its salt or solvates thereof of the present invention, the synthetic

intermediates and the starting materials for production of the compound (I), and reaction agents used in the synthesis methods of the above (A) and (B), compounds including deuterium in the substituent groups may be
5 obtained by substituting the desired positions with deuterium according to the known method described in, for example, Synthesis, 2009, 2674 or Angewandte Chemie International Edition, 47, 29, 5394, etc.

0106

10 The compound (I) of the present invention or a salt or solvate thereof, produced by the method of (A) or (B) and the synthetic intermediates for production of the compound (I) may be purified by known methods, for example, solvent extraction, pH change, solvent exchange,
15 salting out, crystallization, recrystallization and chromatography, etc. When the compound (I) of the present invention and the synthetic intermediate for production of the compound (I) are optically active compounds and include another optical isomer, a general optical
20 resolution method may be used for separation into the enantiomers.

0107

When the compound (I) of the present invention produced by the method of the above (A) or (B) has an
25 amine or other basic group as a substituent group, salts with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and other mineral acids, salts with formic acid, acetic acid, fumaric acid, maleic acid, oxalic acid, citric acid, malic acid, tartaric acid,
30 asparatic acid, glutamic acid, and other organic carboxylic acids, salts with methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydroxybenzenesulfonic acid, and other sulfonic acids, etc. may be formed according to an ordinary method. When
35 the compound (I) has a carboxylic acid or other acid group as a substituent group, sodium, potassium, or other alkali metal salt, calcium, magnesium, or other alkali

earth metal salt, or a salts with ammonia, triethylamine, ethylenediamine, propanediamine, pyrrolidine, piperidine, piperadine, pyridine and lysine, choline, ethanolamine, N,N-dimethylethanolamine, 4-hydroxypiperidine,
5 glucosamine, N-methylglucamine, or other organic base may be formed according to an ordinary method.

0108

The compound (I) or a salt thereof of the present invention produced by the method of (A) or (B) may be
10 brought into contact with a solvent such as water, methanol, ethanol, 1-propanol, 2-propanol, formic acid, ethyl formate, acetic acid, methyl acetate, ethyl acetate, propyl acetate, and isobutyl acetate, or mixed solvent including these solvent, or recrystallized from
15 these solvents etc. so as to form their solvates.

0109

The compound (I) or a salt or solvate thereof of the present invention, have superior chymase inhibitory activity and have low toxicity ($LD_{50} > 1$ g/kg), so can be
20 safely used for mammals (for example, humans, rats, mice, dogs and cattle, etc.) for the prevention and/or treatment of bronchial asthma, chronic obstructive pulmonary disease, urticaria, atopic dermatitis, allergic conjunctivitis, rhinitis, rheumatoid arthritis, food
25 allergies, colitis, allergic enteritis, mastocytosis, scleroderma, heart failure, cardiac hypertrophy, hypertension, arrhythmia, atherosclerosis, abdominal aortic aneurysm, myocardial infarction, restenosis after PTCA, restenosis after bypass graft surgery, ischemic
30 peripheral circulatory disorders, hyperaldosteronism, diabetes, diabetic retinopathy, diabetic nephropathy, nephritis, glomerulosclerosis, renal insufficiency, solid tumor, fibrosis, postoperative adhesion, cicatrix, glaucoma, and ocular hypertension.

35 0110

The administration route of the pharmaceutical for prevention or treatment of above-mentioned diseases may

be oral or parenteral.

0111

The preparation used in the present invention may also contain, as active ingredients, other pharmaceutical ingredients, other than the compound (I) or pharmaceutically acceptable salt thereof.

0112

As such a pharmaceutical active ingredient, for example, steroids (for example, betamethasone etc.), immunosuppressants (for example, tacrolimus and pimecrolimus etc.), antiallergic agent (clemastine fumarate, d-chlorpheniramine maleate, cyproheptadine hydrochloride, promethazine hydrochloride, homochlorcyclizine hydrochloride, mequitazine, diphenhydramine hydrochloride, ebastine, cetirizine hydrochloride, olopatadine hydrochloride, fexofenadine hydrochloride, sodium cromoglicate, emedastine fumarate, suplatast tosilate and epinastine hydrochloride, etc.) etc. may be mentioned. These ingredients are not particularly limited so long as the object of the present invention is achieved, and may be used in approximate ratios. As specific examples of the dosage forms, for example, tablets (including sugar-coated tablets and film-coated tablets), pills, capsules (including microcapsules), granules, fine subtilaes, powders, syrups, emulsions, suspensions, injections, inhalants, ointments and eye drops etc. may be used. These drug products may be prepared according to ordinary methods (for example, methods described in the Japan Pharmacopeia etc.)

0113

In the preparations of the present invention, the content of the compound according to the present invention differs according to the type of the preparation, but usually is about 0.01 to about 100% by weight, based upon the total weight of the preparation, preferably about 0.1 to about 50% by weight, more

preferably about 0.5 to about 20% by weight or so.

0114

Specifically, tablets can be produced by granulating a homogenous mixture of pharmaceutical as it is or with
5 an excipient, binder, disintegrating agent, or other suitable additives by a suitable method, then adding a lubricant agent, and subjecting the mixture to compressive shaping; subjecting a homogenous mixture of pharmaceutical as it is or with an excipient, binder,
10 disintegrating agent, or other suitable additives, to directly compressive shaping; or subjecting a homogenous mixture of granules of pharmaceutical as it is prepared in advance or with suitable additives, to directly compressive shaping. Further, these tablets may, if
15 necessary, be given a coloring agent, flavoring agent, and may be coated with a suitable coating agent.

0115

As the production method of an injections, it is possible to dissolve, suspend, or emulsify a certain
20 amount of the pharmaceutical in injection water, physiological saline and Ringer's solution, etc. in the case of a water-based solvent, or in an ordinary vegetable oil etc. in the case of a non-water-based solvent, to obtain a certain volume, or to take a certain
25 amount of the pharmaceutical and seal it in an injection use container.

0116

As the carriers for oral preparations, for example, starch, mannitol, crystalline cellulose, sodium
30 carboxymethylcellulose, and other substances commonly used in the field of preparations may be used. As the carriers for injections, for example, distilled water, physiological saline, glucose solution and transfusions, etc. may be used. In addition, it is possible to suitably
35 add additives generally used in preparations.

0117

The dosage of these preparations differs according

to age, body weight, symptoms, route of administration, number of dosages, etc., but for example, for an adult patient, daily dose of these preparation is usually about 0.1 to about 100 mg/kg, preferably about 1 to 50 mg/kg, more preferably about 1 to about 10 mg/kg, based on daily dose of active ingredient (the compound of the present invention), administered orally once or in three portions daily.

EXAMPLES

0118

Reference Examples, Examples, and Test Examples will now be used to explain the present invention in more detail, but the present invention is by no means limited thereto. The fractions including the desired substances in the Examples and Reference Examples were detected by TLC (thin-layer chromatography) or LC/MS (liquid chromatography/mass spectrometry). In TLC observation, as a TLC plate, a Merck 60F₂₅₄ was used, while as the detection method, a UV detector was used. For the MS, the ESI method (i.e., electron spray ionization method) was used to detect the positive ions.

0119

Reference Example 1: tert-butyl 4-[(1S)-1-hydroxyethyl]benzoate (compound S1)

To tert-butyl 4-acetylbenzoate (3.33 g) in a tetrahydrofuran (23 ml) solution, (-)-B-chlorodiisopinocampheylborane in a 65% hexane solution (11.2 ml) was added dropwise under ice cooling, then the mixture was stirred at that temperature for 1.5 hours. The reaction solution was concentrated, and the residue was diluted by diethyl ether. To the thus solution obtained, diethanolamine (4.3 ml) was added under ice cooling, and the mixture was stirred at room temperature for 2 hours. The precipitates were removed by filtration, and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=9/1 to 4/1) to obtain the title

compound (3.47 g).

¹H-NMR (CDCl₃) δ1.50 (3H, d, J=6.5Hz), 1.59(9H, s), 1.90 (1H, br.s), 4.87-4.99 (1H, m), 7.41 (2H, d, J=8.3Hz), 7.96 (2H, d, J=8.3Hz)

5 0120

Reference Example 2: tert-butyl 4-[(1R)-1-aminoethyl]benzoate hydrochloride (compound S2)

Step (1): To the compound S1 (2.45 g) in a tetrahydrofuran (24 ml) solution, phthalimide (2.43 g),
10 triphenylphosphine (5.78 g) and diethyl azodicarboxylate in a 10% toluene solution (10 ml) were successively added under ice cooling, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated, then the residue was purified by flash
15 column chromatography (silica gel, hexane/ethyl acetate=5/1 to 1/1) to obtain tert-butyl 4-[(1R)-1-(1,3-dioxoisindolyn-2-yl)ethyl]benzoate (compound S2a) (2.21 g).

Step (2): To the compound S2a (2.21 g) in a methanol
20 (22 ml) solution, hydrazine hydrate (0.92 ml) was added at 60°C, and the mixture was stirred at that temperature for 1.5 hours. The reaction solution was concentrated, water was added to the residue, then the mixture was extracted with ethyl acetate. The organic layer was back
25 extracted by 1M hydrochloric acid, then the aqueous layer was basified using a 4M aqueous sodium hydroxide solution, and the mixture extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, then 4M hydrochloric acid in an ethyl acetate
30 solution (1.6 ml) was added to the solution, and the resulting mixture was concentrated. The residue was triturated using diethyl ether and hexane, then the appeared solid was filtered to obtain the title compound (1.02 g).

35 ¹H-NMR (DMSO-d₆) δ1.51 (3H, d, J=6.5Hz), 1.55(9H, s), 4.48 (1H, m), 7.64 (2H, d, J=8.1Hz), 7.93 (2H, d, J=8.1Hz),

8.66 (3H, br.s)

0121

Reference Example 3: tert-butyl 4-[(1R)-1-azidopropyl]benzoate (compound S3)

5 Step (1): Instead of the starting material of Reference Example 1, that is, tert-butyl 4-acetylbenzoate, tert-butyl 4-propionylbenzoate was used for a similar procedure as in Reference Example 1 to obtain tert-butyl 4-[(1S)-1-hydroxypropyl]benzoate
10 (compound S3a).

 Step (2): To the compound S3a (3.62 g) in a tetrahydrofuran solution, triethylamine (4.38 ml) and methanesulfonyl chloride (1.46 ml) were added under ice cooling, and the mixture was stirred at that temperature
15 for 30 minutes. Further, triethylamine (1.1 ml) and methanesulfonyl chloride (0.48 ml) were added, and the mixture was further stirred for 30 minutes. To the reaction solution, water was added, and the mixture was extracted with ethyl acetate. The organic layer was
20 washed with brine, then dried over anhydrous sodium sulfate, then concentrated. The residue was dissolved in N,N-dimethylformamide (15 ml), sodium azide was added under ice cooling (1.32 g), and the mixture was stirred at room temperature for 1.5 hours. To the reaction
25 solution, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, then dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=19/1 to
30 9/1) to obtain the title compound (1.63 g).

¹H-NMR (CDCl₃) δ0.92 (3H, t, J=7.3Hz), 1.60(9H, s), 1.70-1.95 (2H, m), 4.41 (1H, t, J=7.1Hz), 7.34 (2H, d, J=8.1Hz), 8.00 (2H, d, J=8.1Hz)

0122

35 Reference Example 4: tert-butyl 4-[(1R)-1-aminopropyl]benzoate (compound S4)

 To the compound S3 (1.63 g) in a tetrahydrofuran

(15.2 ml) solution, water (0.8 ml) and triphenylphosphine (1.64 g) were added under ice cooling, and the mixture was stirred at 50°C for 16 hours. The reaction solution was concentrated, toluene (20 ml) was added to the residue, and the mixture was extracted with 0.5M hydrochloric acid (20 ml×3). The aqueous layer was basified using a 1M aqueous sodium hydroxide solution, then the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (NH₂ silica gel, hexane/ethyl acetate=8/1 to 3/1) to obtain the title compound (1.37 g).

¹H-NMR (CDCl₃) δ0.86 (3H, t, J=7.3Hz), 1.58(9H, s), 1.63-1.80 (2H, m), 3.87 (1H, t, J=6.7Hz), 7.35 (2H, d, J=8.3Hz), 7.95 (2H, d, J=8.3Hz)

MS: 236(M+H)⁺

0123

Reference Example 5: tert-butyl 4-[(1R)-1-aminopentyl]benzoate (compound S5)

Instead of the starting material of Reference Example 1, that is, tert-butyl 4-acetylbenzoate, tert-butyl 4-pentanoylbenzoate was used for a similar procedure as successively in Reference Example 1, Reference Example 3, and Reference Example 4 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.86 (3H, t, J=7.1Hz), 1.09-1.22 (1H, m), 1.23-1.35 (3H, m), 1.59(9H, s), 1.60-1.717 (2H, m), 3.90-3.96 (1H, m), 7.35 (2H, d, J=8.5Hz), 7.95 (2H, d, J=8.5Hz)

MS: 219(M-NH₂)⁺

0124

Reference Example 6: tert-butyl 4-chloro-2-nitrobenzoate (compound S6)

To 4-chloro-2-nitrobenzoic acid (262 g) in a pyridine (1.3 liter) solution, p-toluenesulfonyl chloride

(272.6 g) was slowly added at room temperature, and the mixture was stirred at that temperature for 15 minutes. To the reaction solution, tert-butyl alcohol (249 ml) was added dropwise, then the mixture was stirred for 5 hours.

5 To the reaction mixture toluene (1 liter) was added, and the mixture was stirred for 1.5 hours, then the precipitate were removed by filtration. The filtrate was concentrated, ethyl acetate (1.3 liter) was added to the residue, the mixture was successively washed with water,

10 saturated aqueous potassium hydrogensulfate solution, aqueous saturated sodium hydrogencarbonate solution, and brine, then the organic layer was dried over anhydrous sodium sulfate, then concentrated. Methanol (470 ml) was added to the residue, and after the precipitation of the

15 crystals was confirmed, water (142 ml) was added. The mixture was stirred under ice cooling for 1.5 hours, then the crystals were collected by filtration. The same recrystallization procedure as the above was performed again to obtain the title compound (297 g).

20 ¹H-NMR (CDCl₃) δ1.55(9H, s), 7.61 (1H, dd, J=2.0, 8.5Hz), 7.71 (1H, d, J=8.5Hz), 7.79 (1H, d, J=2.0Hz)

0125

Reference Example 7: tert-butyl 2-nitro-4-butyrylbenzoate
(compound S7)

25 The compound S6 (15.45 g), tris(dibenzylidene acetone)dipalladium (1.1 g), 2-(di-tert-butyl phosphino)-2'-methylbiphenyl (1.5 g), and tripotassium phosphate (18.6 g) were added to a reaction flask, the inside of the reaction system was made an argon atmosphere, then

30 dimethoxyethane (300 ml) and n-nitrobutane (12 ml) were successively added, and the mixture was vigorously stirred at room temperature for 3 minutes. Furthermore, the reaction mixture was stirred at 60°C for 24 hours. To the reaction mixture, water (75 ml) was added, the

35 reaction system was made an oxygen atmosphere, and the mixture was stirred for 2 days. The dimethoxyethane was distilled off, and the aqueous mixture thus obtained was

extracted with ethyl acetate. The organic layer was successively washed with water and brine, was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=9/1 to 6/1) to obtain the title compound (17.5 g).

¹H-NMR (CDCl₃) δ1.02 (3H, t, J=7.5Hz), 1.57-1.59(9H, m), 1.74-1.86 (2H, m), 2.98 (2H, t, J=7.3Hz), 7.80 (1H, d, J=7.7Hz), 8.20 (1H, dd, J=1.6, 7.7Hz), 8.40 (1H, d, J=1.6Hz)

0126

Reference Example 8: tert-butyl 4-[(1R)-1-aminobutyl]-2-nitrobenzoate D-tartrate (compound S8)

Instead of the starting material of Reference Example 1, that is, tert-butyl 4-acetylbenzoate, the compound S7 was used for successively similar procedures as in Reference Example 1, Reference Example 3, and Reference Example 4 to obtain tert-butyl 4-[(1R)-1-aminobutyl]-2-nitrobenzoate (1.48 g). This was dissolved in ethanol (10 ml), then D-tartaric acid (565 mg) was added to this solution, and the mixture was stirred at 80°C for 1 hour. The solution was gradually cooled down to room temperature, then ethyl acetate (10 ml) was added, and the mixture was stirred at 0°C for further 2 hours. The precipitated crystals were collected by filtration to obtain the title compound (1.21 g).

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J=7.3Hz), 1.08-1.30 (2H, m), 1.50(9H, s), 1.64-1.84 (2H, m), 3.95 (2H, s), 4.23-4.32 (1H, m), 7.83-7.87 (2H, m), 8.11 (1H, s)

0127

Reference Example 9: tert-butyl 4-[(1R)-1-aminopentyl]-2-nitrobenzoate D-tartrate (compound S9)

Step (1): Instead of the reaction agent, that is, n-nitrobutane, of Reference Example 7, n-nitropentane was used for a similar procedure as in Reference Example 7 to obtain tert-butyl 2-nitro-4-pentanoyl benzoate (compound

S9a).

Step (2): Instead of the starting material, that is, tert-butyl 4-acetylbenzoate, of Reference Example 1, the compound S9a was used for a similar procedure as in

5 Reference Example 8 to obtain the title compound.

MS: 309(M+H)⁺

0128

Reference Example 10: tert-butyl 4-[(1R)-1-aminoethyl]-2-nitrobenzoate D-tartrate (compound S10)

10 Step (1): Instead of the reaction agent, that is, n-nitrobutane, of Reference Example 7, nitroethane was used for a similar procedure as in Reference Example 7 to obtain tert-butyl 2-nitro-4-acetylbenzoate (compound S10a).

15 Step (2): Instead of the starting material, that is, tert-butyl 4-acetylbenzoate, of Reference Example 1, the compound S10a was used for a similar procedure as in Reference Example 8 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.44 (3H, d, J=6.9Hz), 1.50(9H, s), 3.17
20 (3H, s), 3.94 (2H, s), 4.47 (1H, q, J=6.9Hz), 7.83-7.91 (2H, m), 8.13 (1H, d, J=0.8Hz)

MS: 267(M+H)⁺

0129

25 Reference Example 11: tert-butyl 2-amino-4-aminomethyl benzoate (compound S11)

30 Step (1): Instead of the reaction agent, that is, n-nitrobutane, of Reference Example 7, nitromethane was used for a similar procedure as in Reference Example 7 to obtain tert-butyl 2-nitro-4-nitromethylbenzoate (compound S11a).

35 Step (2): To the compound S11a (1.69 g) in an ethanol solution, Raney nickel was added, and the mixture was stirred under a hydrogen atmosphere for 2.5 hours. The reaction mixture was diluted by chloroform, then was filtered by a glass filter spread with Celite®. The filtrate was concentrated, then the residue was purified by flash column chromatography (NH₂ silica gel,

chloroform/ethyl acetate/methanol=10/4/1) to obtain the title compound (308 mg).

¹H-NMR (CDCl₃) δ1.58 (9H, s), 3.78 (2H, s), 5.70 (2H, br.s), 6.56 (1H, dd, J=1.2, 8.3Hz), 6.60 (1H, s), 7.77 (1H, d, J=8.3Hz)

0130

Reference Example 12: tert-butyl 2-(benzyloxy)-4-(1-aminoethyl)benzoate (compound S12)

Step (1): Instead of the starting material, that is, 4-chloro-2-nitrobenzoic acid, of Reference Example 6, 2-(benzyloxy)-4-chlorobenzoic acid was used for a similar procedure as in Reference Example 6 to obtain tert-butyl 2-(benzyloxy)-4-chlorobenzoate (compound S12a).

Step (2): Instead of the starting material, that is, the compound S6, of Reference Example 7, the compound S12a was used and instead of the reaction agent, that is, n-nitrobutane, nitroethane was used for a similar procedure as in Reference Example 7 to obtain tert-butyl 2-(benzyloxy)-4-acetylbenzoate (compound S12b) as a crude product.

Step (3): To the compound S12b as a crude product (6.89 g) in an ethanol (10 ml) solution, hydroxylamine hydrochloride (1.3 g) and sodium acetate (2.09 g) were added, then the mixture was heated and refluxed for 4 hours. The mixture was allowed to cool to room temperature, then concentrated. To the residue, water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, then concentrated. The residue was dissolved in acetic acid (170 ml), zinc powder (17 g) was added, and the mixture was stirred at 50°C for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated. The residue was diluted with ethyl acetate, then was washed with an saturated aqueous sodium hydrogencarbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate, then concentrated. The residue was purified by flash column chromatography (NH₂ silica gel,

chloroform/ethyl acetate/methanol=4/6 to 0/1) to obtain the title compound (3.21 g).

¹H-NMR (CDCl₃) δ1.34 (3H, d, J=6.9Hz), 1.51-1.54 (9H, m), 4.07-4.14 (1H, m), 5.16 (2H, s), 6.94 (1H, dd, J=1.2, 8.1Hz), 7.02 (1H, d, J=1.2Hz), 7.28-7.34 (1H, m), 7.34-7.41 (2H, m), 7.49 (2H, d, J=7.3Hz), 7.68 (1H, d, J=8.1Hz)

0131

10 Reference Example 13: tert-butyl 2-(benzyloxy)-4-(1-aminopropyl)benzoate (compound S13)

Step (1): Instead of the starting material, that is, the compound S6, of Reference Example 7, the compound S12a was used and instead of the reaction agent, that is, n-nitrobutane, n-nitropropane was used for a similar procedure as in Reference Example 7 to obtain tert-butyl 2-(benzyloxy)-4-propionylbenzoate (compound S13a) as a crude product.

20 Step (2): Instead of the starting material, that is, the compound S12b crude product, of Reference Example 12, Step (3), the compound S13a crude product obtained at Step (1) was used for a similar procedure as in Reference Example 12, Step (3), to obtain the title compound.

¹H-NMR (CDCl₃) δ0.81 (3H, t, J=7.5Hz), 1.52 (9H, s), 1.58-1.80 (2H, m), 2.03 (3H, s), 3.83 (1H, t, J=7.1Hz), 4.60 (3H, br.s), 5.16 (2H, s), 6.90 (1H, dd, J=1.2, 8.1Hz), 6.98 (1H, d, J=1.2Hz), 7.28-7.34 (1H, m), 7.34-7.41 (2H, m), 7.48 (2H, d, J=7.3Hz), 7.68 (1H, d, J=8.1Hz)

MS: 342 (M+H)⁺

0132

30 Reference Example 14: tert-butyl 2-amino-4-[(1R)-1-aminopentyl]benzoate tosylate (compound S14)

35 Instead of the starting material, that is, the compound S12b, of Reference Example 12 Step (3), the compound S9a crude product was used for a similar procedure as in Reference Example 12 Step (3) to obtain the title compound.

¹H-NMR (DMSO-d₆) 80.82 (3H, t, J=7.1Hz), 0.96-1.32(4H, m), 1.53(9H, s), 1.64-1.88 (2H, m), 2.29 (3H, s), 3.98-4.08 (1H, m), 6.59 (1H, dd, J=1.6, 8.1Hz), 6.73 (1H, d, J=1.6Hz), 7.06-7.16 (2H, m), 7.44-7.51 (2H, m), 7.69 (1H, d, J=8.1Hz), 8.19 (2H, br.s)

0133

Reference Example 15: 2,2,2-trichloroethyl 2-[(1R)-1-aminopropyl]oxazole-4-carboxylate hydrochloride (compound S15)

Step (1): To (2R)-2-(tert-butoxycarbonylamino)butanoic acid (5 g) in a dichloromethane (100 ml) solution, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.1 g), 1-hydroxybenzotriazole (5 g), L-serine methylester hydrochloride (5.7 g), and N,N-diethylisopropylamine (6.4 ml) were successively added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was diluted with ethyl acetate, successively washed with water, saturated aqueous potassium hydrogensulfate solution, saturated aqueous sodium hydrogencarbonate solution, and brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=4/6 to 3/7) to obtain methylester methyl (2S)-2-[(2R)-2-tert-butoxycarbonylamino] butyrylamino)-3-hydroxypropanoate (compound S15a) (5.27 g).

Step (2): To the compound S15a (2.64 g) in a dichloromethane (50 ml) solution, N,N-diethylsulfur trifluoride (DAST) (1.26 ml) was added dropwise at -20°C, and the mixture was stirred at that temperature for 1 hour. To the reaction solution, bromotrichloromethane (3.0 ml) and 1,8-diazabicyclo[5.4.0]undeca-7-ene (4.5 ml) were successively added, the mixture was stirred at 0°C for 4 hours. Then saturated aqueous sodium hydrogencarbonate solution was added and the mixture was

extracted with ethyl acetate. The organic layer was combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=8/2 to 7/3) to obtain methyl 2-[(1R)-1-(tert-butoxycarbonylamino)propyl]oxazole 4-carboxylate (compound S15b) (1.0 g).

¹H-NMR (CDCl₃) δ0.93 (3H, t, J=7.5Hz), 1.44(9H, s), 1.78-1.91 (1H, m), 1.91-2.04 (1H, m), 3.92 (3H, s), 4.83-4.94 (1H, m), 5.17-5.26 (1H, m), 8.19 (1H, s)

MS: 229(M-tBu)⁺

0134

Step (3): To the compound S15b (1.0 g) in a methanol (20 ml) solution, 4M aqueous sodium hydroxide solution (1.18 ml) was added, and the mixture was stirred at room temperature for 3 hours. The methanol was distilled off, then the residue was diluted with water and ethyl acetate, and the layers were separated. The aqueous layer was adjusted to pH 4 by 6M hydrochloric acid, then the mixture was extracted with ethyl acetate. The extract was combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to obtain 2-[(1R)-1-(tert-butoxycarbonylamino)propyl]oxazole 4-carboxylic acid (compound S15c) (0.76 g).

Step (4): To the compound S15c (0.76 g) in a dichloromethane (15 ml) solution, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.65 g), 4-dimethylaminopyridine (34 mg), and 2,2,2-trichloroethanol (0.4 ml) were successively added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, then the residue was diluted by ethyl acetate, and successively washed with water, saturated aqueous potassium hydrogensulfate solution, saturated aqueous sodium hydrogencarbonate solution, and brine. The organic layer was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography

(silica gel, hexane/ethyl acetate=6/1 to 3/1) to obtain 2,2,2-trichloroethyl 2-[(1R)-1-(tert-butoxycarbonylamino)propyl]oxazole-4-carboxylate (compound S15d) (0.75 g).

5 Step (5): To the compound S15d (0.75 g), 4M hydrochloric acid in ethyl acetate solution (5 ml) was added, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated to obtain the title compound (0.51 g).

10 ¹H-NMR (CDCl₃) δ1.11 (3H, t, J=7.5Hz), 2.27-2.38 (2H, m), 4.75-4.83 (1H, m), 4.92 (1H, d, J=14.2Hz), 4.93 (1H, d, J=14.2Hz), 8.39 (1H, s), 9.43 (3H, br.s)

MS: 301(M+H)⁺

0135

15 Reference Example 16: 2-[(1R)-1-aminopropyl]thiazole 4-carboxylic acid 2,2,2-trichloroethyl hydrochloride (compound S16)

 Step (1): To tert-butyl [(1R)-1-amino-1-thioxo]butan-2-yl)carbamate (2.8 g) in a dimethoxyethane
20 (60 ml) solution, potassium hydrogencarbonate (10.3 g) and ethyl bromopyruvate (4.9 ml) were successively added at 0°C, and the mixture was stirred at that temperature for 30 minutes and at room temperature for 18 hours. The reaction solution was concentrated, the residue was
25 diluted with chloroform, and the mixture was successively washed with water and brine. The organic layer was washed with brine, then concentrated. The residue was dissolved in dimethoxyethane (60 ml), trifluoroacetic acid anhydride (3.6 ml) and pyridine (4.7 ml) were
30 successively added at 0°C, and the mixture was stirred at that temperature for 1 hour. The reaction solution was concentrated, then the residue was diluted by ethyl acetate, and successively washed with saturated aqueous potassium hydrogensulfate solution, saturated aqueous
35 sodium hydrogencarbonate solution, and brine. The organic layer was dried over anhydrous sodium sulfate, then

concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=9/1 to 6/1) to obtain ethyl 2-[(1R)-1-(tert-butoxycarbonylamino)propyl]thiazole 4-carboxylate

5 (compound S16a) (4.25 g).

¹H-NMR (CDCl₃) δ0.98 (3H, t, J=7.3Hz), 1.40 (3H, t, J=7.7Hz), 1.45 (9H, s), 1.79-1.94 (1H, m), 2.09-2.22 (1H, m), 4.38-4.46 (2H, m), 4.88-5.00 (1H, m), 5.17-5.27 (2H, m), 8.08 (1H, s)

10 MS: 315 (M+H)⁺

Step (2): Instead of the starting material of Reference Example 15, Step (3), that is, the compound S15b, the compound S16a was used for a similar procedure as in Reference Example 15, Steps (3) to (5), to obtain

15 the title compound.

¹H-NMR (CDCl₃) δ1.02 (3H, t, J=7.3Hz), 1.70-1.88 (1H, m), 1.97-2.11 (1H, m), 4.28-4.34 (1H, m), 4.95-5.03 (2H, m), 8.26 (1H, s)

MS: 316 (M+H)⁺

20 0136

Reference Example 17: (6S)-6-(5-chloro-2-methoxybenzyl)-1-methyl-1,4-diazepane-2,5-dione (compound S17)

Step (1): To a 60% mineral oil dispersion of sodium hydride (1.9 g) in a tetrahydrofuran (50 ml) solution, methyl iodide (2.7 ml) was added under ice cooling, then the (2S)-3-[(tert-butoxycarbonyl)amino]-2-(5-chloro-2-methoxybenzyl)propanoic acid (5 g), described in WO 06-059801A, in a tetrahydrofuran (20 ml) solution was slowly added, then the mixture was stirred at room temperature for 72 hours. To the reaction solution, water (50 ml) and ethyl acetate (20 ml) were added and the layers were separated. The organic layer was extracted with water (20 ml) and was combined with the aqueous layer previously obtained, and acidified (pH2) with 6M hydrochloric acid. This aqueous mixture was extracted with ethyl acetate, then the combined extract was washed with water, saturated aqueous sodium thiosulfate solution, and brine.

The organic layer was dried over sodium sulfate, then concentrated to obtain (2S)-3-[tert-butoxycarbonyl(methyl)amino]-2-(5-chloro-2-methoxybenzyl)propanoic acid (5.28 g) (compound S17a).

5 Step (2): To the compound S17a obtained at Step (1) (7.12 g) in an acetonitrile solution (75 ml), glycine ethylester hydrochloride (3.05 g), 1-hydroxybenzotriazole (1.83 g), and triethylamine (2.62 ml) were added at room temperature, and the mixture was stirred at room
10 temperature for 20 minutes. To the reaction solution, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (4.77 g) was added, and the mixture was stirred at room temperature for 1 hour. To the reaction solution, a 3% aqueous sodium hydrogencarbonate solution
15 was added, and the mixture was extracted with ethyl acetate. The extract was combined, washed with saturated potassium hydrogensulfate and brine, dried over sodium sulfate, then concentrated to obtain N-[(2S)-3-[tert-butoxycarbonyl(methyl)amino]-2-(5-chloro-2-
20 methoxybenzyl)propanoyl] glycine ethylester (9.04 g) (compound S17b).

 Step (3): To the compound S17b obtained at Step (2) (9.04 g) in an ethanol (35 ml) solution, methanesulfonic acid (2.7 ml) was added, and the mixture was stirred at
25 40°C for 14 hours, then 4M aqueous sodium hydroxide solution was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution, 6M hydrochloric acid was added, the mixture was completely concentrated, then water (10 ml) was added to the
30 residue. The suspension thus obtained was stirred at 80°C for 30 minutes. The suspension was allowed to cool down to room temperature, then was further cooled down to -20°C, and the mixture was stirred at that temperature for 1.5 hours. The solid was collected by filtration and
35 dried to obtain N-[(2S)-3-(methylamino)-2-(5-chloro-2-methoxybenzyl)propanoyl]glycine as a crude product (2.7

g) (compound S17c).

Step (4): 1-hydroxybenzotriazole (339 mg) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (319 mg) in an acetonitrile (15 ml) solution were heated to 60°C. To this solution, the compound S17c obtained at Step (3) (473 mg) was added in batches. After the end of addition, the mixture was stirred at 60°C for 15 minutes. The reaction solution was allowed to cool down to room temperature, then water and ethyl acetate were added and the solution separated. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over sodium sulfate, then concentrated to obtain the title compound as a crude product. The crude product of the title compound obtained by the same procedure as above in another experimental was combined and purified by flash column chromatography (silica gel, hexane/ethyl acetate/methanol=45/45/10 to 40/40/20) to obtain the title compound (3.30 g).

¹H-NMR (CDCl₃) δ2.69 (1H, dd, J=7.9, 13.6Hz), 2.91 (3H, s), 3.15-3.36 (3H, m), 3.41-3.52 (1H, m), 3.83 (3H, s), 3.91 (1H, dd, J=6.1, 16.6Hz), 4.04 (1H, dd, J=5.7, 16.6Hz), 6.00-6.13 (1H, m), 6.80 (1H, d, J=8.5Hz), 7.16-7.18 (1H, m), 7.18-7.22 (1H, m)

MS: 297(M+H)⁺

0137

Reference Example 18: O-(3,4-difluorophenyl) hydroxylamine hydrochloride (compound S18)

Step (1): To molecular sieves 4A (1.5 g) in a dichloroethane (120 ml) suspension, 3,4-difluorobenzene boronic acid (5.2 g), N-hydroxyphthalimide (3.9 g), and pyridine (1.5 ml) were successively added, then the mixture was stirred under an oxygen atmosphere at 60°C for 18 hours. The reaction mixture was filtered using a silica gel column, then the eluate was concentrated to obtain 2-(3,4-difluorophenoxy) isoindolyn-1,3-dione (compound S18a) (2.55 g).

Step (2): To the compound S18a (1.64 g) in a chloroform (25 ml) and methanol (2 ml) solution, hydrazine monohydrate was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered, the filtrate was concentrated, then the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=4/1 to 3/2) to obtain 3,4-difluorophenyl hydroxylamine (1.18 g). This was dissolved in diethyl ether (10 ml), 4M hydrochloric acid in dioxane solution was added at 0°C, and the mixture was stirred at that temperature for 1 hour. The precipitates were collected by filtration to obtain the title compound (0.92 g).

¹H-NMR (CDCl₃) δ6.94-7.01 (1H, m), 7.05-7.19 (2H, m), 7.80-7.87 (2H, m), 7.89-7.96 (2H, m)

MS: 276(M+H)⁺

0138

Reference Example 19: tert-butyl 4-[(1R)-1-isocyanatopropyl]benzoate (compound S19)

To the compound S4 (891 mg) in a methylene chloride (15 ml) solution, 2M aqueous sodium hydroxide solution (15 ml) and trichloromethyl chloroformate (0.46 ml) were added under ice cooling, and the mixture was stirred at that temperature for 20 minutes. The reaction solution was extracted with methylene chloride. The extract was washed with brine, dried over anhydrous sodium sulfate, then concentrated to obtain the title compound (988 mg).

¹H-NMR (CDCl₃) δ0.97 (3H, t, J=7.3Hz), 1.59(9H, s), 1.77-1.92 (2H, m), 4.61 (1H, t, J=6.7Hz), 7.34 (2H, d, J=8.5Hz), 7.98 (2H, d, J=8.5Hz)

0139

Reference Example 20: tert-butyl 4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound S20)

To the compound S140c described in WO 06-059801A,

that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (1.35 g) in an acetonitrile (20 ml) solution, the compound S19 obtained at Reference Example 19 (988 mg) was added under ice cooling, and the mixture was stirred for several minutes. Then potassium tert-butoxide in a 1M tetrahydrofuran solution (0.29 ml) was added, and the mixture was stirred at that temperature for 10 minutes. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=1/1 to 1/2) to obtain the title compound (2.07 g).

¹H-NMR (CDCl₃) 80.90 (3H, t, J=7.3Hz), 1.57(9H, s), 1.71-1.97 (2H, m), 2.40 (1H, dd, J=9.3, 14.0Hz), 2.96-3.07 (2H, m), 3.12 (1H, dd, J=4.5, 14.0Hz), 3.45-3.63 (1H, m), 3.71(6H, s), 3.78 (3H, s), 3.85 (3H, s), 4.20 (1H, d, J=17.3Hz), 4.33 (1H, d, J=13.8Hz), 4.78 (1H, d, J=13.8Hz), 4.85 (1H, dt, J=7.7, 7.7Hz), 5.31 (1H, d, J=17.3Hz), 6.08 (2H, s), 6.75 (1H, d, J=8.8Hz), 6.93 (1H, d, J=2.5Hz), 7.19 (1H, dd, J=2.5, 8.8Hz), 7.33 (2H, d, J=8.3Hz), 7.95 (2H, d, J=8.3Hz), 9.52 (1H, d, J=7.7Hz)
MS: 724(M+H)⁺

0140

Reference Example 21: tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)propyl] benzoate (compound S21)

To the compound S20 (1.67 g) in a methylene chloride (20 ml) solution, water (1 ml) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (1.57 g) were added, and the mixture was stirred at room temperature for 3 days. To the reaction mixture, sodium sulfate and chloroform were added. The mixture was stirred at room temperature for 1 hour, then filtered. The filtrate was concentrated, then the residue was purified by flash column chromatography

(NH₂ silica gel, hexane/ethyl acetate=3/2 to 1/2) to obtain the title compound (1.0 g).

¹H-NMR (CDCl₃) δ 0.92 (3H, t, J=7.5Hz), 1.58 (9H, s), 1.75-1.97 (2H, m), 2.61 (1H, dd, J=8.5, 13.8Hz), 3.19 (1H, dd, J=5.3, 13.8Hz), 3.25-3.38 (2H, m), 3.58-3.74 (1H, m), 3.82 (3H, s), 4.07 (1H, d, J=17.5Hz), 4.82 (1H, dt, J=7.3, 7.3Hz), 5.34 (1H, d, J=17.5Hz), 5.97 (1H, br.s), 6.79 (1H, d, J=8.7Hz), 7.13 (1H, d, J=2.8Hz), 7.22 (1H, dd, J=2.8, 8.7Hz), 7.33 (2H, d, J=8.3Hz), 7.96 (2H, d, J=8.3Hz), 9.54 (1H, d, J=7.3Hz)

0141

Reference Example 22: tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)propyl] benzoate (compound S22)

To the compound S21 (995 mg) in a tetrahydrofuran (25 ml) solution, Belleau's reagent (582 mg) was added under ice cooling, and the mixture was stirred at that temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, then was successively washed with an saturated aqueous sodium hydrogencarbonate solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=3/1 to 2/1) to obtain the title compound (717 mg).

¹H-NMR (CDCl₃) δ 0.92 (3H, t, J=7.3Hz), 1.55 (9H, s), 1.76-1.96 (2H, m), 2.60 (1H, dd, J=8.7, 13.8Hz), 3.20 (1H, dd, J=4.7, 13.8Hz), 3.33-3.52 (2H, m), 3.73-3.88 (4H, m), 4.36 (1H, d, J=17.9Hz), 4.71-4.89 (1H, m), 5.91 (1H, d, J=17.9Hz), 6.81 (1H, d, J=8.5Hz), 7.13 (1H, d, J=2.2Hz), 7.23 (1H, dd, J=2.2, 8.5Hz), 7.29-7.41 (2H, d, J=8.1Hz), 7.89 (1H, br.s), 7.92-8.04 (2H, d, J=8.1Hz), 9.43 (1H, d, J=7.3Hz)

MS: 504 (M-tBu)⁺

0142

Example 1: 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(isopropoxyimino)-7-oxo-1,4-diazepan-1-

yl]carbonyl}amino)propyl]benzoic acid (compound 1)

Step (1): To the compound S22 (110 mg) in a tetrahydrofuran (2 ml) and methanol (4 ml) solution, O-isopropyl hydroxylamine hydrochloride (44 mg),
5 triethylamine (55 μ l), and mercury acetate (75 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 20 minutes. The reaction mixture was filtered, then the filtrate was concentrated. The residue was purified by flash column chromatography
10 (silica gel, hexane/ethyl acetate=2/1) to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(isopropoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoate (106 mg) (compound 1a).

Step (2): To the compound 1a obtained at Step (1)
15 (102 mg), 4M hydrochloric acid in ethyl acetate (4 ml) was added and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was concentrated, then the residue was triturated with chloroform/hexane. The solid thus obtained was collected by filtration to
20 obtain the title compound (61 mg).

$^1\text{H-NMR}$ (CDCl_3) δ 0.93 (3H, t, $J=7.3\text{Hz}$), 1.16 (3H, d, $J=6.3\text{Hz}$), 1.18 (3H, d, $J=6.3\text{Hz}$), 1.72-1.97 (2H, m), 2.62 (1H, dd, $J=8.3, 13.6\text{Hz}$), 3.07-3.30 (2H, m), 3.30-3.44 (1H, m), 3.65-3.73 (1H, m), 3.81 (3H, s), 4.11 (1H, d, $J=16.2\text{Hz}$),
25 4.15-4.25 (1H, m), 4.84 (1H, dt, $J=7.3, 7.3\text{Hz}$), 5.12-5.31 (2H, m), 6.78 (1H, d, $J=8.6\text{Hz}$), 7.14 (1H, d, $J=2.7\text{Hz}$), 7.20 (1H, dd, $J=2.7, 8.6\text{Hz}$), 7.37 (2H, d, $J=8.3\text{Hz}$), 8.04 (2H, d, $J=8.3\text{Hz}$), 9.62 (1H, d, $J=7.3\text{Hz}$)
MS: 545(M+H) $^+$

30 0143

Example 2: 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(isobutoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 2)

Instead of the reaction agent in Example 1, that is,
35 O-isopropyl hydroxylamine hydrochloride, O-isobutyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.85-0.95 (9H, m), 1.76-2.02 (3H, m), 2.62 (1H, dd, J=8.3, 14.0Hz), 3.11-3.30 (2H, m), 3.32-3.43 (1H, m), 3.61-3.75 (3H, m), 3.82 (3H, s), 4.11 (1H, d, J=16.2Hz), 4.85 (1H, dt, J=7.3, 7.3Hz), 5.14-5.29 (2H, m), 6.79 (1H, d, J=8.8Hz), 7.15 (1H, d, J=2.7Hz), 7.21 (1H, dd, J=2.7, 8.8Hz), 7.37 (2H, d, J=8.3Hz), 8.04 (2H, d, J=8.3Hz), 9.61 (1H, d, J=7.3Hz)

MS: 559 (M+H)⁺

0144

10 Example 3: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-((pyridin-2-yloxy)imino)-1,4-diazepan-1-yl)carbonyl)amino]propyl)benzoic acid (compound 3)

15 Instead of the reaction agent in Example 1, that is, O-isopropyl hydroxylamine hydrochloride, O-(pyridin-2-yl)hydroxylamine was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.95 (3H, t, J=7.3Hz), 1.81-1.95 (2H, m), 2.71 (1H, dd, J=7.3, 13.8Hz), 3.16 (1H, dd, J=5.7, 13.8Hz), 3.34-3.51 (1H, m), 3.60 (1H, m), 3.77 (1H, m), 3.84 (3H, s), 4.25 (1H, d, J=16.8Hz), 4.80 (1H, dt, J=6.9, 6.9Hz), 5.29 (1H, d, J=16.8Hz), 6.80 (1H, d, J=8.4Hz), 6.88 (1H, br.s), 7.16-7.25 (3H, m), 7.38 (2H, d, J=8.1Hz), 7.77 (1H, d, J=8.3Hz), 8.05 (2H, d, J=8.1Hz), 8.09-8.21 (2H, m), 9.60 (1H, d, J=6.9Hz)

25 MS: 580 (M+H)⁺

0145

30 Example 4: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-((cyclopropylmethoxy)imino)-7-oxo-1,4-diazepan-1-yl)carbonyl) amino]propyl)benzoic acid (compound 4)

35 Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, O-(cyclopropylmethyl)hydroxylamine was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.18-0.26 (2H, m), 0.44-0.48 (2H, m),

0.85 (3H, t, J=7.3Hz), 1.01-1.11 (1H, m), 1.76-1.86 (2H, m), 2.70 (1H, dd, J=8.9, 14.3Hz), 2.98 (1H, dd, J=5.1, 14.3Hz), 3.22 (2H, d, J=8.5Hz), 3.56-3.74 (2H, m), 3.80 (3H, s), 3.83-3.95 (1H, m), 4.64 (1H, d, J=16.6Hz), 4.69-4.93 (2H, m), 7.02 (1H, d, J=8.8Hz), 7.28 (1H, dd, J=2.7, 8.8Hz), 7.33 (1H, d, J=2.7Hz), 7.42 (2H, d, J=8.5Hz), 7.91 (2H, d, J=8.5Hz), 9.46 (1H, d, J=7.3Hz)

MS: 557(M+H)⁺

0146

10 Example 5: 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,4-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]propyl} benzoic acid
(compound 5)

15 Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, the compound S18 was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.7Hz), 1.74-1.85 (2H, m), 2.72 (1H, dd, J=8.9, 14.0Hz), 3.00 (1H, dd, J=4.9, 14.0Hz), 3.18-3.22 (2H, m), 3.80 (3H, s), 3.85-4.01 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.76 (1H, dt, J=7.7, 7.7Hz), 4.88 (1H, d, J=16.2Hz), 6.80-6.85 (1H, m), 7.00-7.07 (3H, m), 7.23-7.37 (3H, m), 7.42 (2H, d, J=8.3Hz), 7.91 (2H, d, J=8.3Hz), 9.50 (1H, d, J=7.7Hz), 12.85 (1H, br.s)

25 MS: 615(M+H)⁺

0147

30 Example 6: 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]propyl} benzoic acid
(compound 6)

35 Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.70-1.93 (2H, m), 2.72 (1H, dd, J=8.7, 14.3Hz), 3.00 (1H, dd, J=4.9,

14.3Hz), 3.10-3.29 (2H, m), 3.81 (3H, s), 3.84-4.01 (1H, m), 4.65 (1H, d, J=16.2Hz), 4.76 (1H, dt, J=7.7, 7.7Hz), 4.88 (1H, d, J=16.2Hz), 6.94 (1H, s), 6.98-7.16 (5H, m), 7.28 (1H, dd, J=2.5, 8.7Hz), 7.35 (1H, d, J=2.5Hz), 7.42 (2H, d, J=8.3Hz), 7.91 (2H, d, J=8.3Hz), 9.51 (1H, d, J=7.7Hz)

MS: 597(M+H)⁺

0148

Example 7: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)propyl} benzoic acid (compound 7)

Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, O-(3-fluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ 0.78-0.93 (3H, m), 1.70-1.88 (2H, m), 2.72 (1H, dd, J=8.9, 14.5Hz), 3.00 (1H, dd, J=4.7, 14.5Hz), 3.14-3.28 (2H, m), 3.79 (3H, s), 3.86-4.05 (1H, m), 4.66 (1H, d, J=16.4Hz), 4.77 (1H, dt, J=7.3, 7.3Hz), 4.89 (1H, d, J=16.4Hz), 6.65-6.78 (1H, m), 6.81-6.93 (2H, m), 6.96-7.07 (2H, m), 7.22-7.32 (2H, m), 7.35 (1H, d, J=2.8Hz), 7.42 (2H, d, J=8.3Hz), 7.91 (2H, d, J=8.3Hz), 9.50 (1H, d, J=7.3Hz)

MS: 597(M+H)⁺

0149

Example 8: 4-[(1R)-1-(((6R)-3-[(benzyloxy)imino]-6-(5-chloro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)propyl}benzoic acid (compound 8)

Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, O-benzyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (CDCl₃) δ 0.94 (3H, t, J=7.5Hz), 1.78-2.00 (2H, m), 2.61 (1H, dd, J=8.5, 13.8Hz), 3.06-3.27 (2H, m), 3.27-3.43 (1H, m), 3.57-3.73 (1H, m), 3.80 (3H, s), 4.11 (1H,

d, J=16.2Hz), 4.85 (1H, dt, J=7.3, 7.3Hz), 4.90-5.04 (2H, m), 5.14-5.37 (2H, m), 6.78 (1H, d, J=8.8Hz), 7.13 (1H, d, J=2.7Hz), 7.20 (1H, dd, J=2.7, 8.8Hz), 7.28-7.35 (5H, m), 7.38 (2H, d, J=8.3Hz), 8.05 (2H, d, J=8.3Hz), 9.61 (1H, d, J=7.3Hz)

MS: 593(M+H)⁺

0150

Example 9: 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(cyclopentyloxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]propyl] benzoic acid (compound 9)

Instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, in Example 1, O-cyclopentyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (CDCl₃) 80.93 (3H, t, J=7.5Hz), 1.46-1.91 (10H, m), 2.61 (1H, dd, J=8.5, 13.8Hz), 3.09-3.29 (2H, m), 3.29-3.44 (1H, m), 3.58-3.76 (1H, m), 3.81 (3H, s), 4.11 (1H, d, J=16.6Hz), 4.45-4.62 (1H, m), 4.85 (1H, dt, J=7.3, 7.3Hz), 5.15-5.34 (2H, m), 6.78 (1H, d, J=8.8Hz), 7.14 (1H, d, J=2.5Hz), 7.20 (1H, dd, J=2.5, 8.8Hz), 7.37 (2H, d, J=8.3Hz), 8.04 (2H, d, J=8.3Hz), 9.61 (1H, d, J=7.3Hz)

MS: 571(M+H)⁺

0151

Reference Example 23: tert-butyl 4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino]propyl] benzoate (compound S23)

Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (1.35 g), of Reference Example 20, the compound S140B described in WO 06-059801A, that is, (6S)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, was used for a similar procedure as in Reference Examples 20, 21, and 22 to obtain the title compound.

0152

Example 10: 4-[(1R)-1-[(6S)-6-(5-chloro-2-

methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 10)

Step (1): To the compound S23 (55 mg) in a tetrahydrofuran (1 ml) and methanol (0.54 ml) solution, O-ethyl hydroxylamine hydrochloride (14 mg), triethylamine (21 μ l), and mercury acetate (38 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 1 hour. The reaction mixture was filtered, then the filtrate was concentrated to obtain tert-butyl 4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoate (compound 10a) as a crude product.

Step (2): To the compound 10a crude product obtained at Step (1), trifluoroacetic acid (2 ml) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated, then the residue was purified by preparative thin layer chromatography (silica gel, chloroform/ethyl acetate/methanol/acetic acid) to obtain the title compound (15 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ 0.83 (3H, t, $J=7.4\text{Hz}$), 1.07 (3H, t, $J=6.9\text{Hz}$), 1.70-1.85 (2H, m), 2.67 (1H, dd, $J=9.0$, 14.2Hz), 2.96 (1H, dd, $J=5.3$, 14.2Hz), 3.00-3.19 (2H, m), 3.79 (3H, s), 3.71-3.87 (3H, m), 4.48 (1H, d, $J=16.2\text{Hz}$), 4.70-4.81 (2H, m), 6.12 (1H, br.s), 7.00 (1H, d, $J=8.5\text{Hz}$), 7.27 (1H, dd, $J=2.4$, 8.5Hz), 7.32 (1H, d, $J=2.4\text{Hz}$), 7.40 (2H, d, $J=8.2\text{Hz}$), 7.90 (2H, d, $J=8.2\text{Hz}$), 9.51 (1H, d, $J=7.7\text{Hz}$)

MS: 531 ($\text{M}+\text{H}$) $^+$

0153

Reference Example 24: tert-butyl 4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)pentyl] benzoate (compound S24)

Step (1): Instead of the starting material of Reference Example 19, that is, the compound S4, the compound S5 was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-[(1R)-1-

isocyanatopentyl]benzoate (compound S24a).

Step (2): Instead of the starting material of Reference Example 20, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (1.35 g), the compound S140B described in WO 06-059801A, that is, (6S)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione was used, and instead of the reaction agent, that is, the compound S19, the compound S24a was used for a similar procedure as in Reference Examples 20, 21, and 22 to obtain the title compound.

0154

Example 11: 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)pentyl]benzoic acid (compound 11)

Instead of the starting material, that is, the compound S23, of Example 10, the compound S24 was used for a similar reaction as in Example 10 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.1Hz), 1.07 (3H, t, J=6.9Hz), 1.22-1.33(4H, m), 1.66-1.85 (2H, m), 2.66 (1H, dd, J=9.0, 13.9Hz), 2.96 (1H, dd, J=5.5, 13.9Hz), 3.00-3.20 (2H, m), 3.79 (3H, s), 3.71-3.87 (3H, m), 4.48 (1H, d, J=16.2Hz), 4.71-4.85 (2H, m), 6.12 (1H, br.s), 7.00 (1H, d, J=8.9Hz), 7.26 (1H, dd, J=2.4, 8.9Hz), 7.31 (1H, d, J=2.4Hz), 7.42 (2H, d, J=8.2Hz), 7.90 (2H, d, J=8.2Hz), 9.51 (1H, d, J=7.7Hz)

MS: 599(M+H)⁺

0155

Reference Example 25: tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S25)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S8 was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-[(1R)-1-isocyanatobutyl]-2-nitrobenzoate (compound S25a).

Step (2): To the compound S25a obtained at Step (1) (2.69 g) and the compound S140B described in WO 06-059801A, that is, (6S)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (3.74 g), in an acetonitrile (55 ml) solution, a 1M solution of potassium tert-butoxide in tetrahydrofuran (0.7 ml) was added under ice cooling, and the mixture was stirred at that temperature for 30 minutes. Further, a 1M solution of potassium tert-butoxide in tetrahydrofuran (0.19 ml) was added, and the mixture was stirred at that temperature for 30 minutes. To the reaction solution, aqueous saturated potassium hydrogensulfate solution was added, and the mixture was extracted with ethyl acetate. The extract was combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=1/1 to 0/1) to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S25b) (5.0 g).

Step (3): To the compound S25b obtained at Step (2) (0.76 g) in a methylene chloride (8 ml) solution, water (0.4 ml) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.66 g) were added, and the mixture was stirred at room temperature for 15 hours. To the reaction mixture, sodium sulfate and chloroform were added, and the mixture was stirred at room temperature for 20 minutes and filtered. The filtrate was concentrated, then the residue was purified by flash column chromatography (NH₂ silica gel, hexane/ethyl acetate=1/1 to 3/7) to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S25c) (0.41 g).

Step (4): To the compound S25c obtained at Step (3) (0.36 g) in a tetrahydrofuran (7 ml) solution, Belleau's reagent (0.19 g) was added under ice cooling, and the

mixture was stirred at that temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and successively washed with saturated aqueous sodium hydrogencarbonate solution, water, and brine. The organic layer was dried over anhydrous sodium sulfate, then concentrated to obtain the title compound (396 mg).

0156

Example 12: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 12)

Step (1): To the compound S25 (62 mg) in a tetrahydrofuran (1 ml) and methanol (0.5 ml) solution, O-ethyl hydroxylamine hydrochloride (15 mg), triethylamine (21 µl), and mercury acetate (38 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 1 hour. The reaction mixture was filtered, then the filtrate was concentrated to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 12a) as a crude product (36 mg).

Step (2): To the compound 12a crude product obtained at Step (1) (35 mg), trifluoroacetic acid (1 ml) was added, and the mixture was stirred at room temperature for 1.5 hours. To the reaction mixture, zinc powder (100 mg) was added, and the mixture was stirred at room temperature for 3 hours. The insolubles were filtered out, the filtrate was concentrated, then the residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol/acetic acid=15/15/1/0.1) to obtain the title compound (28 mg).

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.08 (3H, t, J=7.1Hz), 1.14-1.34 (2H, m), 1.57-1.78 (2H, m), 2.62-2.71 (1H, m), 2.95 (1H, dd, J=4.9, 14.2Hz), 2.99-3.08 (1H, m), 3.10-3.18 (1H, m), 3.73-3.87 (3H, m), 3.79 (3H, s), 4.49 (1H, d, J=16.2Hz), 4.62 (1H, dt, J=7.3, 7.3Hz), 4.80 (1H, d, J=16.2Hz), 6.19 (1H, br.s), 6.44 (1H, dd, J=1.8,

8.3Hz), 6.64 (1H, d, J=1.8Hz), 7.00 (1H, d, J=8.5Hz),
7.27 (1H, dd, J=2.8, 8.5Hz), 7.31 (1H, d, J=2.8Hz), 7.65
(1H, d, J=8.3Hz), 9.44 (1H, d, J=7.3Hz)

MS: 560 (M+H)⁺

5 0157

Reference Example 26: tert-butyl 4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl]amino)pentyl]-2-nitrobenzoate (compound S26)

10 Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S9 was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-[(1R)-1-isocyanatopentyl]-2-nitrobenzoate (compound S26a).

15 Step (2): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (1.35 g), of Reference Example 20, the compound S140B described in WO 06-059801A, that is, (6S)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione was
20 used, and instead of the reaction agent, that is, the compound S19, the compound S26a was used for a similar procedure as in Reference Examples 20, 21, and 22 to obtain the title compound.

0158

25 Example 13: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)pentyl]benzoic acid (compound 13)

30 Instead of the starting material, that is, the compound S25, of Example 12, the compound S26 was used for a similar procedure as in Example 12 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=6.1Hz), 1.09 (3H, t, J=7.1Hz), 1.19-1.32 (4H, m), 1.61-1.78 (2H, m), 2.62-2.70 (1H, m), 2.96 (1H, dd, J=5.3, 14.2Hz), 3.00-3.10 (1H, m),
35 3.10-3.18 (1H, m), 3.74-3.89 (3H, m), 3.79 (3H, s), 4.51 (1H, d, J=16.2Hz), 4.60 (1H, dt, J=7.7, 7.7Hz), 4.80 (1H, d, J=16.2Hz), 6.28 (1H, br.s), 6.44 (1H, dd, J=1.6,

8.5Hz), 6.64 (1H, d, J=1.6Hz), 7.00 (1H, d, J=8.5Hz),
7.26 (1H, dd, J=2.8, 8.5Hz), 7.31 (1H, d, J=2.8Hz), 7.65
(1H, d, J=8.5Hz), 9.44 (1H, d, J=7.7Hz)

MS: 574(M+H)⁺

5 0159

Example 14: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-
yl]carbonyl}amino)butyl]benzoic acid (compound 14)

10 Instead of the reaction agent, that is, O-ethyl
hydroxylamine hydrochloride, of Example 12, hydroxylamine
hydrochloride was used for a similar procedure as in
Example 12 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J=7.7Hz), 1.14-1.35 (2H,
m), 1.57-1.76 (2H, m), 2.62-2.70 (1H, m), 2.91-3.07 (2H,
15 m), 3.09-3.18 (1H, m), 3.76-3.88 (3H, m), 3.79 (3H, s),
4.45 (1H, d, J=16.2Hz), 4.62 (1H, dt, J=7.7, 7.7Hz), 4.83
(1H, d, J=16.2Hz), 5.98 (1H, br.s), 6.41 (1H, d,
J=8.1Hz), 6.60 (1H, s), 7.00 (1H, d, J=8.9Hz), 7.26 (1H,
dd, J=2.8, 8.9Hz), 7.31 (1H, d, J=2.8Hz), 7.64 (1H, d,
20 J=8.1Hz), 9.27 (1H, s), 9.45 (1H, d, J=7.7Hz)

MS: 532(M+H)⁺

0160

Example 15: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-3-(isopropoxyimino)-7-oxo-1,4-diazepan-1-
yl]carbonyl}amino)butyl]benzoic acid (compound 15)

25 Instead of the reaction agent, that is, O-ethyl
hydroxylamine hydrochloride, of Example 12, O-isopropyl
hydroxylamine hydrochloride was used for a similar
procedure as in Example 12 to obtain the title compound.

30 ¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.0Hz), 1.07(6H, d,
J=6.1Hz), 1.17-1.35 (2H, m), 1.59-1.76 (2H, m), 2.64-2.69
(1H, m), 2.90-3.08 (1H, m), 3.10-3.18 (2H, m), 3.75-3.87
(2H, m), 3.79 (3H, s), 4.48 (1H, d, J=16.2Hz), 4.63 (1H,
dt, J=7.7, 7.7Hz), 4.80 (1H, d, J=16.2Hz), 6.02 (1H,
35 br.s), 6.44 (1H, d, J=8.5Hz), 6.64 (1H, s), 7.00 (1H, d,
J=8.9Hz), 7.27 (1H, dd, J=2.4, 8.9Hz), 7.31 (1H, d,
J=2.4Hz), 7.65 (1H, d, J=8.5Hz), 9.45 (1H, d, J=7.7Hz)

MS: 574 (M+H)⁺

0161

Example 16: 2-amino-4-[(1R)-1-([(6S)-3-(tert-butoxyimino)-6-(5-chloro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]benzoic acid (compound 16)

Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, of Example 12, O-tert-butyl hydroxylamine hydrochloride was used for a similar

procedure as in Example 12 to obtain the title compound.

¹H-NMR (CDCl₃) δ 0.87 (3H, t, J=7.3Hz), 1.12 (9H, s), 1.17-1.36 (2H, m), 1.59-1.77 (2H, m), 2.62-2.71 (1H, m), 2.95 (1H, dd, J=4.7, 14.0Hz), 3.00-3.09 (1H, m), 3.10-3.18 (1H, m), 3.73-3.85 (1H, m), 3.79 (3H, s), 4.49 (1H, d, J=16.2Hz), 4.64 (1H, dt, J=7.3, 7.3Hz), 4.84 (1H, d, J=16.2Hz), 5.97 (1H, br.s), 6.44 (1H, dd, J=1.6, 8.5Hz), 6.64 (1H, d, J=1.6Hz), 7.00 (1H, d, J=8.5Hz), 7.27 (1H, dd, J=2.8, 8.5Hz), 7.31 (1H, d, J=2.8Hz), 7.64 (1H, d, J=8.5Hz), 9.46 (1H, d, J=7.3Hz)

MS: 588 (M+H)⁺

0162

Example 17: 2-amino-4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-[(2-methoxyethoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino] butyl]benzoic acid (compound 17)

Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, of Example 12, O-(2-methoxyethyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 12 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ 0.87 (3H, t, J=7.3Hz), 1.14-1.35 (2H, m), 1.57-1.77 (2H, m), 2.62-2.69 (1H, m), 2.95 (1H, dd, J=5.5, 14.4Hz), 2.99-3.08 (1H, m), 3.11-3.19 (2H, m), 3.18 (3H, s), 3.40-3.46 (2H, m), 3.76-3.88 (3H, m), 3.79 (3H, s), 4.49 (1H, d, J=16.2Hz), 4.62 (1H, dt, J=7.7, 7.7Hz), 4.79 (1H, d, J=16.2Hz), 6.17 (1H, br.s), 6.43 (1H, dd, J=1.4, 8.5Hz), 6.63 (1H, d, J=1.4Hz), 7.00 (1H,

d, J=8.9Hz), 7.27 (1H, dd, J=2.4, 8.9Hz), 7.31 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.5Hz), 9.44 (1H, d, J=7.7Hz)
MS: 590 (M+H)⁺

0163

5 Example 18: 2-amino-4-[(1R)-1-[([(6S)-6-(5-chloro-2-methoxybenzyl)-3-[(2-hydroxyethoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]butyl] benzoic acid (compound 18)

10 Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, of Example 12, O-(2-hydroxyethyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 12 to obtain the title compound.

15 ¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.12-1.35 (2H, m), 1.57-1.77 (2H, m), 2.62-2.71 (1H, m), 2.96 (1H, dd, J=4.9, 14.2Hz), 3.01-3.18 (2H, m), 3.44-3.52 (2H, m), 3.71-3.88 (3H, m), 3.79 (3H, s), 4.41-4.53 (2H, m), 4.62 (1H, dt, J=7.7, 7.7Hz), 4.79 (1H, d, J=16.2Hz), 6.26 (1H, br.s), 6.43 (1H, dd, J=1.8, 8.1Hz), 6.63 (1H, d, J=1.8Hz), 7.00 (1H, d, J=8.9Hz), 7.27 (1H, dd, J=2.8, 8.9Hz), 7.32 (1H, d, J=2.8Hz), 7.65 (1H, d, J=8.1Hz), 9.45 (1H, d, J=7.7Hz)

MS: 576 (M+H)⁺

0164

25 Example 19: 2-amino-4-[(1R)-1-[([(6S)-6-(5-chloro-2-methoxybenzyl)-3-(methoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]butyl]benzoic acid (compound 19)

30 Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, of Example 12, O-methyl hydroxylamine hydrochloride was used for a similar procedure as in Example 12 to obtain the title compound.

35 ¹H-NMR (DMSO-d₆) δ0.87 (2H, t, J=7.7Hz), 1.13-1.35 (2H, m), 1.57-1.76 (2H, m), 2.61-2.69 (1H, m), 2.91-3.07 (2H, m), 3.09-3.16 (1H, m), 3.54 (3H, s), 3.79 (3H, s), 3.78-3.88 (1H, m), 4.48 (1H, d, J=16.6Hz), 4.62 (1H, dt, J=8.1, 8.1Hz), 4.78 (1H, d, J=16.6Hz), 6.22 (1H, br.s), 6.43 (1H, dd, J=1.2, 8.5Hz), 6.63 (1H, d, J=1.2Hz), 7.00

(1H, d, J=8.9Hz), 7.27 (1H, dd, J=2.8, 8.9Hz), 7.31 (1H, d, J=2.8Hz), 7.65 (1H, d, J=8.5Hz), 9.45 (1H, d, J=8.1Hz)
MS: 546(M+H)⁺

0165

- 5 Example 20: 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(2,2,2-trifluoroethoxy)imino]-1,4-diazepan-1-yl]carbonyl)amino] butyl]benzoic acid (compound 20)

10 Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, of Example 12, O-(2,2,2-trifluoroethyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 12 to obtain the title compound.

15 ¹H-NMR (DMSO-d₆) 80.87 (3H, t, J=7.3Hz), 1.11-1.36 (2H, m), 1.55-1.79 (2H, m), 2.66 (1H, dd, J=8.7, 14.2Hz), 2.96 (1H, dd, J=5.1, 14.2Hz), 3.01-3.11 (1H, m), 3.11-3.20 (1H, m), 3.79 (3H, s), 3.81-3.91 (1H, m), 4.34 (2H, q, J=9.1Hz), 4.55 (1H, d, J=16.4Hz), 4.62 (1H, dt, J=7.7, 7.7Hz), 4.78 (1H, d, J=16.4Hz), 6.39-6.49 (2H, m), 6.64 (1H, d, J=1.2Hz), 7.00 (1H, d, J=8.8Hz), 7.27 (1H, dd, J=2.8, 8.8Hz), 7.32 (1H, d, J=2.8Hz), 7.65 (1H, d, J=8.1Hz), 9.43 (1H, d, J=7.7Hz)
20 MS: 614(M+H)⁺

0166

- 25 Example 21: tert-butyl 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(dimethylhydrazono)-7-oxo-1,4-diazepan-1-yl]carbonyl) amino]butyl]benzoate (compound 21)

30 Step (1): To the compound S25 (80 mg) in a tetrahydrofuran (1 ml) and 2-propanol (2 ml) solution, N,N-dimethyl hydrazine (15 µl) and mercury acetate (60 mg) were successively added under ice cooling, and the mixture was stirred at room temperature for 2 hours. Further, mercury acetate (12 mg) was added, and the
35 mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered, saturated aqueous ammonium chloride solution was added to the filtrate, and the

mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, then concentrated to obtain tert-butyl 4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-

(dimethylhydrazon)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 21a) as a crude product (36 mg).

Step (2): The compound 21a crude product obtained at Step (1) (35 mg) was dissolved in acetic acid (2 ml), zinc powder (160 mg) was added to the solution, then the mixture was stirred at 50°C for 2 hours. The insolubles were filtered out, the filtrate was concentrated. Then ethyl acetate and saturated aqueous ammonium chloride solution were added to the residue, and the solution was separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (NH₂ silica gel, hexane/ethyl acetate=1/1 to 1/4) and preparative thin layer chromatography (NH₂ silica gel, hexane/ethyl acetate=1/2) to obtain the title compound (28 mg).

0167

Example 22: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(dimethylhydrazono)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 22)

To the compound 21 (16 mg), 1 M hydrochloric acid in acetic acid solution was added, and the mixture was stirred at room temperature for 4 hours. To the reaction solution, toluene (5 ml) was added and the precipitated solid was collected by filtration to obtain the title compound (12.7 mg).

¹H-NMR (DMSO-d₆) δ0.88 (3H, t, J=7.3Hz), 1.14-1.40 (2H, m), 1.58-1.82 (2H, m), 2.48(6H, s), 2.69 (1H, dd, J=9.1, 14.4Hz), 3.00 (1H, dd, J=4.5, 14.4Hz), 3.24-3.43 (2H, m), 3.80 (3H, s), 3.89-4.03 (1H, m), 4.66 (1H, dt, J=7.7, 7.7Hz), 4.94 (1H, d, J=17.5Hz), 5.10 (1H, d, J=17.5Hz), 6.49 (1H, d, J=8.3Hz), 6.67 (1H, s), 7.04 (1H, d,

J=8.7Hz), 7.30 (1H, dd, J=2.6, 8.7Hz), 7.35 (1H, d, J=2.6Hz), 7.66 (1H, d, J=8.3Hz), 9.24-9.34 (2H, m), 11.02 (1H, br.s)

MS: 559(M+H)⁺

5 0168

Reference Example 27: tert-butyl 4-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoate (compound S27)

10 Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S20 was used for a similar reaction as in Reference Example 22 to obtain the title compound (compound S27).

¹H-NMR (CDCl₃) δ0.89 (3H, t, J=7.3Hz), 1.58(9H, s), 1.75-1.94 (2H, m), 2.38 (1H, dd, J=9.5, 13.7Hz), 3.08 (1H, dd, J=4.1, 13.7Hz), 3.11-3.29 (2H, m), 3.29-3.42 (1H, m), 3.66(6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.79-4.91 (2H, m), 4.94 (1H, d, J=14.2Hz), 5.09 (1H, d, J=14.2Hz), 5.57 (1H, d, J=17.0Hz), 6.09 (1H, s), 6.74 (1H, d, J=8.7Hz), 6.79 (1H, d, J=2.5Hz), 7.18 (1H, dd, J=2.5, 8.7Hz), 7.33 (2H, d, J=8.5Hz), 7.95 (2H, d, J=8.5Hz), 9.49 (1H, d, J=7.7Hz)

MS: 740(M+H)⁺

0169

25 Example 23: 4-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoic acid (compound 23)

Step (1): To the compound S27 (102 mg) in a tetrahydrofuran (1 ml) and methanol (2 ml) solution, O-ethyl hydroxylamine hydrochloride (20 mg), triethylamine (29 μl), and mercury acetate (53 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 10 minutes. The reaction mixture was filtered, then the filtrate was concentrated to obtain tert-butyl 4-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-

yl]carbonyl)amino)propyl]benzoate (compound 23a) as a crude product (88 mg).

Step (2): To the compound 23a crude product obtained at Step (1) (86 mg), anisole (0.15 ml) and

5 trifluoroacetic acid (2 ml) were added, and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated, then the residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol/acetic

10 acid=40/40/1/0.1) to obtain the title compound (31 mg).

¹H-NMR (CDCl₃) δ 0.93 (3H, t, J=7.3Hz), 1.20 (3H, t, J=7.1Hz), 1.79-1.93 (2H, m), 2.62 (1H, m), 3.07-3.31 (2H, m), 3.38 (1H, m), 3.70 (1H, m), 3.82 (3H, s), 3.89-4.07 (2H, m), 4.12 (1H, d, J=16.4Hz), 4.84 (1H, dt, J=7.7, 7.7Hz), 5.21 (1H, d, J=16.4Hz), 5.30 (1H, br.s), 6.79 (1H, d, J=8.7Hz), 7.14 (1H, d, J=2.4Hz), 7.20 (1H, dd, J=2.4, 8.7Hz), 7.37 (2H, d, J=8.3Hz), 8.04 (2H, d, J=8.3Hz), 9.60 (1H, d, J=7.7Hz)

MS: 531(M+H)⁺

20 0170

Example 24: 4-[(1R)-1-[(1R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]propyl] benzoic acid (compound 24)

25 Instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, in Example 23, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 23 to obtain the title compound.

30 ¹H-NMR (DMSO-d₆) δ 0.84 (3H, t, J=7.7Hz), 1.70-1.89 (2H, m), 2.72 (1H, dd, J=9.1, 14.3Hz), 3.00 (1H, dd, J=4.9, 14.3Hz), 3.14-3.26 (2H, m), 3.80 (3H, s), 3.84-3.99 (1H, m), 4.68 (1H, d, J=16.6Hz), 4.76 (1H, dt, J=7.3, 7.3Hz), 4.88 (1H, d, J=16.6Hz), 6.63-6.81 (3H, m), 7.02 (1H, d, J=8.8Hz), 7.11 (1H, s), 7.28 (1H, dd, J=2.7, 8.8Hz), 7.35 (1H, d, J=2.7Hz), 7.43 (2H, d, J=8.3Hz), 7.91 (1H, d, J=8.3Hz), 9.50 (1H, d, J=7.3Hz), 12.87 (1H, br.s)

MS: 615(M+H)⁺

0171

Reference Example 28: tert-butyl 5-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)propyl]-2-furane carboxylate (compound S28)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S85 described in WO 06-059801A, that is, tert-butyl 5-[(1R)-1-aminopropyl]-2-furane carboxylate D-tartrate, was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 5-[(1R)-1-isocyanatopropyl]-2-furane carboxylate (compound S28a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S28a was used for a similar procedure as in Reference Examples 20 and 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.92 (3H, t, J=7.3Hz), 1.49-1.60 (9H, s), 1.83-2.03 (2H, m), 2.36 (1H, dd, J=9.5, 14.0Hz), 3.08 (1H, dd, J=3.9, 14.0Hz), 3.11-3.37 (3H, m), 3.66 (6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.89-5.12 (4H, m), 5.53 (1H, d, J=17.0Hz), 6.08 (2H, s), 6.31 (1H, d, J=3.2Hz), 6.74 (1H, d, J=8.8Hz), 6.78 (1H, d, J=2.7Hz), 6.97 (1H, d, J=3.2Hz), 7.18 (1H, dd, J=2.7, 8.8Hz), 9.40 (1H, d, J=8.1Hz)

MS: 730(M+H)⁺

0172

Example 25: 5-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]-2-furane carboxylic acid (compound 25)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S28 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar procedure as in

Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J=7.3Hz), 1.74-1.93 (2H, m), 2.70 (1H, dd, J=9.1, 14.5Hz), 2.98 (1H, dd, J=4.9, 14.5Hz), 3.09-3.25 (2H, m), 3.80 (3H, s), 3.84-4.00 (1H, m), 4.69 (1H, d, J=16.2Hz), 4.81-5.06 (2H, m), 6.48 (1H, d, J=3.4Hz), 6.81-6.96 (2H, m), 7.01 (1H, d, J=8.9Hz), 7.03-7.09 (2H, m), 7.14 (1H, d, J=3.4Hz), 7.19-7.31 (3H, m), 7.34 (1H, d, J=2.8Hz), 9.41 (1H, d, J=8.1Hz), 13.16 (1H, br.s)

MS: 569(M+H)⁺
0173

Reference Example 29: tert-butyl 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino]ethyl]benzoate (compound S29)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S2 was used for a similar procedure as in Reference Example 19 to obtain tert-butyl 4-[(1R)-1-isocyanatoethyl]benzoate (compound S29a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S29a was used for a similar procedure as in Reference Examples 20 and 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.52 (3H, d, J=6.9Hz), 1.58 (9H, s), 2.35 (1H, dd, J=9.7, 13.8Hz), 3.08 (1H, dd, J=4.1, 13.8Hz), 3.12-3.29 (2H, m), 3.29-3.40 (1H, m), 3.67 (6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.89 (1H, d, J=17.0Hz), 4.95 (1H, d, J=14.2Hz), 5.04-5.16 (2H, m), 5.58 (1H, d, J=17.0Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.9Hz), 6.78 (1H, d, J=2.8Hz), 7.18 (1H, dd, J=2.8, 8.9Hz), 7.38 (2H, d, J=8.5Hz), 7.95 (2H, d, J=8.5Hz), 9.46 (1H, d, J=7.3Hz)
MS: 726(M+H)⁺

0174

Example 26: 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]ethyl] benzoic acid

(compound 26)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S29 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.45 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=8.7, 14.2Hz), 2.99 (1H, dd, J=4.9, 14.2Hz), 3.11-3.26 (2H, m), 3.80 (3H, s), 3.85-3.97 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.84-5.01 (2H, m), 6.96 (1H, br.s), 6.99-7.13 (5H, m), 7.28 (1H, dd, J=2.8, 8.7Hz), 7.35 (1H, d, J=2.8Hz), 7.45 (1H, d, J=8.3Hz), 7.91 (1H, d, J=8.3Hz), 9.46 (1H, d, J=7.3Hz), 12.94 (1H, br.s)

MS: 583 (M+H)⁺

0175

Example 27: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-((3,5-difluorophenoxy)imino)-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)ethyl) benzoic acid
(compound 27)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S29 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.46 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=8.7, 14.2Hz), 2.99 (1H, dd, J=4.9, 14.2Hz), 3.15-3.25 (2H, m), 3.80 (3H, s), 3.87-4.00 (1H, m), 4.68 (1H, d, J=16.2Hz), 4.84-5.02 (2H, m), 6.62-6.79 (3H, m), 7.02 (1H, d, J=8.7Hz), 7.11 (1H, br.s), 7.28 (1H, dd, J=2.4, 8.7Hz), 7.35 (1H, d, J=2.4Hz), 7.45 (1H, d, J=8.1Hz), 7.91 (1H, d, J=8.1Hz), 9.44 (1H, d, J=7.3Hz), 12.93 (1H, br.s)

MS: 601 (M+H)⁺

0176

Reference Example 30: tert-butyl 4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-

5 yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S30)

To the compound S25b obtained at Reference Example 25 Steps (1) and (2) (4.5 g) in a tetrahydrofuran (90 ml) solution, Belleau's reagent (1.82 g) was added under ice cooling, and the mixture was stirred at that temperature for 1 hour. Further, Belleau's reagent (0.61 g) was added, and the mixture was stirred at that temperature for 1 hour. To the reaction mixture, aqueous saturated sodium hydrogencarbonate solution was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, then dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=3/7 to 2/3) to obtain the title compound (3.5 g).

20 ¹H-NMR (CDCl₃) δ0.94 (3H, t, J=7.3Hz), 1.22-1.45 (2H, m), 1.68-1.88 (2H, m), 2.48 (1H, dd, J=9.3, 13.8Hz), 3.04-3.16 (2H, m), 3.17-3.35 (2H, m), 3.59(6H, s), 3.74 (3H, s), 3.86 (3H, s), 4.94 (1H, dt, J=6.9, 6.9Hz), 4.98 (1H, d, J=14.6Hz), 5.00 (1H, d, J=14.6Hz), 5.08 (1H, d, J=16.6Hz), 5.32 (1H, d, J=16.6Hz), 6.05 (2H, s), 6.74 (1H, d, J=8.9Hz), 6.83 (1H, d, J=2.4Hz), 7.19 (1H, dd, J=2.4, 8.9Hz), 7.57 (1H, dd, J=1.6, 8.1Hz), 7.68 (1H, d, J=8.1Hz), 7.72 (1H, d, J=1.6Hz), 9.57 (1H, d, J=6.9Hz)
MS: 799(M+H)⁺

30 0177

Example 28: 2-amino-4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]benzoic acid sesquitosylate (compound 28)

35 Step (1): To the compound S30 (2.9 g) in a tetrahydrofuran (60 ml) and methanol (60 ml) solution, O-ethyl hydroxylamine hydrochloride (0.53 g), triethylamine

(0.76 ml), and mercury acetate (1.39 g) were successively added under ice cooling, and the mixture was stirred at that temperature for 30 minutes and at room temperature for 2 hours. To the reaction solution, O-ethyl
5 hydroxylamine hydrochloride (0.18 g), triethylamine (0.25 ml), and mercury acetate (0.46 g) were successively added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered, then the filtrate was concentrated to obtain tert-butyl 4-
10 [(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 28a) as a crude product (4.28 g).

Step (2): To the compound 28a crude product obtained
15 at Step (1) (4.28 g), trifluoroacetic acid (50 ml) was added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was cooled to 0°C, zinc powder (8.5 g) was added, and the mixture was stirred at room temperature for 2 hours. The insolubles were
20 filtered out, and the filtrate was concentrated. The residue was diluted with ethyl acetate, successively washed with saturated aqueous ammonium chloride solution and brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography
25 (silica gel, chloroform/ethyl acetate/methanol/acetic acid=15/15/1/0.1) to obtain 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 12).

Step (3): The compound 12 obtained at Step (2) (503 mg) was dissolved in acetonitrile (0.5 ml), p-toluenesulfonic acid monohydrate in an acetonitrile solution (0.69M, 2 ml) was added at 60°C, then the mixture was allowed to gradually cool to room temperature. After
35 3 hours, the mixture was cooled to 0°C and further stirred for 1.5 hours, then the precipitates were collected by

filtration to obtain the title compound (535 mg) as a colorless crystals.

¹H-NMR (DMSO-d₆) δ0.88 (3H, t, J=7.3Hz), 1.14 (3H, t, J=7.1Hz), 1.17-1.39 (2H, m), 1.56-1.82 (2H, m),
5 2.29(4.5H, s), 2.69 (1H, dd, J=9.3, 14.2Hz), 2.99 (1H, dd, J=4.5, 14.2Hz), 3.14-3.40 (2H, m), 3.80 (3H, s),
3.82-4.05 (3H, m), 4.58-4.71 (1H, m), 4.71-4.89 (1H, m),
4.89-5.03 (1H, m), 6.47-6.57 (1H, m), 6.69 (1H, br.s),
7.03 (1H, d, J=8.8Hz), 7.11 (3H, d, J=7.7Hz), 7.29 (1H,
10 dd, J=2.5, 8.8Hz), 7.35 (1H, d, J=2.5Hz), 7.47 (3H, d, J=7.7Hz), 7.67 (1H, d, J=8.3Hz), 9.33 (1H, d, J=7.7Hz)
MS: 560(M+H)⁺

0178

Reference Example 31: tert-butyl 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino]ethyl]-2-nitrobenzoate (compound S31)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound
20 S10 was used for a similar procedure as in Reference Example 19 to obtain tert-butyl 4-[(1R)-1-isocyanatoethyl]-2-nitrobenzoate (compound S31a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound
25 S31a was used for a similar procedure as in Reference Examples 20 and 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.51-1.56(12H, m), 2.34 (1H, dd, J=9.7, 13.8Hz), 3.10 (1H, dd, J=4.5, 13.8Hz), 3.13-3.29 (2H, m),
3.32-3.47 (1H, m), 3.68(6H, s), 3.76 (3H, s), 3.86 (3H, s),
30 4.87 (1H, d, J=16.6Hz), 4.93-5.19 (3H, m), 5.56 (1H, d, J=16.6Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.8Hz), 6.78 (1H, d, J=2.7Hz), 7.19 (1H, dd, J=2.7, 8.8Hz), 7.61 (1H, dd, J=1.6, 8.1Hz), 7.69 (1H, d, J=8.1Hz), 7.77 (1H, d, J=1.6Hz), 9.50 (1H, d, J=6.9Hz)
35 MS: 771(M+H)⁺

0179

Example 29: 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-

methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl}carbonyl)amino]ethyl} benzoic acid (compound 29)

Step (1): To the compound S31 (218 mg) in a tetrahydrofuran (2 ml) and methanol (4 ml) solution, O-(4-fluorophenyl)hydroxylamine hydrochloride (70 mg), triethylamine (59 μ l), and mercury acetate (110 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 1 hour. The reaction mixture was filtered, then the filtrate was concentrated to obtain tert-butyl 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl}carbonyl)amino]ethyl]-2-nitrobenzoate (compound 29a) as a crude product.

Step (2): To the compound 29a crude product obtained at Step (1), anisole (0.31 ml) and trifluoroacetic acid (2 ml) were added, and the mixture was stirred at room temperature for 15 minutes. The reaction mixture was cooled to 0°C, then zinc powder (440 mg) was added, and the mixture was stirred at that temperature for 20 minutes. Then the insolubles were filtered out, and the filtrate was concentrated. The residue was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution and brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate=4/1 to 2/1) to obtain the title compound (98 mg). ¹H-NMR (DMSO-d₆) δ 1.39 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=9.1, 14.3Hz), 2.98 (1H, dd, J=4.5, 14.3Hz), 3.11-3.26 (2H, m), 3.80 (3H, s), 3.84-4.01 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.75 (1H, m), 4.93 (1H, d, J=16.2Hz), 6.47 (1H, dd, J=1.6, 8.3Hz), 6.68 (1H, d, J=1.6Hz), 6.95 (1H, s), 6.98-7.14 (5H, m), 7.28 (1H, dd, J=2.6, 8.9Hz), 7.35 (1H, d, J=2.6Hz), 7.66 (1H, d, J=8.3Hz), 9.40 (1H, d, J=7.3Hz)

MS: 598 (M+H)⁺

0180

Example 30: 2-amino-4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl) amino)ethyl)benzoic acid
(compound 30)

Instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, in Example 29, O-(3,5-difluorophenyl) hydroxylamine hydrochloride was used for a similar procedure as in Example 29 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.39 (3H, d, J=6.9Hz), 2.69 (1H, dd, J=9.3, 14.5Hz), 2.98 (1H, dd, J=4.7, 14.5Hz), 3.19 (2H, m), 3.80 (3H, s), 3.84-4.03 (1H, m), 4.59-4.83 (2H, m), 4.93 (1H, d, J=16.2Hz), 6.48 (1H, dd, J=1.8, 8.2Hz), 6.61-6.84 (4H, m), 7.02 (1H, d, J=8.8Hz), 7.11 (1H, s), 7.28 (1H, dd, J=2.5, 8.8Hz), 7.35 (1H, d, J=2.5Hz), 7.66 (1H, d, J=8.2Hz), 9.38 (1H, d, J=7.3Hz)

MS: 616 (M+H)⁺

0181

Example 31: 2-amino-4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(pyridin-2-yloxy)imino]-1,4-diazepan-1-yl)carbonyl) amino)ethyl) benzoic acid
(compound 31)

Instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, in Example 29, O-(pyridin-2-yl)hydroxylamine hydrochloride was used for a similar procedure as in Example 29 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.39 (3H, d, J=6.9Hz), 2.68 (1H, dd, J=8.5, 14.3Hz), 2.97 (1H, dd, J=5.1, 14.3Hz), 3.06-3.26 (2H, m), 3.79 (3H, s), 3.86-4.02 (1H, m), 4.62-4.85 (2H, m), 4.95 (1H, d, J=16.2Hz), 6.46 (1H, dd, J=1.4, 8.3Hz), 6.66 (1H, s), 6.90-7.08 (3H, m), 7.17 (1H, d, J=8.3Hz), 7.26 (1H, dd, J=2.6, 8.9Hz), 7.33 (1H, d, J=2.6Hz), 7.65 (1H, d, J=8.3Hz), 7.69-7.80 (1H, m), 8.13 (1H, dd, J=2.0, 4.9Hz), 9.38 (1H, d, J=7.3Hz)

MS: 581(M+H)⁺

0182

Example 32: 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)ethyl]benzoic acid (compound 32)

Instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, in Example 29, O-phenyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.39 (3H, d, J=7.1Hz), 2.70 (1H, dd, J=8.9, 14.1Hz), 2.98 (1H, dd, J=4.7, 14.1Hz), 3.09-3.25 (2H, m), 3.80 (3H, s), 3.85-4.01 (1H, m), 4.67 (1H, d, J=16.4Hz), 4.74 (1H, m), 4.95 (1H, d, J=16.4Hz), 6.47 (1H, dd, J=1.7, 8.4Hz), 6.68 (1H, d, J=1.7Hz), 6.84-6.97 (2H, m), 7.00-7.07 (3H, m), 7.20-7.32 (3H, m), 7.35 (1H, d, J=2.4Hz), 7.66 (1H, d, J=8.4Hz), 9.40 (1H, d, J=7.3Hz)
MS: 580(M+H)⁺

0183

Reference Example 32: tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-4-methyl-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S32)

Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione, of Reference Example 20, the compound S17 was used, and instead of the reaction agent, that is, the compound S19, the compound S25a was used for a similar procedure as in Reference Examples 20 and 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.94 (3H, t, J=7.3Hz), 1.23-1.46 (2H, m), 1.56(9H, s), 1.68-1.91 (2H, m), 2.63 (1H, dd, J=7.7, 14.0Hz), 3.21 (1H, dd, J=5.5, 14.0Hz), 3.35 (3H, s), 3.42-3.49 (1H, m), 3.55-3.65 (1H, m), 3.78-3.90(4H, m), 4.59 (1H, d, J=17.7Hz), 4.94 (1H, dt, J=7.3, 7.3Hz), 5.92 (1H, d, J=17.7Hz), 6.82 (1H, d, J=8.7Hz), 7.17 (1H, d, J=2.6Hz), 7.24 (1H, dd, J=2.6, 8.7Hz), 7.58 (1H, dd,

J=1.6, 8.1Hz), 7.68 (1H, d, J=8.1Hz), 7.73 (1H, d, J=1.6Hz), 9.45 (1H, d, J=7.3Hz)
MS: 633(M+H)⁺

0184

5 Example 33: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-4-methyl-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl] benzoic acid (compound 33)

10 Instead of the starting material, that is, the compound S25, of Example 12, the compound S32 was used for a similar procedure as in Example 12 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J=7.3Hz), 1.14 (3H, t, J=7.1Hz), 1.17-1.33 (2H, m), 1.56-1.78 (2H, m), 2.47 (3H, s), 2.62-2.76 (2H, m), 2.88-3.05 (2H, m), 3.61-3.74 (1H, m), 3.79 (3H, s), 3.82-3.95 (2H, m), 4.20 (1H, d, J=19.1Hz), 4.60 (1H, dt, J=7.7, 7.7Hz), 5.90 (1H, d, J=19.1Hz), 6.44 (1H, d, J=8.1Hz), 6.64 (1H, s), 6.98 (1H, d, J=8.5Hz), 7.25 (1H, dd, J=2.4, 8.5Hz), 7.30 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.1Hz), 9.52 (1H, d, J=7.7Hz)
20 MS: 574(M+H)⁺

0185

25 Example 34: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(methoxyimino)-4-methyl-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl] benzoic acid (compound 34)

30 Instead of the starting material, that is, the compound S25, of Example 12, the compound S32 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-methyl hydroxylamine hydrochloride was used for a similar procedure as in Example 12 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J=7.3Hz), 1.23 (2H, dt, J=8.7, 15.9Hz), 1.57-1.78 (2H, m), 2.48 (3H, s), 2.63-2.78 (2H, m), 2.90-3.06 (2H, m), 3.65 (3H, s), 3.66-3.75 (1H, m), 3.79 (3H, s), 4.20 (1H, d, J=18.9Hz), 4.60 (1H, dt, J=7.7, 7.7Hz), 5.89 (1H, d, J=18.9Hz), 6.44 (1H, d,

J=8.1Hz), 6.63 (1H, s), 6.98 (1H, d, J=8.7Hz), 7.25 (1H, dd, J=2.4, 8.7Hz), 7.29 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.1Hz), 9.51 (1H, d, J=7.7Hz)

MS: 560(M+H)⁺

5 0186

Example 35: 4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]-2-nitrobenzoic acid hydrochloride (compound 35)

10 To the compound 28a obtained at Example 28, Step (1) (300 mg), anisole (0.395 ml) and 4M hydrochloric acid in ethyl acetate solution (3 ml) were added, and the mixture was stirred at room temperature for 17 hours. The precipitated crystals were collected by filtration to
15 obtain the title compound (214 mg) as a colorless crystals.

¹H-NMR (DMSO-d₆) 80.89 (3H, t, J=7.5Hz), 1.09 (3H, t, J=6.9Hz), 1.20-1.43 (2H, m), 1.66-1.89 (2H, m), 2.63-2.73 (1H, m), 2.99 (1H, dd, J=4.9, 14.2Hz), 3.12-3.21 (2H, m),
20 3.75-3.89 (3H, m), 3.80 (3H, s), 4.60 (1H, d, J=17.0Hz), 4.79 (1H, d, J=17.0Hz), 4.89 (1H, dt, J=7.3, 7.3Hz), 7.01 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.4, 8.9Hz), 7.33 (1H, d, J=2.4Hz), 7.74 (1H, dd, J=1.6, 8.1Hz), 7.83 (1H, d, J=8.1Hz), 7.96 (1H, d, J=1.6Hz), 9.42 (1H, d, J=7.3Hz)

25 MS: 590(M+H)⁺

0187

Example 36: 2-amino-4-[(1R)-1-([[(3Z, 6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]benzoic acid acetic acid solvate (compound 36)

30 To the compound 35 (874 mg) in an ethyl acetate (2.7 ml) and acetic acid (1.4 ml) suspension, zinc powder was added under ice cooling, and the mixture was stirred at that temperature for 10 minutes and at room temperature
35 for 4 hours.

The reaction mixture was diluted with ethyl acetate (10 ml) and filtered by a glass filter spread with

Celite®, and further the residue was washed with ethyl acetate (20 ml). The filtrate and the washings were combined, then successively washed with saturated aqueous ammonium chloride solution and brine, dried over sodium sulfate, then concentrated. The concentrated residue was purified by flash column chromatography to obtain 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 12) (698 mg). To the compound 12 (558 mg) thus obtained, acetic acid (1.1 ml) was added and the mixture was stirred at room temperature for 30 minutes. Then water (2.75 ml) was added, and the mixture was stirred for 10 minutes. Further, acetic acid/water (2/5, 2.5 ml) was added, and the mixture was stirred for 15 minutes, then the mixture was cooled to 0°C and stirred for 30 minutes. The precipitated crystals were collected by filtration to obtain the title compound (543 mg) as a light yellow crystals.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.08 (3H, t, J=7.1Hz), 1.14-1.35 (2H, m); 1.55-1.77 (2H, m); 2.66 (1H, dd, J=8.9, 14.6Hz), 2.95 (1H, dd, J=4.9, 14.6Hz), 2.98-3.07 (1H, m); 3.08-3.19 (1H, m); 3.70-3.92 (6H, m); 4.48 (1H, d, J=15.8Hz), 4.62 (1H, dt, J=7.7, 7.7Hz), 4.79 (1H, d, J=15.8Hz), 6.14 (1H, s); 6.44 (1H, dd, J=1.6, 8.5Hz), 6.63 (1H, d, J=1.6Hz), 7.00 (1H, d, J=8.9Hz), 7.27 (1H, dd, J=2.6, 8.9Hz), 7.31 (1H, d, J=2.6Hz), 7.65 (1H, d, J=8.5Hz), 9.46 (1H, d, J=7.7Hz)

MS: 560 (M+H)⁺

0188

Reference Example 33: tert-butyl 5-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)propyl]-2-thiophene carboxylate (compound S33)

Step (1): Instead of the starting material, that is,

the compound S4, of Reference Example 19, the compound S90 described in WO 06-059801A, that is, tert-butyl 5-(1-aminopropyl)-2-thiophene carboxylate hydrochloride was used for a similar procedure as in Reference Example 19 to obtain tert-butyl 5-(1-isocyanatopropyl)-2-thiophene carboxylate hydrochloride (compound S33a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S33a was used for a similar procedure as in Reference Example 20 to obtain tert-butyl 5-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino)propyl]-2-thiophene carboxylate (compound S33b) and tert-butyl 5-[(1S)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino)propyl]-2-thiophene carboxylate (compound S33c).

Step (3): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S33b was used for a similar procedure as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.97 (3H, t, J=7.5Hz), 1.85-2.01 (2H, m), 2.36 (1H, dd, J=9.7, 13.8Hz), 3.08 (1H, dd, J=4.1, 13.8Hz), 3.12-3.42 (3H, m), 3.67 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.86-5.18 (4H, m), 5.57 (1H, d, J=16.6Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.9Hz), 6.77 (1H, d, J=2.6Hz), 6.95 (1H, dd, J=0.8, 3.9Hz), 7.18 (1H, dd, J=2.6, 8.9Hz), 7.56 (1H, d, J=3.9Hz), 9.44 (1H, d, J=7.7Hz)

MS: 746(M+H)⁺

0189

Example 37: 5-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl]amino)propyl]thiophene-2-carboxylic acid (compound 37)

Instead of the starting material, that is, the

compound S27, of Example 23, the compound S33 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.90 (3H, t, J=7.3Hz), 1.82-1.96 (2H, m), 2.69 (1H, dd, J=8.9, 14.2Hz), 2.99 (1H, dd, J=4.5, 14.2Hz), 3.11-3.26 (2H, m), 3.80 (3H, s), 3.85-3.99 (1H, m), 4.70 (1H, d, J=16.2Hz), 4.94 (1H, d, J=16.2Hz), 5.01 (1H, dt, J=7.7, 7.7Hz), 6.84-6.97 (2H, m), 6.98-7.12 (4H, m), 7.19-7.31 (3H, m), 7.34 (1H, d, J=2.8Hz), 7.59 (1H, d, J=3.7Hz), 9.48 (1H, d, J=7.7Hz), 12.82 (1H, br.s)
MS: 585 (M+H)⁺

0190

Reference Example 34: tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-fluorobenzoate (compound S34)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S81 described in WO 06-059801A, that is, tert-butyl 4-(1-aminopropyl)-2-fluorobenzoate hydrochloride, was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-(1-isocyanatopropyl)-2-fluorobenzoate (compound S34a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S34a was used for a similar reaction as in Reference Example 20 to obtain tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-fluorobenzoate (compound S34b) and tert-butyl 4-((1S)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-fluorobenzoate (compound S34c).

Step (3): Instead of the starting material, that is,

the compound S21, of Reference Example 22, the compound S34b was used for a similar reaction as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.91 (3H, t, J=7.3Hz), 1.57-1.62 (9H, m),
5 1.72-1.91 (2H, m), 2.37 (1H, dd, J=9.7, 13.8Hz), 3.10
(1H, dd, J=4.1, 13.8Hz), 3.13-3.30 (2H, m), 3.31-3.47
(1H, m), 3.67 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.75-
4.91 (2H, m), 4.95 (1H, d, J=14.2Hz), 5.08 (1H, d,
J=14.2Hz), 5.58 (1H, d, J=16.6Hz), 6.09 (2H, s), 6.75
10 (1H, d, J=8.7Hz), 6.78 (1H, d, J=2.4Hz), 7.02 (1H, dd,
J=1.4, 11.6Hz), 7.11 (1H, dd, J=1.6, 8.0Hz), 7.19 (1H,
dd, J=2.4, 8.7Hz), 7.82 (1H, t, J=8.0Hz), 9.50 (1H, d,
J=7.3Hz)

MS: 758 (M+H)⁺

15 0191

Example 38: 4-[(1R)-1-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]propyl]-2-fluorobenzoic acid (compound 38)

20 Instead of the starting material, that is, the compound S27, of Example 23, the compound S34 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a
25 similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J=7.3Hz), 1.72-1.89 (2H, m), 2.72 (1H, dd, J=9.1, 14.1Hz), 3.01 (1H, dd, J=4.9, 14.1Hz), 3.12-3.25 (2H, m), 3.81 (3H, s), 3.84-4.00 (1H, m),
30 4.65 (1H, d, J=16.2Hz), 4.75 (1H, dt, J=7.1, 7.1Hz), 4.87 (1H, d, J=16.2Hz), 6.95 (1H, s), 6.98-7.14 (5H, m), 7.19-7.32 (3H, m), 7.35 (1H, d, J=2.8Hz), 7.83 (1H, t, J=7.7Hz), 9.47 (1H, d, J=7.1Hz), 13.14 (1H, br.s)

MS: 615 (M+H)⁺

35 0192

Example 39: 4-[(1R)-1-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-

yl}carbonyl}amino)propyl]-2-fluorobenzoic acid (compound 39)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S34 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J=7.3Hz), 1.72-1.87 (2H, m), 2.72 (1H, dd, J=9.1, 14.3Hz), 3.01 (1H, dd, J=4.9, 14.3Hz), 3.11-3.24 (2H, m), 3.81 (3H, s), 3.85-3.98 (1H, m), 4.66 (1H, d, J=16.0Hz), 4.75 (1H, dt, J=7.3, 7.3Hz), 4.88 (1H, d, J=16.0Hz), 6.81-6.96 (2H, m), 6.96-7.10 (3H, m), 7.18-7.33 (5H, m), 7.35 (1H, d, J=2.8Hz), 7.82 (1H, t, J=7.9Hz), 9.47 (1H, d, J=7.3Hz), 13.20 (1H, br.s)

MS: 597 (M+H)⁺

0193

Reference Example 35: tert-butyl (4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl))-1,4-diazepan-1-yl}carbonyl)amino]ethyl}phenyl)acetate (compound S35)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, tert-butyl [4-(1-aminoethyl)phenyl]acetate was used for a similar reaction as in Reference Example 19 to obtain tert-butyl [4-(1-isocyanatoethyl)phenyl]acetate (compound S35a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S35a was used for a similar procedure as in Reference Example 20 to obtain tert-butyl (4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl))-1,4-diazepan-1-yl}carbonyl)amino]ethyl}phenyl)acetate (compound S35b) and tert-butyl (4-((1S)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl))-1,4-diazepan-1-yl}carbonyl)amino]ethyl}phenyl)acetate (compound S35c).

Step (3): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S35b was used for a similar reaction as in Reference Example 22 to obtain the title compound.

5 ¹H-NMR (CDCl₃) δ1.44(9H, s), 1.51 (3H, d, J=6.9Hz), 2.34 (1H, dd, J=9.7, 13.8Hz), 3.07 (1H, dd, J=4.1, 13.8Hz), 3.11-3.27 (2H, m), 3.29-3.39 (1H, m), 3.50 (2H, s), 3.66(6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.87 (1H, d, J=17.0Hz), 4.94 (1H, d, J=14.2Hz), 5.02-5.14 (2H, m),
10 5.61 (1H, d, J=17.0Hz), 6.08 (2H, s), 6.74 (1H, d, J=8.7Hz), 6.78 (1H, d, J=2.8Hz), 7.18 (1H, dd, J=2.8, 8.7Hz), 7.21-7.25 (2H, m), 7.27-7.31 (2H, m), 9.38 (1H, d, J=7.3Hz)

MS: 740(M+H)⁺

15 0194

Example 40: (4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)ethyl) phenyl)acetic acid (compound 40)

20 Instead of the starting material, that is, the compound S27, of Example 23, the compound S35 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a
25 similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.43 (3H, d, J=6.9Hz), 2.69 (1H, dd, J=9.1, 14.4Hz), 2.97 (1H, dd, J=4.5, 14.4Hz), 3.12-3.25 (2H, m), 3.53 (2H, s), 3.80 (3H, s), 3.85-3.96 (1H, m),
30 4.64 (1H, d, J=16.2Hz), 4.82-4.98 (2H, m), 6.95 (1H, br.s), 6.98-7.13(5H, m), 7.19-7.24 (2H, m), 7.24-7.30 (3H, m), 7.34 (1H, d, J=2.8Hz), 9.42 (1H, d, J=7.3Hz), 12.41 (1H, br.s)

MS: 597(M+H)⁺

35 0195

Example 41: (4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-

diazepan-1-yl}carbonyl)amino]ethyl} phenyl)acetic acid
(compound 41)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S35 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.43 (2H, d, J=6.9Hz), 2.69 (1H, dd, J=8.9, 14.2Hz), 2.97 (1H, dd, J=4.9, 14.2Hz), 3.13-3.24 (2H, m), 3.53 (2H, s), 3.80 (3H, s), 3.85-3.98 (1H, m), 4.66 (1H, d, J=16.6Hz), 4.80-4.98 (2H, m), 6.64-6.80 (3H, m), 7.01 (1H, d, J=8.5Hz), 7.10 (1H, s), 7.19-7.25 (2H, m), 7.25-7.31 (3H, m), 7.34 (1H, d, J=2.8Hz), 9.40 (1H, d, J=7.7Hz), 12.27 (1H, br.s)
MS: 615(M+H)⁺

0196

Example 42: (4-((1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(pyridin-2-yloxy)imino]-1,4-diazepan-1-yl}carbonyl)amino]ethyl} phenyl)acetic acid
(compound 42)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S35 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(pyridin-2-yl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.44 (3H, d, J=7.1Hz), 2.68 (1H, dd, J=8.5, 14.6Hz), 2.97 (1H, dd, J=5.3, 14.6Hz), 3.11-3.30 (2H, m), 3.54 (2H, s), 3.80 (3H, s), 3.86-3.99 (1H, m), 4.68 (1H, d, J=16.6Hz), 4.88 (1H, dq, J=7.1, 7.1Hz), 4.96 (1H, d, J=16.6Hz), 6.96-7.03 (2H, m), 7.05 (1H, s), 7.15-7.20 (1H, m), 7.20-7.25 (2H, m), 7.25-7.31 (3H, m), 7.34 (1H, d, J=2.4Hz), 7.77 (1H, ddd, J=2.0, 7.1, 8.3Hz), 8.15 (1H, ddd, J=0.8, 2.0, 4.9Hz), 9.42 (1H, d, J=7.1Hz), 12.34 (1H, br.s)

MS: 580 (M+H)⁺

0197

Reference Example 36: tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-(benzyloxy)benzoate (compound S36)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S13 was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-(1-isocyanatopropyl)-2-benzyloxybenzoate (compound S36a).

Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S36a was used for a similar procedure as in Reference Example 20 to obtain tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-benzyloxybenzoate (compound S36b) and tert-butyl 4-((1S)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-benzyloxybenzoate (compound S36c).

Step (3): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S36b was used for a similar reaction as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.85 (3H, t, J=7.5Hz), 1.51 (9H, s), 1.69-1.88 (2H, m), 2.35 (1H, dd, J=9.7, 13.8Hz), 3.05-3.28 (3H, m), 3.32-3.45 (1H, m), 3.66 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.74-4.87 (2H, m), 4.92 (1H, d, J=14.2Hz), 5.05-5.21 (3H, m), 5.61 (1H, d, J=17.0Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.5Hz), 6.79 (1H, d, J=2.4Hz), 6.86-6.93 (2H, m), 7.18 (1H, dd, J=2.4, 8.5Hz), 7.27-7.33 (1H, m), 7.33-7.40 (2H, m), 7.48 (2H, d, J=6.9Hz), 7.68 (1H, d, J=7.7Hz), 9.42 (1H, d, J=7.7Hz)

MS: 846 (M+H)⁺

0198

Example 43: 4-[(1R)-1-[([(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino]propyl]-2-hydroxybenzoic acid (compound 43)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S36 was used and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ 0.83 (2H, t, J=7.1Hz), 1.69-1.85 (1H, m), 2.72 (1H, dd, J=9.1, 14.2Hz), 3.00 (1H, dd, J=4.1, 14.2Hz), 3.15-3.23 (2H, m), 3.81 (3H, s), 3.85-3.98 (1H, m), 4.58-4.73 (2H, m), 4.91 (1H, d, J=16.6Hz), 6.77 (2H, br.s), 6.95 (1H, br.s), 6.99-7.14 (5H, m), 7.28 (1H, dd, J=2.4, 8.5Hz), 7.35 (1H, d, J=2.4Hz), 9.47 (1H, d, J=7.7Hz)

MS: 613(M+H)⁺

0199

Example 44: 4-[(1R)-1-[([(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino]propyl]-2-hydroxybenzoic acid (compound 44)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S36 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ 0.83 (3H, t, J=6.9Hz), 1.76 (2H, s), 2.71 (1H, dd, J=9.1, 14.4Hz), 3.00 (1H, dd, J=4.7, 14.0Hz), 3.16-3.23 (2H, m), 3.80 (3H, s), 3.85-3.98 (1H, m), 4.66 (1H, s), 4.91 (1H, d, J=16.6Hz), 6.61-6.81 (5H, m), 7.02 (1H, d, J=8.7Hz), 7.10 (1H, s), 7.28 (1H, dd,

J=2.6, 8.7Hz), 7.35 (1H, d, J=2.6Hz), 7.69 (1H, br.s),
9.44 (1H, d, J=8.1Hz)

MS: 631 (M+H)⁺

0200

5 Reference Example 37: tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]ethyl)-2-(benzyloxy)benzoate (compound S37)

10 Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S12 was used for a similar reaction as in Reference Example 19 to obtain tert-butyl 4-(1-isocyanatoethyl)-2-benzyloxybenzoate (compound S37a).

15 Step (2): Instead of the reaction agent, that is, the compound S19, of Reference Example 20, the compound S37a was used for a similar procedure as in Reference Example 20 to obtain tert-butyl 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]ethyl)-2-benzyloxybenzoate (compound S37b) and tert-butyl 4-((1S)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]ethyl)-2-benzyloxybenzoate (compound S37c).

25 Step (3): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S37b was used for a similar reaction as in Reference Example 22 to obtain the title compound.

30 ¹H-NMR (CDCl₃) δ 1.47 (3H, d, J=6.9Hz), 1.50 (9H, s), 2.35 (1H, dd, J=10.1, 14.0Hz), 3.09 (1H, dd, J=4.3, 14.0Hz), 3.12-3.28 (2H, m), 3.31-3.43 (1H, m), 3.66 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.87 (1H, d, J=17.0Hz), 4.96 (1H, d, J=14.2Hz), 4.99-5.19 (4H, m), 5.58 (1H, d, J=17.0Hz),
35 6.08 (2H, s), 6.74 (1H, d, J=8.5Hz), 6.78 (1H, d, J=2.4Hz), 6.91-6.98 (2H, m), 7.18 (1H, dd, J=2.4, 8.5Hz), 7.27-7.33 (1H, m), 7.33-7.40 (2H, m), 7.48 (2H, d,

J=7.3Hz), 7.68 (1H, d, J=7.7Hz), 9.38 (1H, d, J=7.3Hz)
MS: 832(M+H)⁺

0201

5 Example 45: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl}carbonyl)amino)ethyl)-2-hydroxybenzoate (compound 45)

10 Instead of the starting material, that is, the compound S27, of Example 23, the compound S37 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

15 ¹H-NMR (DMSO-d₆) δ1.42 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=9.1, 14.4Hz), 2.99 (1H, dd, J=4.9, 14.4Hz), 3.11-3.24 (2H, m), 3.81 (3H, s), 3.85-3.98 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.77-4.98 (2H, m), 6.80 (2H, br.s), 6.95 (1H, br.s), 6.98-7.14 (5H, m), 7.28 (1H, dd, J=2.4, 8.7Hz),
20 7.35 (1H, d, J=2.4Hz), 7.71 (1H, br.s), 9.41 (1H, d, J=7.3Hz)

MS: 599(M+H)⁺

0202

25 Example 46: 4-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl}carbonyl)amino)ethyl)-2-hydroxybenzoic acid (compound 46)

30 Instead of the starting material, that is, the compound S27, of Example 23, the compound S37 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

35 ¹H-NMR (DMSO-d₆) δ1.42 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=9.1, 14.0Hz), 2.99 (1H, dd, J=4.7, 14.0Hz), 3.15-3.23 (2H, m), 3.80 (3H, s), 3.85-3.99 (1H, m), 4.68 (1H, d,

J=16.6Hz), 4.79-4.98 (2H, m), 6.64-6.89 (5H, m), 7.02 (1H, d, J=8.7Hz), 7.10 (1H, br.s), 7.28 (1H, dd, J=2.4, 8.7Hz), 7.35 (1H, d, J=2.4Hz), 7.72 (1H, br.s), 9.39 (1H, d, J=6.9Hz)

5 MS: 617 (M+H)⁺
0203

Reference Example 38: tert-butyl 5-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-
10 yl)carbonyl)amino]propyl)-2-(benzyloxy)benzoate (compound S38)

Step (1): Instead of the starting material, that is, the compound S4, of Reference Example 19, the compound S89 described in WO 06-059801A, that is, tert-butyl 5-(1-aminopropyl)-2-benzyloxybenzoate hydrochloride, was used
15 for a similar reaction as in Reference Example 19 to obtain tert-butyl 5-(1-isocyanatopropyl)-2-benzyloxybenzoate (compound S38a).

Step (2): Instead of the reaction agent, that is,
20 the compound S19, of Reference Example 20, the compound S38a was used for a similar procedure as in Reference Example 20 to obtain tert-butyl 5-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-
25 yl)carbonyl)amino]propyl)-2-benzyloxybenzoate (compound S38b) and tert-butyl 5-((1S)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino]propyl)-2-benzyloxybenzoate (compound S38c).

30 Step (3): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S38b was used for a similar reaction as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ 0.89 (3H, t, J=7.3Hz), 1.51 (9H, s), 1.72-
35 1.94 (2H, m), 2.34 (1H, dd, J=9.7, 13.8Hz), 3.08 (1H, dd, J=4.1, 13.8Hz), 3.11-3.28 (2H, m), 3.28-3.43 (1H, m), 3.65 (6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.71-4.98 (3H,

m), 5.05-5.16 (3H, m), 5.60 (1H, d, J=17.0Hz), 6.08 (2H, s), 6.74 (1H, d, J=8.8Hz), 6.77 (1H, d, J=2.5Hz), 6.93 (1H, d, J=8.5Hz), 7.18 (1H, dd, J=2.5, 8.8Hz), 7.27-7.42 (4H, m), 7.43-7.50 (2H, m), 7.61 (1H, d, J=2.4Hz), 9.39 (1H, d, J=7.7Hz)

MS: 846(M+H)⁺

0204

Example 47: 5-[(1R)-1-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl]amino]propyl]-2-hydroxybenzoic acid (compound 47)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S38 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) 80.81 (3H, t, J=7.3Hz), 1.63-1.89 (2H, m), 2.72 (1H, dd, J=9.3, 14.2Hz), 2.98 (1H, dd, J=4.9, 14.2Hz), 3.08-3.24 (2H, m), 3.80 (3H, s), 3.83-3.99 (1H, m), 4.55-4.71 (2H, m), 4.91 (1H, d, J=16.2Hz), 6.84-6.96 (3H, m), 7.01 (1H, d, J=8.9Hz), 7.05 (2H, d, J=7.7Hz), 7.18-7.31 (3H, m), 7.34 (1H, d, J=2.2Hz), 7.45 (1H, d, J=8.9Hz), 7.71 (1H, d, J=2.2Hz), 9.42 (1H, d, J=7.7Hz)

MS: 595(M+H)⁺

0205

Reference Example 39: tert-butyl 2-[(1R)-1-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino]propyl]isonicotinate (compound S39)

Step (1): To the compound S105 described in WO 06-059801A, that is, tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-tartrate (157 mg) in an N,N-dimethylformamide (1.5 ml) solution, triethylamine (0.113 ml) was added under ice cooling, and the mixture was stirred at that temperature for 5 minutes. To the reaction solution, the compound S141C described in WO 06-

059801A, that is, (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepane-1-carboxylate (250 mg) and 4-dimethylaminopyridine (49 mg) were added, and the mixture
5 was stirred at 0°C for 18 hours. The reaction solution was diluted with ethyl acetate, then was successively washed with saturated aqueous ammonium chloride solution and brine. The organic layer was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified
10 by flash column chromatography (silica gel, hexane/ethyl acetate=1/1 to 1/2) to obtain tert-butyl 2-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)propyl]isonicotinate (compound S39a)
15 (210 mg).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S39a was used for a similar reaction as in Reference Example 22 to obtain the title compound.

20 ¹H-NMR (CDCl₃) δ0.88 (3H, t, J=7.5Hz), 1.61(9H, s), 1.93 (2H, m), 2.39 (1H, dd, J=9.9, 14.0Hz), 3.05-3.31 (3H, m), 3.31-3.45 (1H, m), 3.67(6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.80-4.98 (2H, m), 5.05 (1H, dt, J=7.7, 7.7Hz), 5.13 (1H, d, J=14.2Hz), 5.60 (1H, d, J=17.5Hz), 6.09 (2H, s),
25 6.74 (1H, d, J=8.8Hz), 6.79 (1H, d, J=2.7Hz), 7.18 (1H, dd, J=2.7, 8.8Hz), 7.67 (1H, dd, J=1.6, 4.9Hz), 7.73 (1H, s), 8.71 (1H, dd, J=0.8, 4.9Hz), 9.80 (1H, d, J=7.7Hz)
MS: 741(M+H)⁺

0206

30 Example 48: 2-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]isonicotinic acid (compound 48)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S39 was used,
35 and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar procedure as in

Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.79 (3H, t, J=7.3Hz), 1.77-1.89 (2H, m), 2.71 (1H, dd, J=8.9, 14.1Hz), 3.00 (1H, dd, J=4.7, 14.1Hz), 3.12-3.25 (2H, m), 3.81 (3H, s), 3.84-3.99 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.89-5.02 (2H, m), 6.85-6.96 (2H, m), 7.01 (1H, d, J=8.9Hz), 7.03-7.09 (2H, m), 7.21-7.30 (3H, m), 7.35 (1H, d, J=2.4Hz), 7.72 (1H, dd, J=1.6, 4.9Hz), 7.81 (1H, br.s), 8.76 (1H, dd, J=0.8, 4.9Hz), 9.78 (1H, d, J=7.7Hz), 13.69 (1H, br.s)

MS: 580(M+H)⁺

0207

Reference Example 40: tert-butyl 5-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)propyl]nicotinate (compound S40)

Instead of the starting material, that is, tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-tartrate, of Reference Example 39, the compound S103 described in WO 06-059801A, that is, 5-[(1R)-1-aminopropyl]-nicotinate D-tartrate was used for a similar reaction as in Reference Example 39 to obtain the title compound.

MS: 741(M+H)⁺

0208

Example 49: 5-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]nicotinic acid (compound 49)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S40 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J=7.3Hz), 1.72-1.99 (2H, m), 2.72 (1H, dd, J=9.1, 14.3Hz), 3.01 (1H, dd, J=4.9, 14.3Hz), 3.12-3.23 (2H, m), 3.81 (3H, s), 3.84-4.04 (1H, m), 4.64 (1H, d, J=16.2Hz), 4.71-4.95 (2H, m), 6.79-6.96 (2H, m), 6.96-7.08 (3H, m), 7.16-7.31 (3H, m), 7.35 (1H,

d, J=2.8Hz), 8.22 (1H, t, J=2.2Hz), 8.78 (1H, d, J=2.2Hz), 8.96 (1H, d, J=2.2Hz), 9.50 (1H, d, J=6.9Hz), 13.51 (1H, br.s)

MS: 580 (M+H)⁺

5 0209

Reference Example 41: tert-butyl 6-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)propyl]nicotinate (compound S41)

10 Instead of the starting material, that is, tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-tartrate, of Reference Example 39, the compound S106 described in WO 06-059801A, that is, tert-butyl 6-[(1R)-1-aminopropyl]-nicotinate D-tartrate, was used for a similar reaction as
15 in Reference Example 39 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.87 (3H, t, J=7.3Hz), 1.59 (9H, s), 1.82-2.01 (2H, m), 2.40 (1H, dd, J=9.7, 14.2Hz), 3.03-3.19 (1H, m), 3.19-3.43 (3H, m), 3.67 (6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.83-4.96 (2H, m), 4.96-5.15 (2H, m), 5.58
20 (1H, d, J=17.0Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.8Hz), 6.79 (1H, d, J=2.5Hz), 7.18 (1H, dd, J=2.5, 8.8Hz), 7.30 (1H, d, J=8.1Hz), 8.19 (1H, dd, J=2.0, 8.1Hz), 9.16 (1H, d, J=2.0Hz), 9.84 (1H, d, J=6.9Hz)

MS: 741 (M+H)⁺

25 0210

Example 50: 6-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)propyl]nicotinic acid (compound 51)

30 Instead of the starting material, that is, the compound S27, of Example 23, the compound S41 as used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

35 ¹H-NMR (CDCl₃) δ0.92 (3H, t, J=7.3Hz), 1.88-2.06 (2H, m), 2.66 (1H, dd, J=8.3, 13.9Hz), 3.24 (1H, dd, J=4.9, 13.9Hz), 3.28-3.40 (1H, m), 3.40-3.53 (1H, m), 3.74 (1H,

m), 3.83 (3H, s), 4.25 (1H, d, J=16.6Hz), 5.01 (1H, dt, J=6.9, 6.9Hz), 5.40 (1H, d, J=16.6Hz), 5.55 (1H, br.s), 6.79 (1H, d, J=8.5Hz), 6.94 (1H, t, J=7.1Hz), 7.04-7.31(6H, m), 7.37 (1H, d, J=8.3Hz), 8.30 (1H, d, J=8.3Hz), 9.28 (1H, s), 9.86 (1H, d, J=6.9Hz)
MS: 580(M+H)⁺

0211

Reference Example 42: tert-butyl 4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)ethyl]benzoate (compound S42)

Instead of the starting material, that is, tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-tartrate, of Reference Example 39, the compound S2 was used for a similar reaction as in Reference Example 39 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.52 (3H, d, J=6.9Hz), 1.56-1.61(9H, m), 2.36 (1H, dd, J=9.5, 13.9Hz), 3.07 (1H, dd, J=4.1, 13.9Hz), 3.12-3.38 (3H, m), 3.67(6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.79-5.21(4H, m), 5.57 (1H, d, J=16.6Hz), 6.08 (2H, s), 6.74 (1H, d, J=8.6Hz), 6.79 (1H, d, J=2.5Hz), 7.18 (1H, dd, J=2.5, 8.6Hz), 7.33-7.43 (2H, d, J=8.5Hz), 7.92-8.00 (2H, d, J=8.5Hz), 9.45 (1H, d, J=7.3Hz)

MS: 726(M+H)⁺

0212

Example 51: 4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)ethyl]benzoic acid (compound 51)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S42 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.46 (3H, d, J=6.9Hz), 2.70 (1H, dd, J=9.1, 14.3Hz), 3.00 (1H, dd, J=4.9, 14.3Hz), 3.11-3.26

(2H, m), 3.81 (3H, s), 3.84-4.04 (1H, m), 4.66 (1H, d, J=16.2Hz), 4.82-5.06 (2H, m), 6.79-6.96 (2H, m), 6.96-7.12 (3H, m), 7.19-7.31 (3H, m), 7.35 (1H, d, J=2.4Hz), 7.46 (2H, d, J=8.1Hz), 7.91 (2H, d, J=8.1Hz), 9.45 (1H, d, J=6.9Hz), 12.85 (1H, br.s)

MS: 565 (M+H)⁺

0213

Reference Example 43: tert-butyl 2-amino-4-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino)methyl}benzoate (compound S43)

Step (1): To the compound S11 (306 mg) and the compound S141C described in WO 06-059801A, that is, (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepane-1-carboxylate (850 mg) in an N,N-dimethylformamide (4 ml) solution, 4-dimethylaminopyridine (169 mg) was added under ice cooling, and the mixture was stirred at 0°C for 18 hours. The reaction solution was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate=2/1) to obtain tert-butyl 2-amino-4-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl)carbonyl)amino)methyl}benzoate (compound S43a) (685 mg).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S43a was used for a similar reaction as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.57(9H, s), 2.38 (1H, dd, J=8.7, 13.7Hz), 3.04 (1H, dd, J=3.7, 13.7Hz), 3.12-3.34 (3H, m), 3.65(6H, s), 3.74 (3H, s), 3.85 (3H, s), 4.42 (2H, d, J=5.7Hz), 4.92-5.13 (3H, m), 5.53 (1H, d, J=16.6Hz), 5.72 (2H, br.s), 6.07 (2H, s), 6.55 (1H, d, J=8.1Hz), 6.58 (1H, s), 6.73 (1H, d, J=8.8Hz), 6.80 (1H, d, J=2.7Hz), 7.17 (1H,

dd, J=2.7, 8.8Hz), 7.76 (1H, d, J=8.1Hz), 9.34 (1H, t, J=5.7Hz)

MS: 727(M+H)⁺

0214

5 Example 52: 2-amino-4-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]methyl] benzoic acid (compound 52)

10 Instead of the starting material, that is, the compound S27, of Example 23, the compound S43 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(4-fluorophenyl)hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title
15 compound.

¹H-NMR (DMSO-d₆) δ2.68 (1H, dd, J=8.1, 14.0Hz), 2.99 (1H, dd, J=4.9, 14.0Hz), 3.07-3.24 (2H, m), 3.80 (3H, s), 3.86-4.04 (1H, m), 4.21-4.38 (2H, m), 4.70 (1H, d, J=16.4Hz), 4.98 (1H, d, J=16.4Hz), 6.43 (1H, dd, J=1.4, 8.3Hz), 6.64 (1H, d, J=1.4Hz), 6.96 (1H, s), 7.01 (1H, d, J=8.8Hz), 7.03-7.12 (4H, m), 7.27 (1H, dd, J=2.7, 8.8Hz), 7.35 (1H, d, J=2.7Hz), 7.63 (1H, d, J=8.3Hz), 9.37 (1H, t, J=5.9Hz)

MS: 584(M+H)⁺

25 0215

Example 53: 2-amino-4-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]methyl] benzoic acid (compound 53)

30 Instead of the starting material, that is, the compound S27, of Example 23, the compound S43 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-(3,5-difluorophenyl) hydroxylamine hydrochloride was used for a similar
35 reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ2.68 (1H, dd, J=8.7, 14.3Hz), 2.99 (1H, dd, J=5.3, 14.3Hz), 3.10-3.27 (2H, m), 3.80 (3H, s),

3.85-4.05 (1H, m), 4.22-4.40 (2H, m), 4.73 (1H, d, J=16.8Hz), 4.97 (1H, d, J=16.8Hz), 6.43 (1H, dd, J=1.4, 8.5Hz), 6.64 (1H, d, J=1.4Hz), 6.66-6.83 (3H, m), 7.01 (1H, d, J=8.9Hz), 7.11 (1H, s), 7.27 (1H, dd, J=2.6, 8.9Hz), 7.35 (1H, d, J=2.6Hz), 7.63 (1H, d, J=8.5Hz), 9.36 (1H, t, J=5.9Hz)

MS: 602 (M+H)⁺

0216

Reference Example 44: tert-butyl (2R)-2-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino)butanoate (compound S44)

Instead of the starting material, that is, tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-tartrate, of Reference Example 39, tert-butyl (2R)-2-aminobutanoate hydrochloride was used for a similar reaction as in Reference Example 39 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.94 (3H, t, J=7.3Hz), 1.48 (9H, s), 1.73-1.96 (2H, m), 2.34 (1H, dd, J=9.7, 13.8Hz), 3.04-3.30 (3H, m), 3.36 (1H, m), 3.68 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 4.39-4.49 (1H, m), 4.85-4.97 (2H, m), 5.11 (1H, d, J=14.2Hz), 5.61 (1H, d, J=17.0Hz), 6.09 (2H, s), 6.74 (1H, d, J=8.8Hz), 6.77 (1H, d, J=2.7Hz), 7.17 (1H, dd, J=2.7, 8.8Hz), 9.48 (1H, d, J=7.3Hz)

MS: 664 (M+H)⁺

0217

Example 54: (2R)-2-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl]amino)butanoic acid (compound 54)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S44 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.04 (3H, t, J=7.5Hz), 1.80-2.08 (2H, m), 2.62 (1H, dd, J=8.9, 14.0Hz), 3.23 (1H, dd, J=4.9,

14.0Hz), 3.27-3.35 (1H, m), 3.38-3.50 (1H, m), 3.69-3.81 (1H, m), 3.84 (3H, s), 4.30 (1H, d, J=16.2Hz), 4.43-4.55 (1H, m), 5.43 (1H, d, J=16.2Hz), 5.54 (1H, s), 6.80 (1H, d, J=8.9Hz), 6.94 (1H, t, J=7.3Hz), 7.09-7.17 (3H, m), 7.18-7.28 (3H, m), 9.52 (1H, d, J=6.9Hz)

MS: 503(M+H)⁺

0218

Example 55: (6R)-6-(5-chloro-2-methoxybenzyl)-N-[(1R)-1-(methylcarbamoyl)propyl]-7-oxo-3-(phenoxyimino)-1,4-diazepane-1-carboxamide (compound 55)

To the compound 54 (70 mg) in a methylene chloride (3 ml) solution, dimethylamine in a methanol solution (2M, 0.14 ml), triethylamine (0.291 ml), and propyl phosphonate anhydride (T3P) (50% ethyl acetate solution, 0.21 ml) were successively added, and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off, and the residue was diluted with ethyl acetate. Then the resultant mixture was successively washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogencarbonate solution, and brine. The organic layer was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate=9/1 to 1/1) to obtain the title compound (42.5 mg).

¹H-NMR (DMSO-d₆) δ 0.81 (3H, t, J=7.3Hz), 1.52-1.79 (2H, m), 2.60 (3H, d, J=4.5Hz), 2.68 (1H, dd, J=8.5, 14.4Hz), 3.00 (1H, dd, J=4.9, 14.4Hz), 3.08-3.26 (2H, m), 3.81 (3H, s), 3.87-4.04 (1H, m), 4.21 (1H, dt, J=7.7, 7.7Hz), 4.68 (1H, d, J=16.4Hz), 4.96 (1H, d, J=16.4Hz), 6.80-6.96 (2H, m), 7.02 (1H, d, J=8.9Hz), 7.04-7.13 (2H, m), 7.18-7.31 (3H, m), 7.35 (1H, d, J=2.8Hz), 8.06 (1H, dt, J=4.5Hz), 9.40 (1H, d, J=7.7Hz)

MS: 516(M+H)⁺

0219

Example 56: (6R)-N-[(1R)-1-carbamoylpropyl]-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepane-1-

carboxamide (compound 56)

To the compound 54 (114 mg) in a methylene chloride (2 ml) solution, carbonyl diimidazole (45 mg) was added, and the mixture was stirred at room temperature for 45 minutes. The reaction solution was cooled to 0°C, then 28% ammonia aqueous solution (2 ml) was added, and the mixture was stirred at that temperature for 1 hour. The reaction solution was diluted with chloroform and the resultant mixture successively washed with water, 1M hydrochloric acid, and brine. The organic layer was dried over anhydrous sodium sulfate, then was concentrated. The residue was purified by flash column chromatography (silica gel, chloroform /ethyl acetate=7/3 to 1/2) to obtain the title compound (40 mg).

¹H-NMR (DMSO-d₆) δ0.82 (3H, t, J=7.3Hz), 1.58-1.79 (2H, m), 2.68 (1H, dd, J=8.9, 14.3Hz), 3.00 (1H, dd, J=4.7, 14.3Hz), 3.07-3.26 (2H, m), 3.81 (3H, s), 3.85-4.02 (1H, m), 4.24 (1H, dt, J=7.3, 7.3Hz), 4.68 (1H, d, J=16.2Hz), 4.97 (1H, d, J=16.2Hz), 6.85-6.95 (2H, m), 7.02 (1H, d, J=8.9Hz), 7.04-7.11 (2H, m), 7.16 (1H, s), 7.19-7.31 (3H, m), 7.35 (1H, d, J=2.8Hz), 7.57 (1H, s), 9.40 (1H, d, J=7.3Hz)

MS: 502 (M+H)⁺

0220

Example 57: (6R)-6-(5-chloro-2-methoxybenzyl)-N-[(1R)-1-(dimethylcarbamoyl)propyl]-7-oxo-3-(phenoxyimino)-1,4-diazepane-1-carboxamide (compound 57)

Instead of the reaction agent, that is, methylamine in a methanol solution, in Example 55, dimethylamine in a tetrahydrofuran solution was used for a similar reaction as in Example 55 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.46-1.85 (2H, m), 2.68 (1H, dd, J=8.5, 14.4Hz), 2.85 (3H, s), 3.00 (1H, dd, J=5.3, 14.4Hz), 3.05 (3H, s), 3.10-3.27 (2H, m), 3.81 (3H, s), 3.86-4.03 (1H, m), 4.68 (1H, d, J=16.0Hz), 4.74 (1H, dt, J=7.7, 7.7Hz), 4.97 (1H, d, J=16.0Hz), 6.84-6.96

(2H, m), 7.01 (1H, d, J=8.9Hz), 7.04-7.11 (2H, m), 7.19-7.31 (3H, m), 7.34 (1H, d, J=2.8Hz), 9.46 (1H, d, J=7.7Hz)

MS: 530 (M+H)⁺

5 0221

Example 58: (6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-N-[(1R)-1-(1H-tetrazole-5-ylcarbamoyl)propyl]-1,4-diazepane-1-carboxamide (compound 58)

10 Instead of the reaction agent, that is, methylamine in a methanol solution, in Example 55, 1H-tetrazole-5-amine monohydrate was used for a similar reaction as in Example 55 to obtain the title compound.

15 ¹H-NMR (DMSO-d₆) δ0.90 (3H, t, J=7.3Hz), 1.66-1.96 (2H, m), 2.70 (1H, dd, J=8.9, 14.5Hz), 3.01 (1H, dd, J=5.1, 14.5Hz), 3.09-3.26 (2H, m), 3.81 (3H, s), 3.87-4.09 (1H, m), 4.53 (1H, dt, J=6.5, 6.5Hz), 4.72 (1H, d, J=16.2Hz), 4.95 (1H, d, J=16.2Hz), 6.86-6.97 (2H, m), 7.02 (1H, d, J=8.9Hz), 7.04-7.09 (2H, m), 7.17-7.32 (3H, m), 7.36 (1H, d, J=2.8Hz), 9.53 (1H, d, J=6.5Hz), 12.24 (1H, br.s), 15.99 (1H, br.s)

20 MS: 570 (M+H)⁺

 0222

25 Reference Example 45: (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepane-1-carboxylate (compound S45)

30 To the compound S141C described in WO 06-059801A, that is, (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-carboxylate (996 mg), anisole (1.75 ml) and trifluoroacetic acid (10 ml) were added, and the mixture was stirred at room temperature for 4.5 hours. The reaction solution was diluted with toluene and concentrated in vacuo. This operation was repeated two
35 times and excessive anisole was distilled off under reduced pressure of a vacuum pump. To the residue, ethyl acetate was added. The precipitated solid was collected

by filtration to obtain the title compound (396 mg).
Furthermore, the filtrate was concentrated, and the
residue was purified by flash column chromatography
(silica gel, hexane/ethyl acetate=2/1 to 1/3) to obtain
5 the title compound (198 mg).

¹H-NMR (CDCl₃) δ2.63 (1H, dd, J=8.9, 14.2Hz), 3.26-3.41
(2H, m), 3.48 (1H, t, J=12.4Hz), 3.58-3.72 (1H, m), 3.85
(3H, s), 4.40 (1H, d, J=17.9Hz), 5.07 (1H, d, J=17.9Hz),
10 5.91 (1H, d, J=4.5Hz), 6.82 (1H, d, J=8.5Hz), 7.15 (1H,
d, J=2.8Hz), 7.19-7.36(4H, m), 7.46 (1H, dd, J=1.6,
8.1Hz)

MS: 437 (M+H)⁺

0223

Reference Example 46: tert-butyl 4-[(1R)-1-[(6R)-6-(5-
15 chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-
yl]carbonyl)amino]ethyl] benzoate (compound S46)

Step (1): Instead of the starting material, that is,
tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-
tartrate, of Reference Example 39, the compound S2 was
20 used, and instead of (6R)-2-chlorophenyl 6-(5-chloro-2-
methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-
diazepan-1-carboxylate, the compound S45 was used for a
similar reaction as in Reference Example 39 to obtain
tert-butyl 4-[(1R)-1-[(6R)-6-(5-chloro-2-
25 methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-
yl]carbonyl)amino] ethyl]benzoic acid (compound S46a).

Step (2): Instead of the starting material, that is,
the compound S21, of Reference Example 22, the compound
S46a was used for a similar reaction as in Reference
30 Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.53 (3H, d, J=6.9Hz), 1.58(9H, s), 2.59
(1H, dd, J=8.5, 13.9Hz), 3.20 (1H, dd, J=5.1, 13.9Hz),
3.33-3.49 (2H, m), 3.69-3.87(4H, m), 4.38 (1H, d,
J=17.9Hz), 5.05 (1H, dq, J=6.9, 6.9Hz), 5.92 (1H, d,
35 J=17.9Hz), 6.81 (1H, d, J=8.8Hz), 7.12 (1H, d, J=2.5Hz),
7.23 (1H, dd, J=2.5, 8.8Hz), 7.37 (2H, d, J=8.3Hz), 7.91
(1H, br.s), 7.96 (2H, d, J=8.3Hz), 9.37 (1H, d, J=6.9Hz)

MS: 490 (M-tBu)⁺

0224

Example 59: 4-{{(1R)-1-[[{((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino]ethyl} benzoic acid (compound 59)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S46 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-(3-fluorophenyl) hydroxylamine hydrochloride was used for a similar reaction as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ1.46 (3H, d, J=6.9Hz), 2.71 (1H, dd, J=8.9, 14.4Hz), 2.99 (1H, dd, J=4.5, 14.4Hz), 3.10-3.27 (2H, m), 3.80 (3H, s), 3.83-4.02 (1H, m), 4.67 (1H, d, J=16.6Hz), 4.82-5.06 (2H, m), 6.67-6.77 (1H, m), 6.81-6.92 (2H, m), 6.97-7.07 (2H, m), 7.21-7.33 (2H, m), 7.35 (1H, d, J=2.4Hz), 7.46 (2H, d, J=8.5Hz), 7.91 (2H, d, J=8.5Hz), 9.44 (1H, d, J=7.3Hz)

MS: 583 (M+H)⁺

0225

Reference Example 47: tert-butyl 4-{{{((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl)carbonyl)amino)methyl} benzoate (compound S47)

Step (1): Instead of the starting material, that is, the compound S11, of Reference Example 43, tert-butyl 4-(aminomethyl)benzoate was used, and instead of (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-carboxylate, the compound S45 was used for a similar reaction as in Reference Example 43 to obtain tert-butyl 4-{{{((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl)carbonyl)amino)methyl}benzoate (compound S47a).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S47a was used for a similar reaction as in Reference Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.59(9H, s), 2.58 (1H, dd, J=8.1, 14.0Hz),
3.17 (1H, dd, J=5.7, 14.0Hz), 3.28-3.54 (2H, m), 3.72-
3.90(4H, m), 4.45 (1H, d, J=17.9Hz), 4.48-4.64 (2H, m),
5.98 (1H, d, J=17.9Hz), 6.81 (1H, d, J=8.8Hz), 7.12 (1H,
5 d, J=2.5Hz), 7.22 (1H, dd, J=2.5, 8.8Hz), 7.36 (2H, d,
J=8.5Hz), 7.91 (1H, br.s), 7.96 (2H, d, J=8.5Hz), 9.34
(1H, t, J=5.5Hz)

MS: 476(M-tBu)⁺

0226

10 Example 60: 4-[[[(6R)-6-(5-chloro-2-methoxybenzyl)-3-
[(3-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-
yl]carbonyl)amino]methyl] benzoic acid (compound 60)

Instead of the starting material, that is, the
compound S22, of Example 1, the compound S47 was used,
15 and instead of the reaction agent, that is, O-isopropyl
hydroxylamine hydrochloride, O-(3-
fluorophenyl)hydroxylamine hydrochloride was used for a
similar reaction as in Example 1 to obtain the title
compound.

20 ¹H-NMR (DMSO-d₆) δ2.68 (1H, dd, J=8.1, 14.3Hz), 2.99 (1H,
dd, J=5.1, 14.3Hz), 3.10-3.25 (2H, m), 3.80 (3H, s), 3.94
(1H, m), 4.43-4.54 (2H, m), 4.71 (1H, d, J=16.4Hz), 4.97
(1H, d, J=16.4Hz), 6.66-6.77 (1H, m), 6.81-6.92 (2H, m),
6.97-7.08 (2H, m), 7.21-7.32 (2H, m), 7.35 (1H, d,
25 J=2.4Hz), 7.41 (2H, d, J=8.1Hz), 7.90 (2H, d, J=8.1Hz),
9.46 (1H, t, J=6.0Hz)

MS: 569(M+H)⁺

0227

30 Reference Example 48: 2,2,2-trichloroethyl 2-[(1R)-1-
([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(thioxo)-
1,4-diazepan-1-yl]carbonyl)amino)propyl]-1,3-oxazole-4-
carboxylate (compound S48)

Step (1): Instead of the starting material, that is,
tert-butyl 2-[(1R)-1-aminopropyl]-isonicotinate D-
35 tartrate, of Reference Example 39, the compound S15 was
used, and instead of (6R)-2-chlorophenyl 6-(5-chloro-2-
methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-

diazepan-1-carboxylate, the compound S45 was used for a similar reaction as in Reference Example 39 to obtain 2,2,2-trichloroethyl 2-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-

5 yl]carbonyl)amino)propyl]-1,3-oxazole-4-carboxylate (compound S48a).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S48a was used for a similar reaction as in Reference

10 Example 22 to obtain the title compound.

¹H-NMR (CDCl₃) δ1.00 (3H, t, J=7.5Hz), 1.92-2.13 (2H, m), 2.57 (1H, dd, J=8.5, 13.8Hz), 3.22 (1H, dd, J=4.9, 13.8Hz), 3.35-3.47 (2H, m), 3.77-3.86 (1H, m), 3.84 (3H, s), 4.43 (1H, d, J=17.9Hz), 4.94 (2H, s), 5.11 (1H, dt, J=7.3, 7.3Hz), 5.87 (1H, d, J=17.9Hz), 6.81 (1H, d, J=8.9Hz), 7.11 (1H, d, J=2.4Hz), 7.22 (2H, dd, J=2.4, 8.9Hz), 7.95 (1H, br.s), 8.26 (1H, s), 9.51 (1H, d, J=7.3Hz)

MS: 627(M+H)⁺

20 0228

Example 61: 2-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)propyl]-1,3-oxazole-4-carboxylic acid (compound 61)

25 Step (1): Instead of the starting material, that is, the compound S22, of Example 1, the compound S48 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar

30 reaction as in Example 1, Step (1) to obtain 2,2,2-trichloroethyl 2-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-5-oxo-2-(phenoxyimino)-1,4-diazepan-4-yl]carbonyl)amino)propyl]-1,3-oxazole-4-carboxylate (compound 61a).

35 Step (2): To the compound 61a obtained in Step (1) (90 mg) was dissolved in acetic acid (2 ml), zinc powder (180 mg) was added, and the mixture was stirred at room

temperature for 3 hours. The insolubles were filtered out, then the filtrate was concentrated, and the residue was purified by preparative thin layer chromatography (silica gel, chloroform/methanol/acetic acid=8/1/0.25) to obtain the title compound (17.4 mg).

¹H-NMR (DMSO-d₆) 80.78-0.89 (3H, m), 1.90 (2H, m), 2.65-2.76 (1H, m), 2.92-3.05 (1H, m), 3.15-3.22 (2H, m), 3.80 (3H, s), 3.92 (1H, m), 4.70 (1H, d, J=16.2Hz), 4.86-5.00 (2H, m), 6.82-6.96 (2H, m), 6.97-7.10 (3H, m), 7.19-7.32 (3H, m), 7.35 (1H, s), 8.00 (1H, br.s), 9.56 (1H, d, J=6.5Hz)

MS: 570 (M+H)⁺

0229

Reference Example 49: (6R)-6-(5-chloro-2-methoxybenzyl)-N-[(1R)-1-(3-tert-butoxyisooxazole-5-yl)propyl]-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepane-1-carboxamide (compound S49)

Step (1): To the compound S141C described in WO 06-059801A, that is, (6R)-2-chlorophenyl 6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepane-1-carboxylate (395 mg) in an N,N-dimethylformamide (0.64 ml) solution, the compound S94 described in WO 06-059801A, that is, 1-(3-tert-butoxyisoxazol-5-yl)propylamine hydrochloride (150 mg), 4-dimethylaminopyridin (78 mg) and N,N-diisopropylethylamine (0.111 ml) were added at 0°C, and the mixture was stirred at that temperature for 15 hours. To the reaction solution, water was added, and the mixture was extracted with ethyl acetate. The extract was combined, successively washed with saturated aqueous potassium hydrogensulfate solution, saturated aqueous sodium hydrogencarbonate solution, and brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=50/50 to 35/65) to obtain (6R)-6-(5-chloro-2-methoxybenzyl)-N-[(1R)-1-(3-tert-butoxyisooxazole-5-yl)propyl]-3,7-dioxo-4-(2,4,6-

trimethoxybenzyl)-1,4-diazepane-1-carboxamide (189 mg)
(compound S49a) and (6R)-6-(5-chloro-2-methoxybenzyl)-N-
[(1S)-1-(3-tert-butoxyisooxazol-5-yl)propyl]-3,7-dioxo-4-
(2,4,6-trimethoxybenzyl)-1,4-diazepane-1-carboxamide
5 (compound S49b).

Step (2): Instead of the starting material, that is,
the compound S21, of Reference Example 22, the compound
S49a was used for a similar reaction as in Reference
Example 22 to obtain the title compound.

10 0230

Example 62: (6R)-6-(5-chloro-2-methoxybenzyl)-3-
(ethoxyimino)-N-[(1R)-1-(3-hydroxyisooxazole -5-
yl)propyl]-7-oxo-1,4-diazepane-1-carboxamide (compound
62)

15 Instead of the starting material, that is, the
compound S23, of Example 10, the compound S49 was used
for a similar reaction as in Example 10 to obtain the
title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.12 (3H, t,
20 J=6.9Hz), 1.78-1.88 (2H, m), 2.61-2.71 (1H, m), 2.95 (1H,
dd, J=4.9, 14.2Hz), 3.00-3.19 (2H, m), 3.76-3.90 (6H, m),
4.52 (1H, d, J=16.2Hz), 4.72-4.88 (2H, m), 5.91 (1H, s),
6.34 (1H, br.s), 7.00 (1H, d, J=8.7Hz), 7.27 (1H, dd,
J=2.8, 8.7Hz), 7.34 (1H, d, J=2.8Hz), 9.41 (1H, d,
25 J=8.1Hz), 11.24 (1H, br.s)

MS: 494 (M+H)⁺

0231

Example 63: (6R)-6-(5-chloro-2-methoxybenzyl)-N-[(1R)-1-
(3-hydroxyisooxazole -5-yl)propyl]-7-oxo-3-
30 (phenoxyimino)-1,4-diazepane-1-carboxamide (compound 63)

Instead of the starting material, that is, the
compound S23, of Example 10, the compound S49 was used,
and instead of the reaction agent, that is, O-ethyl
hydroxylamine hydrochloride, O-phenyl hydroxylamine
35 hydrochloride was used for a similar reaction as in
Example 10 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.75-1.88 (2H,

m), 2.69 (1H, dd, J=9.6, 14.0Hz), 2.99 (1H, dd, J=4.7, 14.0Hz), 3.12-3.22 (2H, m), 3.81 (3H, s), 3.88-4.00 (1H, m), 4.70 (1H, d, J=16.2Hz), 4.85 (1H, dt, J=7.7, 7.7Hz), 4.94 (1H, d, J=16.2Hz), 5.93 (1H, s), 6.83-6.95 (2H, m),
5 6.99-7.09 (3H, m), 7.22-7.31 (3H, m), 7.35 (1H, d, J=2.4Hz), 9.41 (1H, d, J=7.7Hz), 11.24 (1H, s)

MS: 542 (M+H)⁺

0232

10 Reference Example 50: tert-butyl {4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)propyl] phenyl}acetate (compound S50)

Step (1): Instead of the starting material, that is, 1-(3-tert-butoxyisoxazol-5-yl)propylamine hydrochloride, of Reference Example 49, the compound S186 described in
15 WO 06-059801A, that is, tert-butyl [4-(1-aminopropyl)phenyl]acetate hydrochloride was used for a similar reaction as in Reference Example 49 to obtain tert-butyl {4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino) propyl]phenyl}acetate (compound S50a)
20 and tert-butyl {4-[(1S)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino) propyl]phenyl}acetate (compound S50b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S50a was used for a similar reaction as in Reference Example 22 to obtain the title compound.

MS: 754 (M+H)⁺

0233

30 Example 64: {4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]phenyl}acetic acid (compound 64)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S50 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar reaction as in
35

Example 23 to obtain the title compound.

¹H-NMR (CDCl₃) δ0.92 (3H, t, J=7.5Hz), 1.75-1.95 (2H, m),
2.64 (1H, dd, J=8.9, 13.8Hz), 3.19 (1H, dd, J=4.9,
13.8Hz), 3.26-3.38 (1H, m), 3.39-3.50 (1H, m), 3.64 (2H,
5 s), 3.67-3.78 (1H, m), 3.83 (3H, s), 4.20 (1H, d,
J=16.0Hz), 4.78 (1H, dt, J=7.5, 7.5Hz), 5.41 (1H, d,
J=16.0Hz), 5.53 (1H, br.s), 6.79 (1H, d, J=8.9Hz), 6.93
(1H, t, J=7.3Hz), 7.10-7.17 (3H, m), 7.17-7.34 (7H, m),
9.52 (1H, d, J=7.5Hz)

10 MS: 593(M+H)⁺

0234

Example 65: (4-((1R)-1-(((6R)-6-(5-chloro-2-
methoxybenzyl)-3-[(4-fluorophenoxy)imino]-7-oxo-1,4-
diazepan-1-yl)carbonyl)amino)propyl) phenyl)acetic acid
15 (compound 65)

Instead of the starting material, that is, the
compound S27, of Example 23, the compound S50 was used,
and instead of the reaction agent, that is, O-ethyl
hydroxylamine hydrochloride, O-(4-
20 fluorophenyl)hydroxylamine hydrochloride was used for a
similar reaction as in Example 23 to obtain the title
compound.

¹H-NMR (DMSO-d₆) δ0.82 (3H, t, J=7.3Hz), 1.67-1.88 (2H,
m), 2.71 (1H, dd, J=9.7, 14.7Hz), 2.98 (1H, dd, J=5.1,
25 14.7Hz), 3.10-3.26 (2H, m), 3.54 (2H, s), 3.80 (3H, s),
3.83-3.97 (1H, m), 4.56-4.74 (2H, m), 4.91 (1H, d,
J=16.6Hz), 6.94 (1H, s), 6.97-7.13 (5H, m), 7.18-7.25 (4H,
m), 7.28 (1H, dd, J=2.7, 8.7Hz), 7.34 (1H, d, J=2.7Hz),
9.47 (1H, d, J=7.7Hz), 12.26 (1H, br.s)

30 MS: 611(M+H)⁺

0235

Reference Example 51: tert-butyl 2-amino-4-((1R)-1-
(((6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-
(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-
35 yl)carbonyl)amino)pentyl]benzoate (compound S51)

Step (1): Instead of the starting material, that is,
1-(3-tert-butoxyisoxazol-5-yl)propylamine hydrochloride,

of Reference Example 49, the compound S14 was used for a similar reaction as in Reference Example 49 to obtain tert-butyl 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)pentyl]benzoate (compound S51a) and tert-butyl 2-amino-4-[(1S)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)pentyl]benzoate (compound S51b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S51a was used for a similar reaction as in Reference Example 22 to obtain the title compound.

0236

Example 66: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(methoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)pentyl]benzoic acid (compound 66)

Instead of the starting material, that is, the compound S27, of Example 23, the compound S51 was used, and instead of the reaction agent, that is, O-ethyl hydroxylamine hydrochloride, O-methyl hydroxylamine hydrochloride was used for a similar reaction as in Example 23 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=6.9Hz), 1.05-1.32 (4H, m), 1.55-1.83 (2H, m), 2.66 (1H, dd, J=8.5, 14.4Hz), 2.95 (1H, dd, J=5.3, 14.4Hz), 2.99-3.07 (1H, m), 3.08-3.18 (1H, m), 3.54 (3H, s), 3.79 (3H, s), 3.81-3.91 (1H, m), 4.49 (1H, d, J=16.2Hz), 4.60 (1H, dt, J=7.5, 7.5Hz), 4.78 (1H, d, J=16.2Hz), 6.26 (1H, br.s), 6.44 (1H, dd, J=1.4, 8.3Hz), 6.64 (1H, d, J=1.4Hz), 7.00 (1H, d, J=8.8Hz), 7.26 (1H, dd, J=2.7, 8.8Hz), 7.31 (1H, d, J=2.7Hz), 7.65 (1H, d, J=8.3Hz), 9.45 (1H, d, J=7.5Hz)

MS: 560 (M+H)⁺

0237

Reference Example 52: 2,2,2-trichloroethyl 2-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-

yl]carbonyl)amino)propyl]-1,3-thiazole-4-carboxylate
(compound S52)

Step (1): Instead of the starting material, that is,
the compound S4, of Reference Example 19, the compound
5 S16 was used for a similar reaction as in Reference
Example 19 to obtain 2,2,2-trichloroethyl (R)-2-(1-
isocyanatopropyl)thiazole 4-carboxylate (compound S52a).

Step (2): Instead of the reaction agent, that is,
the compound S19, of Reference Example 20, the compound
10 S52a was used for a similar procedure as in Reference
Examples 20 and 22 to obtain the title compound.

0238

Example 67: 2-[(1R)-1-([(6R)-6-(5-chloro-2-
methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-
15 yl]carbonyl)amino)propyl]-1,3-thiazole-4-carboxylic acid
(compound 67)

Step (1): Instead of the starting material, that is,
the compound S31, of Example 29, the compound S52 was
used, and instead of the reaction agent, that is, O-(4-
20 fluorophenyl)hydroxylamine hydrochloride, O-phenyl
hydroxylamine hydrochloride was used for a similar
procedure as in Example 29 to obtain 2,2,2-trichloroethyl
2-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-
(phenoxyimino)-1,4-diazepan-1-yl]carbonyl) amino)propyl]-
25 1,3-thiazole-4-carboxylate (compound 67a) as a crude
product.

Step (2): Instead of the starting material, that is,
the compound 61a, of Example 61, Step (2), the compound
67a crude product obtained at Step (1) was used for a
30 similar procedure as in Example 61, Step (2) to obtain
the title compound.

¹H-NMR (DMSO-d₆) δ0.89 (3H, br.s), 1.85-2.10 (2H, m),
2.65-2.77 (1H, m), 2.90-3.08 (1H, m), 3.13-3.26 (2H, m),
3.81 (3H, s), 3.85-4.00 (1H, m), 4.71 (1H, d, J=17.9Hz),
35 4.87-5.00 (1H, m), 5.06 (1H, br.s), 6.84-6.97 (2H, m),
6.98-7.10 (3H, m), 7.19-7.30 (3H, m), 7.36 (1H, br.s),
7.56 (1H, br.s), 9.60 (1H, d, J=8.1Hz)

MS: 586 (M+H)⁺

0239

Reference Example 53: (6R)-6-(5-chloro-2-methoxybenzyl)-
2-thioxo-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-5-one
5 (compound S53)

To the compound S140c described in WO 06-059801A,
that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-
trimethoxybenzyl)-1,4-diazepane-2,5-dione (2.2 g) in a
10 tetrahydrofuran (80 ml) solution, Belleau's reagent (1.5
g) was added under ice cooling, and the mixture was
stirred at that temperature for 3 hours. The reaction
solution was diluted with ethyl acetate, successively
washed with saturated aqueous sodium hydrogencarbonate
15 solution, water, and brine, dried over anhydrous sodium
sulfate, then concentrated. The residue was purified by
flash column chromatography (silica gel, hexane/ethyl
acetate=35/65 to 1/99) to obtain the title compound (1.69
g).

¹H-NMR (CDCl₃) δ2.23-2.34 (1H, m), 2.54 (1H, dd, J=11.0,
20 13.4Hz), 3.07-3.16 (2H, m), 3.59-3.69 (1H, m), 3.64 (6H,
s), 3.71 (3H, s), 3.84 (3H, s), 4.24 (1H, dd, J=7.9,
15.6Hz), 4.52 (1H, d, J=14.2Hz), 4.61 (1H, dd, J=3.4,
15.6Hz), 5.46 (1H, d, J=14.2Hz), 5.95 (2H, s), 6.11-6.18
(1H, m), 6.67 (1H, d, J=8.5Hz), 6.85 (1H, d, J=2.4Hz),
25 7.13 (1H, dd, J=2.4, 8.5Hz)

MS: 479 (M+H)⁺

0240

Reference Example 54: (6R)-6-(5-chloro-2-methoxybenzyl)-
2-(phenoxyimino)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-
30 5-one (compound S54)

To the compound S53 (0.5 g) in a tetrahydrofuran (5
ml) and methanol (10 ml) solution, O-phenyl hydroxylamine
hydrochloride (0.23 g), triethylamine (0.22 ml), and
mercury acetate (0.4 g) were successively added at 0°C,
35 and the mixture was stirred at room temperature for 15
hours. The insolubles were filtered out, and the filtrate
was concentrated. Then the residue was purified by flash

column chromatography (silica gel, hexane/ethyl acetate=1/1 to 1/3) to obtain the title compound (0.28 g).

¹H-NMR (CDCl₃) δ2.49 (1H, dd, J=10.1, 13.4Hz), 2.60-2.71 (1H, m), 2.89 (1H, dd, J=5.9, 14.4Hz), 3.08 (1H, dd, J=3.9, 13.4Hz), 3.18 (1H, dd, J=12.0, 14.4Hz), 3.68 (6H, s), 3.73 (3H, s), 3.81-3.85 (3H, m), 4.26 (1H, dd, J=5.1, 16.8Hz), 4.36 (1H, d, J=13.4Hz), 4.51 (1H, d, J=13.4Hz), 4.58 (1H, dd, J=7.1, 16.8Hz), 5.79-5.87 (1H, m), 6.03 (2H, s), 6.69 (1H, d, J=8.5Hz), 6.90 (1H, d, J=2.4Hz), 6.91-6.97 (1H, m), 7.13 (1H, dd, J=2.4, 8.5Hz), 7.16-7.21 (2H, m), 7.27-7.31 (2H, m)

MS: 554(M+H)⁺

0241

Example 68: 4-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound 68)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, the compound S54 was used for a similar procedure as in Reference Example 20 to obtain tert-butyl 4-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)propyl] benzoate (compound 68a).

Step (2): To the compound 68a obtained at Step (1) (100 mg), anisole (0.113 ml) and trifluoroacetic acid (2 ml) were added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, then the residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol/acetic acid=20/20/1/0.1) to obtain the title compound (57 mg).

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.5Hz), 1.74-1.86 (2H, m), 2.71 (1H, dd, J=8.8, 14.4Hz), 3.00 (1H, dd, J=4.7, 14.4Hz), 3.14-3.25 (2H, m), 3.81 (3H, s), 3.92 (1H, m), 4.65 (1H, d, J=16.2Hz), 4.77 (1H, dt, J=7.3, 7.3Hz), 4.90

(1H, d, J=16.2Hz), 6.86-6.94 (2H, m), 6.99-7.08 (3H, m), 7.21-7.30 (3H, m), 7.35 (1H, d, J=2.8Hz), 7.41 (2H, d, J=8.2Hz), 7.91 (2H, d, J=8.2Hz), 9.52 (1H, d, J=7.3Hz), 12.81 (1H, s)

5 MS: 579 (M+H)⁺

0242

Reference Example 55: tert-butyl 3-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)propyl] benzoate (compound S55)

10 Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione, of Reference Example 53, the compound S163 described in WO 06-059801A, that is, tert-butyl (3-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-15 3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoate was used for a similar procedure as in Reference Example 53 to obtain the title compound.

0243

20 Example 69: 3-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 69)

Step (1): To the compound S55 (100 mg) in a tetrahydrofuran (1 ml) and methanol (2 ml) solution, 25 hydroxylamine hydrochloride (18.6 mg), triethylamine (37 μ l), and mercury acetate (66 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 30 minutes. The reaction mixture was filtered, and the filtrate was concentrated to obtain 30 tert-butyl 3-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl} amino)propyl]benzoate (compound 69a) (18.4 mg).

Step (2): To the compound 69a obtained at Step (1) 35 (35 mg), 1M hydrochloric acid in acetic acid solution (1 ml) was added, and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted

with toluene and concentrated, then the residue was triturated with ethyl acetate-toluene to obtain the title compound (14.1 mg).

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J=7.3Hz), 1.71-1.91 (2H, m), 2.70 (1H, dd, J=9.5, 14.4Hz), 3.00 (1H, dd, J=4.7, 14.4Hz), 3.19-3.34 (2H, m), 3.80 (3H, s), 3.89-4.04 (1H, m), 4.68-4.87 (2H, m), 4.93 (1H, d, J=16.2Hz), 7.02 (1H, d, J=8.9Hz), 7.29 (1H, dd, J=2.8, 8.9Hz), 7.35 (1H, d, J=2.8Hz), 7.47 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz), 7.83 (1H, d, J=7.5Hz), 7.89 (1H, s), 9.38 (1H, d, J=7.3Hz), 13.01 (1H, br.s)
MS: 503(M+H)⁺

0244

Example 70: 3-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 70)

Instead of the reaction agent, that is, hydroxylamine hydrochloride, in Example 69, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 69 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.15 (3H, t, J=6.9Hz), 1.73-1.90 (2H, m), 2.70 (1H, dd, J=9.1, 14.2Hz), 2.98 (1H, dd, J=4.5, 14.2Hz), 3.13-3.29 (2H, m), 3.80 (3H, s), 3.82-3.94 (3H, m), 4.66 (1H, d, J=16.6Hz), 4.73 (1H, dt, J=7.3, 7.3Hz), 4.83 (1H, d, J=16.6Hz), 7.02 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.6, 8.9Hz), 7.34 (1H, d, J=2.6Hz), 7.47 (1H, t, J=7.7Hz), 7.57 (1H, d, J=7.7Hz), 7.83 (1H, d, J=7.7Hz), 7.88 (1H, s), 9.45 (1H, d, J=7.3Hz)

MS: 531(M+H)⁺

0245

Example 71: 3-[(1R)-1-({[(6R)-3-[(allyloxy)imino]-6-(5-chloro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 71)

Step (1): Instead of the reaction agent, that is, hydroxylamine hydrochloride, in Example 69, O-allyl hydroxylamine hydrochloride was used for a similar

procedure as in Example 69, Step (1) to obtain tert-butyl 3-[(1R)-1-([[(6R)-3-[(allyloxy)imino]-6-(5-chloro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoate (compound 71a).

5 Step (2): The compound 71a obtained at Step (1) was used for a similar procedure as in Example 69, Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.73-1.89 (2H, m), 2.69 (1H, dd, J=9.5, 14.2Hz), 2.97 (1H, dd, J=4.9, 14.2Hz), 3.12-3.22 (2H, m), 3.79 (3H, s), 3.82-3.91 (1H, m), 4.31 (2H, d, J=5.7Hz), 4.56 (1H, d, J=15.8Hz), 4.68-4.84 (2H, m), 5.16 (1H, d, J=10.6Hz), 5.23-5.34 (1H, m), 5.83-5.97 (1H, m), 7.01 (1H, d, J=8.7Hz), 7.27 (1H, dd, J=2.8, 8.7Hz), 7.33 (1H, d, J=2.8Hz), 7.47 (1H, t, J=7.5Hz), 7.56 (1H, d, J=7.5Hz), 7.83 (1H, d, J=7.5Hz), 7.87 (1H, s), 9.48 (1H, d, J=7.3Hz)

MS: 543(M+H)⁺

0246

20 Example 72: 3-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(propoxyimino)-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoic acid (compound 72)

25 Step (1): To the compound 71a obtained at Example 71, Step (1) (46.4 mg) in a tetrahydrofuran solution (1 ml), platinum oxide (7.5 mg) was added, and the mixture was stirred under a hydrogen atmosphere for 30 minutes. The insolubles were filtered out, the filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=3/2/ to 1/2) to obtain tert-butyl 3-[(1R)-1-([[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(propoxyimino)-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoate (compound 72a) (57 mg).

35 Step (2): To the compound 72a obtained at Step (1) (36.5 mg), 1M hydrochloric acid in acetic acid solution (1 ml) was added and the mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with toluene and concentrated, then the residue was

tritulated with ethyl acetate to obtain the title compound (22.8 mg).

¹H-NMR (DMSO-d₆) δ0.80-0.90 (6H, m), 1.55 (1H, dq, J=7.1, 7.1Hz), 1.74-1.90 (2H, m), 2.69 (1H, dd, J=9.1, 14.4Hz),
5 2.97 (1H, dd, J=4.7, 14.4Hz), 3.11-3.24 (1H, m), 3.75 (2H, t, J=7.1Hz), 3.79 (3H, s), 3.81-3.92 (1H, m), 4.59 (1H, d, J=16.2Hz), 4.70-4.83 (2H, m), 7.01 (1H, d, J=8.7Hz), 7.27 (1H, dd, J=2.8, 8.7Hz), 7.33 (1H, d, J=2.8Hz), 7.47 (1H, t, J=7.7Hz), 7.56 (1H, d, J=7.7Hz),
10 7.83 (1H, d, J=7.7Hz), 7.87 (1H, s), 9.47 (1H, d, J=7.3Hz)

MS: 545 (M+H)⁺

0247

Example 73: 3-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound 73)

Instead of the reaction agent, that is, hydroxylamine hydrochloride, in Example 69, O-phenyl hydroxylamine hydrochloride was used for a similar
20 procedure as in Example 69 to obtain the title compound.
¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.72-1.88 (2H, m), 2.72 (1H, dd, J=8.9, 14.2Hz), 3.00 (1H, dd, J=4.5, 14.2Hz), 3.14-3.25 (2H, m), 3.81 (3H, s), 3.85-3.96 (1H, m), 4.65 (1H, d, J=16.6Hz), 4.75 (1H, dt, J=7.3, 7.3Hz),
25 4.90 (1H, d, J=16.6Hz), 6.86-6.95 (2H, m), 6.99-7.08 (3H, m), 7.21-7.30 (3H, m), 7.35 (1H, d, J=2.8Hz), 7.47 (1H, t, J=7.7Hz), 7.57 (1H, d, J=7.7Hz), 7.84 (1H, d, J=7.7Hz), 7.88 (1H, s), 9.52 (1H, d, J=7.3Hz), 13.00 (1H, br.s)

30 MS: 579 (M+H)⁺

0248

Example 74: 3-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-3-(dimethylhydrazono)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)propyl] benzoic acid hydrochloride (compound 74)

Instead of the reaction agent, that is, hydroxylamine hydrochloride, in Example 69, N,N-

dimethylhydrazine was used for a similar procedure as in Example 69 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J=7.3Hz), 1.75-1.91 (2H, m), 2.70 (1H, dd, J=9.5, 14.2Hz), 3.00 (1H, dd, J=4.1, 14.2Hz), 3.24-3.47 (2H, m), 3.33(6H, s), 3.80 (3H, s), 3.90-4.01 (1H, m), 4.73 (1H, dt, J=7.3, 7.3Hz), 4.84-5.01 (2H, m), 7.04 (1H, d, J=8.7Hz), 7.29 (1H, dd, J=2.8, 8.7Hz), 7.35 (1H, d, J=2.8Hz), 7.47 (1H, t, J=7.7Hz), 7.59 (1H, d, J=7.7Hz), 7.83 (1H, dd, J=1.2, 7.7Hz), 7.90 (1H, s), 9.24-9.39 (2H, m), 10.98 (1H, br.s), 13.01 (1H, br.s)

MS: 530 (M+H)⁺

0249

Reference Example 56: tert-butyl 2-amino-4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl] benzoic acid (compound S56)

Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 53, the compound S164 described in WO 06-059801A, that is, tert-butyl 2-amino-4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoate, was used for a similar procedure as in Reference Example 53 to obtain the title compound.

0250

Example 75: 2-amino-4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound 75)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S56 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.15 (3H, t,

J=7.0Hz), 1.66-1.81 (2H, m), 2.63-2.73 (1H, m), 2.96 (1H, dd, J=4.7, 14.4Hz), 3.14-3.20 (2H, m), 3.79 (3H, s), 3.80-4.00 (2H, m), 4.68 (1H, dt, J=7.7, 7.7Hz), 4.62 (1H, d, J=17.1Hz), 4.83 (1H, d, J=17.1Hz), 6.45 (1H, dd, J=1.6, 8.5Hz), 6.65 (1H, d, J=1.6Hz), 7.01 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.6, 8.9Hz), 7.33 (1H, d, J=2.6Hz), 7.65 (1H, d, J=8.5Hz), 9.42 (1H, d, J=7.7Hz)
MS: 546(M+H)⁺

0251

10 Example 76: 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 76)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S56 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.65-2.85 (2H, m), 2.72 (1H, dd, J=9.1, 14.4Hz); 2.99 (1H, dd, J=4.7, 14.4Hz), 3.15-3.26 (2H, m), 3.81 (3H, s), 3.88-3.98 (1H, m), 4.56 (1H, dt, J=7.7, 7.7Hz), 4.67 (1H, d, J=16.2Hz), 4.93 (2H, d, J=16.2Hz), 6.48 (1H, dd, J=1.4, 8.3Hz), 6.68 (1H, d, J=1.4Hz), 6.85-7.40(8H, m), 7.67 (1H, d, J=8.3Hz), 9.47 (1H, d, J=7.7Hz)

MS: 594(M+H)⁺

0252

30 Example 77: 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid hydrochloride (compound 77)

Step (1): To the compound S56 (958 mg) in a tetrahydrofuran (10 ml) and methanol (20 ml) solution, O-phenyl hydroxylamine hydrochloride (365 mg), triethylamine (0.348 ml), and mercury acetate(638 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 2 hours. The

reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=9/1/ to 3/1) to obtain tert-butyl 2-amino-4-
5 [(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl)carbonyl)amino)propyl]benzoate (compound 77a) (523 mg).

Step (2): To the compound 77a (523 mg) obtained at
10 Step (1), 1M hydrochloric acid in acetic acid solution (18 ml) was added, and the mixture was stirred at room temperature for 2.5 hours. The reaction solution was concentrated, then the residue was diluted with ethyl acetate. To this solution, a 1M hydrochloric acid in
15 acetic acid solution was added and the mixture was stirred. Further, diethyl ether was added, and the precipitated solid was collected by filtration to obtain the title compound (410 mg).

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.5Hz), 1.63-1.84 (2H, m), 2.72 (1H, dd, J=8.9, 14.2Hz), 2.99 (1H, dd, J=4.9, 14.2Hz), 3.09-3.28 (2H, m), 3.81 (3H, s), 3.85-3.98 (1H, m), 4.56 (1H, dt, J=7.4, 7.4Hz), 4.67 (1H, d, J=16.4Hz), 4.93 (1H, d, J=16.4Hz), 6.48 (1H, dd, J=1.5, 8.4Hz), 6.69 (1H, d, J=1.5Hz), 6.86-6.92 (1H, m), 6.95 (1H, br.s),
20 7.02 (1H, d, J=8.5Hz), 7.03-7.11 (2H, m), 7.19-7.31 (3H, m), 7.35 (1H, d, J=2.8Hz), 7.67 (1H, d, J=8.4Hz), 9.46 (1H, d, J=7.4Hz)

MS: 594 (M+H)⁺

0253

30 Example 78: 2-amino-4-[(1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(2,2,2-trifluoroethoxy)imino]-1,4-diazepan-1-yl)carbonyl)amino] propyl}benzoic acid (compound 78)

Instead of the starting material, that is, the
35 compound S22, of Example 1, the compound S56 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-(2,2,2-trifluoroethyl)

hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.61-1.88 (2H, m), 2.67 (1H, dd, J=9.3, 14.3Hz), 2.96 (1H, dd, J=5.1, 14.3Hz), 3.02-3.22 (2H, m), 3.79 (3H, s), 3.81-3.91 (1H, m), 4.29-4.45 (2H, m), 4.47-4.60 (2H, m), 4.76 (1H, d, J=17.0Hz), 6.42 (1H, dd, J=1.3, 8.2Hz), 6.47 (1H, br.s), 6.63 (1H, d, J=1.3Hz), 7.00 (1H, d, J=8.7Hz), 7.27 (1H, dd, J=2.8, 8.7Hz), 7.32 (1H, d, J=2.8Hz), 7.64 (1H, d, J=8.2Hz), 9.45 (1H, d, J=7.3Hz)

MS: 600(M+H)⁺

0254

Reference Example 57: tert-butyl 2-amino-4-[(1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl] benzoate (compound S57)

Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 53, the compound S165 described in WO 06-059801A, that is, tert-butyl 2-amino-4-[(1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoate, was used for a similar procedure as in Reference Example 53 to obtain the title compound.

0255

Example 79: 2-amino-4-[(1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound 79)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.82 (3H, t, J=7.5Hz), 1.08 (3H, t, J=6.9Hz), 1.65-1.81 (2H, m), 2.61-2.71 (1H, m), 2.90-3.08

(3H, m), 3.79 (3H, s), 3.73-3.88 (3H, m), 4.44-4.59 (2H, m), 4.80 (1H, d, J=16.6Hz), 6.14 (1H, br.s), 6.43 (1H, d, J=8.3Hz), 6.62 (1H, s), 7.00 (1H, d, J=8.5Hz), 7.27 (1H, dd, J=2.8, 8.5Hz), 7.32 (1H, d, J=2.8Hz), 7.65 (1H, d, J=8.3Hz), 9.47 (1H, d, J=7.7Hz)

MS: 546(M+H)⁺

0256

Example 80: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 80)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-phenyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.4Hz), 1.67-1.79 (2H, m), 2.70 (1H, dd, J=9.5, 14.8Hz), 2.99 (1H, dd, J=4.7, 14.8Hz), 3.11-3.22 (2H, m), 3.81 (3H, s), 3.87-3.99 (1H, m), 4.57 (1H, dt, J=7.7, 7.7Hz), 4.69 (1H, d, J=16.6Hz), 4.96 (1H, d, J=16.6Hz), 6.45 (1H, d, J=8.1Hz), 6.64 (1H, s), 6.83-6.94 (2H, m), 6.99-7.05 (3H, m), 7.19-7.25 (2H, m), 7.28 (1H, dd, J=2.8, 8.5Hz), 7.35 (1H, d, J=2.8Hz), 7.65 (1H, d, J=8.1Hz), 9.45 (1H, d, J=7.7Hz)

MS: 594(M+H)⁺

0257

Example 81: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(isopropoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)propyl]benzoic acid (compound 81)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.11 (3H, d, J=6.0Hz), 1.12 (3H, d, J=6.0Hz), 1.67-1.81 (2H, m), 2.68 (1H, dd, J=9.2, 14.4Hz), 2.99 (1H, dd, J=4.7, 14.4Hz), 3.14-3.30 (2H, m), 3.80 (3H, s), 3.85-4.09 (2H, m), 4.58

(1H, dt, J=7.7, 7.7Hz), 4.76 (1H, d, J=17.5Hz), 4.96 (1H, d, J=17.5Hz), 6.47 (1H, dd, J=1.6, 8.1Hz), 6.67 (1H, dt, J=1.6Hz), 7.02 (1H, d, J=8.9Hz), 7.29 (1H, dd, J=2.4, 8.9Hz), 7.34 (1H, d, J=2.4Hz), 7.66 (1H, d, J=8.1Hz), 9.36 (1H, d, J=7.7Hz)

MS: 560(M+H)⁺

0258

Example 82: 2-amino-4-((1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-3-((cyclopentyloxy)imino)-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)propyl) benzoic acid (compound 82)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-cyclopentyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.5Hz), 1.38-1.83(8H, m), 2.68 (1H, dd, J=9.2, 14.4Hz), 2.98 (1H, dd, J=4.7, 14.4Hz), 3.15-3.30 (2H, m), 3.80 (3H, s), 3.85-3.99 (1H, m), 4.35-4.43 (1H, m), 4.58 (1H, dt, J=7.7, 7.7Hz), 4.75 (1H, d, J=17.0Hz), 4.96 (1H, d, J=17.0Hz), 6.48 (1H, dd, J=1.4, 8.1Hz), 6.69 (1H, d, J=1.4Hz), 7.03 (1H, d, J=8.9Hz), 7.29 (1H, dd, J=2.4, 8.9Hz), 7.34 (1H, d, J=2.4Hz), 7.66 (1H, d, J=8.1Hz), 9.36 (1H, d, J=7.7Hz)

MS: 586(M+H)⁺

0259

Example 83: 2-amino-4-((1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)propyl)benzoic acid (compound 83)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.79 (3H, t, J=7.3Hz), 1.61-1.78 (2H,

m), 2.60-2.71 (1H, m), 2.90-3.04 (2H, m), 3.09-3.20 (1H, m), 3.79 (3H, s), 3.80-3.92 (1H, m), 4.39-4.55 (2H, m), 4.85 (1H, d, J=16.2Hz), 5.96 (1H, br.s), 6.36-6.42 (1H, m), 6.58 (1H, br.s), 6.98-7.02 (1H, m), 7.23-7.29 (1H, m), 7.30-7.35 (1H, m), 7.62-7.70 (1H, m), 9.26 (1H, s), 9.42 (1H, d, J=8.1Hz)

MS: 518 (M+H)⁺

0260

Example 84: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(methoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)propyl]benzoic acid (compound 84)

Instead of the starting material, that is, the compound S22, of Example 1, the compound S57 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, O-methyl hydroxylamine hydrochloride was used for a similar procedure as in Example 1 to obtain the title compound.

¹H-NMR (CDCl₃) δ 0.82 (3H, t, J=7.3Hz), 1.65-1.79 (2H, m), 2.62-2.71 (1H, m), 2.91-3.08 (2H, m), 3.08-3.16 (1H, m), 3.54 (3H, s), 3.79 (3H, s), 3.75-3.87 (1H, m), 4.44-4.58 (2H, m), 4.79 (1H, d, J=16.6Hz), 6.20 (1H, br.s), 6.42 (1H, d, J=8.1Hz), 6.61 (1H, s), 7.00 (1H, d, J=8.9Hz), 7.27 (1H, dd, J=2.4, 8.9Hz), 7.31 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.1Hz), 9.45 (1H, d, J=7.7Hz)

MS: 532 (M+H)⁺

0261

Reference Example 58: tert-butyl 3-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl]amino)propyl] benzoate (compound S58)

Instead of the starting material, that is, the compound S20, of Reference Example 21, the compound S142B described in WO 06-059801A, that is, tert-butyl 3-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl]amino)propyl] benzoate was used in a similar procedure as Reference Examples 21 and 22 to obtain the title compound.

0262

Example 85: 3-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl)amino)propyl]benzoic acid (compound 85)

5 Instead of the starting material, that is, the compound S56, of Example 77, Step (1), the compound S58 was used for a similar procedure as in Example 77, Step (1) and Example 22 to obtain the title compound.

10 ¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.70-1.89 (2H, m), 2.71 (1H, dd, J=8.9, 14.4Hz), 3.01 (1H, dd, J=4.9, 14.4Hz), 3.09-3.25 (2H, m), 3.81 (3H, s), 3.86-3.96 (1H, m), 4.69 (1H, d, J=16.2Hz), 4.78 (1H, dt, J=7.7, 7.7Hz), 4.92 (1H, d, J=16.2Hz), 6.84-6.92 (2H, m), 6.98-7.05 (3H, m), 7.18-7.25 (2H, m), 7.28 (1H, dd, J=2.4, 8.7Hz), 7.35 (1H, d, J=2.4Hz), 7.46 (1H, t, J=7.7Hz), 7.57 (1H, d, J=7.7Hz), 7.82 (1H, d, J=7.7Hz), 7.88 (1H, s), 9.51 (1H, d, J=7.7Hz), 12.94 (1H, br.s)

15 MS: 579(M+H)⁺

0263

20 Reference Example 59: 5-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]thiophene-3-carboxylic acid (compound S59)

25 Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound 155 described in WO 06-059801A, that is, 5-[(1R)-1-([(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]-3-thiophenecarboxylic acid was used for a similar procedure as in Reference Example 22 to obtain the title compound (compound S59).

30 ¹H-NMR (CDCl₃) δ1.00 (3H, t, J=7.3Hz), 1.90-2.03 (2H, m), 2.58 (1H, dd, J=8.5, 14.1Hz), 3.20 (1H, dd, J=5.1, 14.1Hz), 3.30-3.54 (2H, m), 3.69-3.92 (4H, m), 4.43 (1H, d, J=17.9Hz), 5.08 (1H, dt, J=7.7, 7.7Hz), 5.94 (1H, d, J=17.9Hz), 6.81 (1H, d, J=8.8Hz), 7.11 (1H, d, J=2.5Hz), 7.22 (1H, dd, J=2.5, 8.8Hz), 7.40 (1H, d, J=1.0Hz), 8.03 (1H, br.s), 8.07 (1H, d, J=1.0Hz), 9.37 (1H, d, J=7.7Hz)

MS: 510 (M+H)⁺

0264

Example 86: 5-((1R)-1-(((6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3-fluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl)carbonyl)amino)propyl) thiophene-3-carboxylic acid (compound 86)

Instead of the starting material, that is, the compound S56, of Example 77, Step (1), the compound S59 was used for a similar procedure as in Example 77, Step (1) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.89 (3H, t, J=7.3Hz), 1.81-1.98 (2H, m), 2.70 (1H, dd, J=9.3, 14.4Hz), 2.98 (1H, dd, J=4.9, 14.4Hz), 3.10-3.24 (2H, m), 3.80 (3H, s), 3.84-4.03 (1H, m), 4.70 (1H, d, J=16.2Hz), 4.86-5.09 (2H, m), 6.65-6.78 (1H, m), 6.82-6.92 (2H, m), 6.96-7.07 (2H, m), 7.20-7.32 (3H, m), 7.34 (1H, d, J=2.4Hz), 8.09 (1H, s), 9.43 (1H, d, J=7.7Hz)

MS: 603 (M+H)⁺

0265

Example 87: 2-amino-4-((1R)-1-(((6S)-6-(5-chloro-2-methoxybenzyl)-3-methyl-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl)carbonyl)amino)propyl)benzoic acid (compound 87)

Step (1): To the compound S57 obtained at Reference Example 57 (100 mg) in a tetrahydrofuran (0.5 ml) and methanol (2 ml) solution, acetohydrazide (19 mg) and mercury acetate (66 mg) were successively added under ice cooling, and the mixture was stirred at that temperature for 40 minutes. The reaction mixture was diluted with ethyl acetate, and the insolubles were filtered out. Then the filtrate was washed with saturated aqueous potassium hydrogencarbonate and a brine. The organic layer was dried over anhydrous sodium sulfate, then concentrated to obtain tert-butyl 2-amino-4-((1R)-1-(((3-(2-acetylhydrazono)-(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl)carbonyl)amino) propyl)benzoic acid (compound 87a) (58.2 mg).

Step (2): The compound 87a obtained at Step (1) (58.2 mg) was dissolved in 1,4-dioxane (1.5 ml), and the mixture was stirred at 100°C for 30 minutes. The reaction solution was concentrated, then the residue was purified by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol=7/7/2) to obtain tert-butyl 2-amino-4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-methyl-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)propyl] benzoate (compound 87b) (33.4 mg).

Step (3): To the compound 87b obtained at Step (2) (33.4 mg), 1M hydrochloric acid in acetic acid solution was added, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, then the residue was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride solution and brine. The organic layer was dried over anhydrous sodium sulfate, then concentrated. The residue was triturated with ethyl acetate/hexane to obtain the title compound (17.3 mg).

¹H-NMR (DMSO-d₆) δ0.81 (3H, t, J=7.3Hz), 1.65-1.83 (2H, m), 2.21 (3H, s), 2.82 (1H, dd, J=7.7, 14.4Hz), 3.07 (1H, dd, J=5.9, 14.4Hz), 3.82 (3H, s), 3.85-4.00 (2H, m), 4.11-4.23 (1H, m), 4.56 (1H, dt, J=7.7, 7.7Hz), 4.94 (1H, d, J=16.6Hz), 5.76 (1H, d, J=16.6Hz), 6.42 (1H, dd, J=1.6, 8.5Hz), 6.62 (1H, d, J=1.6Hz), 7.02 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.4, 8.9Hz), 7.38 (1H, d, J=2.4Hz), 7.62 (1H, d, J=8.5Hz), 9.41 (1H, d, J=7.7Hz)
MS: 541(M+H)⁺

0266

Example 88: 2-amino-4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-hydroxy-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)propyl]benzoic acid (compound 88)

Instead of the reaction agent, that is, acetohydrazide, of Example 87, Step (1), methyl carbazate

was used for a similar procedure as in Example 87 to obtain the title compound.

¹H-NMR (DMSO-d₆) δ 0.83 (3H, t, J=7.3Hz), 1.67-1.80 (2H, m), 2.84 (1H, dd, J=9.5, 14.4Hz), 3.03 (1H, dd, J=4.7, 14.4Hz), 3.38-3.46 (2H, m), 3.81 (3H, s), 3.96-4.08 (1H, m), 4.57 (1H, dt, J=7.7, 7.7Hz), 4.80 (1H, d, J=16.8Hz), 5.38 (1H, d, J=16.8Hz), 6.45 (1H, dd, J=1.4, 8.3Hz), 6.60-6.65 (1H, m), 7.03 (1H, d, J=8.7Hz), 7.29 (1H, dd, J=2.6, 8.7Hz), 7.39 (1H, d, J=2.6Hz), 7.64 (1H, d, J=8.3Hz), 9.43 (1H, d, J=7.7Hz), 11.66 (1H, s)
MS: 543(M+H)⁺

0267

Example 89: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)propyl]benzoate hydrochloride (compound 89)

Step (1): Instead of the reaction agent, that is, acetohydrazide, of Example 87, Step (1), aminoacetaldehyde dimethylacetal was used for a similar procedure as in Example 87, Step (1) to obtain tert-butyl 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(2,2-dimethoxyethylimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)propyl] benzoic acid (compound 89a) as a crude product (94.2 mg).

Step (2): The compound 89a crude product obtained at Step (1) (94.2 mg) was dissolved in 1,4-dioxane (4 ml), pyridinium p-toluenesulfonate (5 mg) was added, and the mixture was stirred at 100°C for 2 hours. The reaction solution was concentrated, then the residue was purified by flash column chromatography (NH₂ silica gel, ethyl acetate/hexane=7/3 to 1/0) to obtain tert-butyl 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-6,7-dihydro-5H-imidazo[1,2-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)propyl]benzoate (compound 89b) (33.4 mg).

Step (3): The compound 89b obtained at Step (2) (27.2 mg) was dissolved in a 1M hydrochloric acid in

acetic acid solution, then the mixture was stirred at room temperature for 3 hours. The precipitated solid was collected by filtration to obtain the title compound (17.8 mg).

5 ¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.68-1.85 (2H, m), 2.79-2.89 (1H, m), 3.02-3.11 (1H, m), 3.83 (3H, s), 4.03-4.14 (1H, m), 4.21-4.32 (2H, m), 4.58 (2H, dt, J=7.7, 7.7Hz), 5.14 (1H, d, J=17.9Hz), 5.94 (1H, d, J=17.9Hz), 6.48 (1H, d, J=8.5Hz), 6.66 (1H, s), 7.05 (1H, d, J=8.7Hz), 7.30 (1H, dd, J=2.4, 8.7Hz), 7.40 (1H, d, J=2.4Hz), 7.56-7.67 (3H, m), 9.35 (1H, d, J=7.7Hz)
10 MS: 526(M+H)⁺
0268

Example 90: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)propyl]benzoic acid (compound 90)

Instead of the reaction agent, that is, acetohydrazide, of Example 87, Step (1), formhydrazide was used for a similar procedure as in Example 87 to obtain the title compound.

20 ¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.66-1.82 (2H, m), 2.83 (1H, dd, J=8.7, 14.4Hz), 3.04 (1H, dd, J=4.7, 14.4Hz), 3.82 (3H, s), 4.02-4.23 (3H, m), 4.57 (1H, dt, J=7.7, 7.7Hz), 4.96 (1H, d, J=16.8Hz), 5.84 (1H, d, J=16.8Hz), 6.43 (1H, dd, J=1.6, 8.5Hz), 6.62 (1H, d, J=1.6Hz), 7.03 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.4, 8.9Hz), 7.39 (1H, d, J=2.4Hz), 7.63 (1H, d, J=8.5Hz), 8.40 (1H, s), 9.43 (1H, d, J=7.7Hz)
25 MS: 527(M+H)⁺
30 0269

Reference Example 60: tert-butyl 4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]-2-nitrobenzoate (compound S60)

35 Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S162 described in WO 06-059801A, that is, tert-butyl 4-[(1R)-

1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl]amino)propyl]-2-nitrobenzoate was used for a similar reaction as in Reference Example 22 to obtain the title compound (compound S60).

5 ¹H-NMR (CDCl₃) δ0.95 (3H, t, J=7.3Hz), 1.56(9H, s), 1.79-1.94 (2H, m), 2.62 (1H, dd, J=8.5, 13.8Hz), 3.20 (1H, dd, J=5.3, 13.8Hz), 3.37-3.44 (2H, m), 3.74-3.82 (1H, m), 3.84 (3H, s), 4.44 (1H, d, J=17.9Hz), 4.86 (1H, dt, J=6.9, 6.9Hz), 5.87 (1H, d, J=17.9Hz), 6.82 (1H, d, J=8.9Hz), 7.14 (1H, d, J=2.8Hz), 7.23 (1H, dd, J=2.8, 8.9Hz), 7.57 (1H, dd, J=1.6, 7.7Hz), 7.69 (1H, d, J=7.7Hz), 7.73 (1H, d, J=1.6Hz), 7.82 (1H, br.s), 9.46 (1H, d, J=6.9Hz)
10 MS: 549(M-tBu)⁺

15 0270

Example 91: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(5H)-yl]carbonyl]amino)propyl]benzoic acid (compound 91)

20 Step (1): Instead of the starting material, that is, the compound S57, of Example 87, Step (1), the compound S60 was used, and instead of the reaction agent, that is, acetylhydrazine, methyl carbazate was used for a similar procedure as in Example 87, Step (1) and Step (2) to
25 obtain tert-butyl 4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-hydroxy-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl]carbonyl]amino)propyl]-2-nitrobenzoate (compound 91a).

Step (2): To the compound 91a obtained at Step (1)
30 (234 mg) in an N,N-dimethylformamide (2.5 ml) solution, potassium carbonate (62 mg) and ethyl iodide (0.15 ml) were added, and the mixture was stirred at room temperature for 3 hours. To the reaction solution, water was added and the mixture was extracted with ethyl
35 acetate. The extract was combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography

(silica gel, hexane/ethyl acetate=1/1 to 1/3) to obtain
tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-
[1,2,4]triazolo[4,3-a][1,4]diazepin-8(5H)-yl]carbonyl}
5 amino)propyl]-2-nitrobenzoate (compound 91b) (91 mg).

Step (3): To the compound 91b obtained at Step (2)
(91 mg), trifluoroacetic acid (2 ml) was added, and the
mixture was stirred at room temperature for 1.5 hours. To
the reaction solution, zinc powder (0.2 g) was added, and
10 the mixture was stirred for 2 hours. Then the insolubles
were filtered out. The filtrate was concentrated, then
the residue was purified by flash column chromatography
(silica gel, chloroform/ethyl acetate/methanol/acetic
acid=15/15/1/0.1) to obtain the title compound (45 mg).

15 ¹H-NMR (DMSO-d₆) δ0.82 (3H, t, J=7.3Hz), 1.12 (3H, t,
J=7.1Hz), 1.66-1.80 (2H, m), 2.82 (1H, dd, J=9.3,
14.6Hz), 3.03 (1H, dd, J=4.7, 14.6Hz), 3.40-3.48 (2H, m),
3.52-3.67 (2H, m), 3.80 (3H, s), 3.97-4.08 (1H, m), 4.56
(1H, dt, J=7.7, 7.7Hz), 4.80 (1H, d, J=16.2Hz), 5.40 (1H,
20 d, J=16.2Hz), 6.44 (1H, dd, J=1.6, 8.1Hz), 6.62 (1H, d,
J=1.6Hz), 7.02 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.8,
8.9Hz), 7.38 (1H, d, J=2.8Hz), 7.63 (1H, d, J=8.1Hz),
9.41 (1H, d, J=7.7Hz

MS: 571(M+H)⁺

25 0271

Example 92: 3-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-3-hydroxy-7-oxo-6,7-dihydro-5H-
[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-
yl]carbonyl}amino)propyl]benzoic acid (compound 92)

30 Step (1): Instead of the starting material, that is,
the compound S57, of Example 87, Step (1), the compound
S58 was used, and instead of the reaction agent, that is,
acetohydrazide, methyl carbazate was used for a similar
procedure as in Example 87, Step (1) and Step (2) to
35 obtain tert-butyl 3-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-3-hydroxy-7-oxo-6,7-dihydro-5H-
[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-

yl]carbonyl}amino)propyl]benzoate (compound 92a).

Step (2): Instead of the starting material of Example 87, Step (3), that is, the compound 87b, the compound 92a was used for a similar procedure as in Example 87, Step (3) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.3Hz), 1.70-1.90 (2H, m), 2.84 (1H, dd, J=9.3, 14.4Hz), 3.04 (1H, dd, J=4.7, 14.4Hz), 3.36-3.45 (2H, m), 3.80 (3H, s), 3.95-4.08 (1H, m), 4.70-4.86 (2H, m), 5.35 (1H, d, J=17.0Hz), 7.03 (1H, d, J=8.7Hz), 7.29 (1H, dd, J=2.4, 8.7Hz), 7.39 (1H, d, J=2.4Hz), 7.47 (1H, t, J=7.7Hz), 7.58 (1H, d, J=7.7Hz), 7.83 (1H, d, J=7.7Hz), 7.87 (1H, s), 9.48 (1H, d, J=7.7Hz), 11.63 (1H, s), 12.93 (1H, br.s)
MS: 528(M+H)⁺

0272

Example 93: 3-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(5H)-yl]carbonyl}amino)propyl]benzoic acid (compound 93)

Instead of the starting material, that is, the compound 91a, of Example 91, Step (2), the compound 92a was used for a similar procedure as in Example 91, Step (2) and Example 87, Step (3) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.12 (3H, t, J=7.1Hz), 1.70-1.90 (2H, m), 2.83 (1H, dd, J=9.3, 14.4Hz), 3.04 (1H, dd, J=4.7, 14.4Hz), 3.40-3.48 (2H, m), 3.51-3.66 (2H, m), 3.81 (3H, s), 3.96-4.10 (1H, m), 4.70-4.88 (2H, m), 5.37 (1H, d, J=17.0Hz), 7.03 (1H, d, J=8.7Hz), 7.29 (1H, dd, J=2.4, 8.7Hz), 7.40 (1H, d, J=2.4Hz), 7.46 (1H, t, J=7.7Hz), 7.57 (1H, d, J=7.7Hz), 7.83 (1H, dd, J=1.2, 7.7Hz), 7.87 (1H, s), 9.47 (1H, d, J=7.7Hz), 13.00 (1H, br.s)
MS: 556(M+H)⁺

0273

Example 94: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-6,7-dihydro-5H-

[1,2,4]oxadiazolo[4,3-a][1,4]diazepin-8(9H)-
yl]carbonyl)amino)propyl]benzoic acid (compound 94)

Step (1): Instead of the starting material, that is, the compound S56, of Example 77, the compound S60 was used, and instead of the reaction agent, that is, O-isopropyl hydroxylamine hydrochloride, hydroxylamine hydrochloride was used for a similar procedure as in Example 77, Step (1) to obtain tert-butyl 4-[(1R)-1-
5 {{{(6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)propyl]-2-nitrobenzoate (compound 94a).

Step (2): To the compound 94a obtained at Step (1) (167 mg) in a methylene chloride (5 ml) solution, triethylamine (0.154 ml) and phenyl chloroformate (42 µl)
15 were added at 0°C, and the mixture was stirred at 0°C for 2.5 hours. Furthermore, phenyl chloroformate (275 µl) was added, and the mixture was stirred at 0°C for 2 hours. Then, to the reaction solution, water was added, and the mixture was extracted with ethyl acetate. The extract was
20 combined, dried over sodium sulfate, then concentrated. The residue was dissolved in toluene (5 ml) and heated and refluxed for 18 hours. The solution was concentrated, then the residue was purified by preparative thin layer chromatography (silica gel, hexane/ethyl acetate=3/2) to
25 obtain tert-butyl 4-[(1R)-1-{{{(6S)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-6,7-dihydro-5H-[1,2,4]oxadiazolo[4,3-a][1,4]diazepin-8(9H)-
yl]carbonyl)amino)propyl]-2-nitrobenzoate (compound 94b) (69 mg).

Step (3): To the compound 94b obtained at Step (3) (68 mg), trifluoroacetic acid (2 ml) was added, and the mixture was stirred at room temperature for 1.5 hours. To the reaction solution, zinc powder (0.2 g) was added, the mixture was stirred for 2 hours, then the insolubles were
35 filtered out. The filtrate was concentrated, then the residue was purified by flash column chromatography

(silica gel, chloroform/ethyl acetate/methanol/acetic acid=15/15/1/0.1) to obtain the title compound (51 mg).

¹H-NMR (DMSO-d₆) δ0.83 (3H, t, J=7.3Hz), 1.67-1.84 (2H, m), 2.81 (2H, dd, J=9.1, 14.4Hz), 3.01 (2H, dd, J=4.5, 14.4Hz), 3.31-3.52 (2H, m), 3.81 (3H, s), 3.96-4.07 (1H, m), 4.56 (1H, dt, J=7.7, 7.7Hz), 4.85 (1H, d, J=16.6Hz), 5.51 (1H, d, J=16.6Hz), 6.44 (2H, dd, J=1.4, 8.1Hz), 6.59 (1H, d, J=1.4Hz), 6.63 (2H, br.s), 7.04 (2H, d, J=8.9Hz), 7.29 (2H, dd, J=2.8, 8.9Hz), 7.39 (2H, d, J=2.8Hz), 7.75 (2H, d, J=8.1Hz), 9.39 (1H, d, J=7.7Hz)

MS: 544 (M+H)⁺

0274

Example 95: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(5H)-yl]carbonyl)amino)pentyl]benzoic acid (compound 95)

Step (1): Instead of the starting material of Example 87, Step (1), that is, the compound S57, the compound S26 was used, and instead of the reaction agent, that is, acetylhydrazide, methyl carbazate was used for a similar procedure as in Example 87, Step (1) and Step (2) to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-hydroxy-7-oxo-6,7-dihydro-5H-[1,2,4]triazolo[4,3-a][1,4]diazepin-8(9H)-yl]carbonyl)amino)pentyl]-2-nitrobenzoate (compound 95a).

Step (2): Instead of the starting material of Example 91, Step (2), that is, the compound 91a, the compound 95a was used for a similar procedure as in Example 91, Step (2) and Step (3) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.84 (3H, t, J=7.1Hz), 1.13 (3H, t, J=7.1Hz), 1.19-1.34 (4H, m), 1.72 (2H, m), 2.79-2.87 (1H, m), 3.00-3.07 (1H, m), 3.41-3.48 (2H, m), 3.55-3.67 (2H, m), 3.81 (3H, s), 3.97-4.10 (1H, m), 4.61 (1H, dt, J=7.7, 7.7Hz), 4.81 (1H, d, J=16.6Hz), 5.40 (1H, d, J=16.6Hz), 6.42 (1H, d, J=8.1Hz), 6.59 (1H, s), 7.03 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.4, 8.9Hz), 7.39 (1H, d,

J=2.4Hz), 7.63 (1H, d, J=8.1Hz), 9.40 (1H, d, J=7.7Hz)
MS: 599(M+H)⁺

0275

5 Example 96: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-
[1,2,4]triazolo [4,3-a] [1,4]diazepin-8(5H)-
yl]carbonyl}amino)butyl]benzoic acid (compound 96)

10 Step (1): Instead of the reaction agent, that is, O-
ethyl hydroxylamine hydrochloride, of Example 12,
hydroxylamine hydrochloride was used for a similar
procedure as in Example 12, Step (1) to obtain tert-butyl
4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-
(hydroxyimino)-7-oxo-1,4-diazepan-1-
yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 96a).

15 Step (2): To the compound 96a obtained at Step (1)
(55 mg) in a methylene chloride (2 ml) solution,
triethylamine (37 µl) and bromoacetyl bromide (13 µl) was
added, and the mixture was stirred at room temperature
for 20 hours. To the reaction solution, saturated aqueous
20 ammonium chloride solution was added, and the mixture was
extracted with ethyl acetate. The extract was combined,
washed with brine, dried over sodium sulfate, then
concentrated. The residue was dissolved in acetonitrile
(2 ml), and sodium hydrogencarbonate (7.5 mg) and sodium
25 iodide (13 mg) were added to the solution. The mixture
was stirred at room temperature for 3 hours. To the
reaction solution, saturated aqueous ammonium chloride
solution was added, and the mixture was extracted with
ethyl acetate. The extract was combined, washed with
30 brine, dried over sodium sulfate, then concentrated. The
residue was purified by preparative thin layer
chromatography (silica gel, hexane/ethyl acetate=2/3) to
obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-
methoxybenzyl)-2-ethyl-3,7-dioxo-2,6,7,9-tetrahydro-3H-
35 [1,2,4]triazolo [4,3-a][1,4]diazepin-8(5H)-
yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 96b)
(12.5 mg).

Step (3): To the compound 96b obtained at Step (2) (20.8 mg), trifluoroacetic acid (1 ml) was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution, zinc powder (50 mg) was added, the mixture was stirred for 2 hours, then the insolubles were filtered out. The filtrate was concentrated, then the residue was purified by preparative thin layer chromatography (silica gel, chloroform/ethyl acetate/methanol/acetic acid=20/20/1/0.1) to obtain the title compound (7 mg).

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J=7.3Hz), 1.13-1.35 (2H, m), 1.59-1.78 (2H, m), 2.77 (1H, dd, J=8.7, 14.4Hz), 3.04 (1H, dd, J=4.3, 14.4Hz), 3.46-3.57 (1H, m), 3.80 (3H, s), 3.82-3.92 (2H, m), 4.27 (1H, d, J=15.4Hz), 4.32 (1H, d, J=15.4Hz), 4.64 (1H, dt, J=7.3, 7.3Hz), 4.80 (1H, d, J=16.6Hz), 5.13 (1H, d, J=16.6Hz), 6.45 (1H, d, J=8.1Hz), 6.64 (1H, s), 7.02 (1H, d, J=8.9Hz), 7.28 (1H, dd, J=2.4, 8.9Hz), 7.36 (1H, d, J=2.4Hz), 7.65 (1H, d, J=8.1Hz), 9.37 (1H, d, J=7.7Hz)

MS: 572 (M+H)⁺

0276

Example 97: 4-[(1R)-1-([(6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoic acid hydrochloride (compound 97)

Step (1): The compound S30 obtained by the method described in Reference Example 30 (10.13 g) was dissolved in tetrahydrofuran (200 ml) and methanol (200 ml), the mixture was cooled to 0°C, then hydroxylamine hydrochloride (1.32 g), triethylamine (2.65 ml), and mercury acetate (4.85 g) were successively added to the solution. The mixture was stirred at 0°C for 3 hours. The insolubles were filtered out, then ethyl acetate (200 ml), saturated aqueous ammonium chloride solution (150 ml), and water (50 ml) were added to the filtrate, and the solution was separated. The aqueous layer was

extracted with ethyl acetate (100 ml), the extract was combined with the organic layer, and the mixture was washed with an saturated aqueous sodium chloride solution. The obtained organic layer was dried over sodium sulfate, then concentrated to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 97a) as a crude product (10.7 g).

Step (2): To the compound 97a crude product obtained at Step (1) (10.7 g), a 4M hydrochloric acid in ethyl acetate solution (100 ml) was added, and the mixture was stirred at room temperature for 5.5 hours. The reaction mixture was concentrated until the crystals were precipitated, and the precipitated crystals were collected by filtration to obtain the title compound (1.74 g).

¹H-NMR (DMSO-d₆) δ 0.90 (3H, t, J = 7.3Hz), 1.20 -1.46 (2H, m), 1.66 -1.94 (2H, m), 2.70 (1H, dd, J = 8.9, 14.5Hz), 3.01 (1H, dd, J = 4.7, 14.5Hz), 3.19 -3.35 (2H, m), 3.81 (3H, s), 3.94 -4.06 (1H, m), 4.85 -4.94 (2H, m), 5.02 (1H, d, J = 17.5Hz), 7.03 (1H, d, J = 8.8Hz), 7.29 (1H, dd, J = 2.7, 8.8Hz), 7.36 (1H, d, J = 2.7Hz), 7.76 (1H, dd, J = 1.2, 7.7Hz), 7.84 (1H, d, J = 7.7Hz), 7.98 (1H, d, J = 1.2Hz), 9.32 (1H, d, J = 7.3Hz), 10.98 (1H, br.s), 13.80 (1H, br.s)

MS: 562(M+H)⁺

0277

Example 98: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid bis p-toluenesulfonate (compound 98)

Step (1): To the compound 97 (1.74 g) in an acetic acid (35 ml) suspension, zinc powder (3.5 g) was added, and the mixture was stirred at room temperature for 4 hours. The insolubles were filtered out and the filtrate was concentrated in vacuo. To the residue, acetic acid

(20 ml) was added, the mixture was stirred at 60°C for 1 hour, then the insolubles were filtered out. The filtrate was concentrated in vacuo, the residue was diluted with chloroform-methanol-acetic acid (5:1:0.1) (20 ml), and
5 the mixture was stirred at room temperature for 1 hour. The insolubles were collected by filtration, then ethyl acetate (105 ml), saturated aqueous ammonium chloride solution (105 ml), and water (53 ml) were added to the obtained crystals, and the mixture was stirred at room
10 temperature for 4 hours. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mlx2). The organic layer and the extract were combined, then the mixture was washed with brine, dried over sodium sulfate, then concentrated. The residue was purified by
15 flash column chromatography (silica gel, chloroform/ethyl acetate/methanol=50/50/5 to 50/50/10) to obtain 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(hydroxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]benzoic acid (compound 14) (1.07
20 g).

Step (2): To the compound 14 obtained at Step (1) (50 mg) in a 2-propanol (0.06 ml) and ethyl acetate (0.25 ml) solution, 1M p-toluenesulfonic acid in 2-propanol solution (188 µl) was added at 60°C, then the mixture was
25 slowly cooled down to 0°C. The precipitated crystals were collected by filtration to obtain the title compound (73 mg) as a colorless crystal.

¹H-NMR (DMSO-d₆) δ 0.88 (3H, t, J = 7.3Hz), 1.20 -1.38 (2H, m), 1.58 -1.80 (2H, m), 2.29 (6H, s), 2.70 (1H, dd, J =
30 9.1, 14.6Hz), 3.01 (1H, dd, J = 4.7, 14.6Hz), 3.23 -3.31 (1H, m), 3.38 (1H, dd, J = 12.8, 12.8Hz), 3.80 (3H, s), 3.99 -4.07 (1H, m), 4.65 (1H, dd, J = 7.2 Hz), 4.96 (1H, d, J = 17.0Hz), 5.01 (1H, d, J = 17.0Hz), 6.49 (1H, dd, J = 1.4, 8.1Hz), 6.66 (1H, d, J = 1.4Hz), 7.03 (1H, d, J =
35 8.8Hz); 7.08 -7.14 (4H, m), 7.29 (1H, dd, J = 2.7, 8.8Hz), 7.35 (1H, d, J = 2.7Hz), 7.46 -7.50 (4H, m), 7.66 (1H, d,

J = 8.1Hz), 9.08 (1H, br.s), 9.25 (1H, d, J = 7.2Hz),
11.02 (1H, br.s)

0278

5 Example 99: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-{{(2H₃)methoxy}imino}-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 99)

Step (1): To the compound 97a obtained by the method of Example 97, Step (1) (135 mg) in an N,N-dimethylformamide (0.5 ml) solution, iodo(2H₃)methane (32
10 µl) and a 60% dispersion of sodium hydride on mineral oil (6.9 mg) were successively added, and the mixture was stirred at room temperature for 45 minutes. To the reaction solution, saturated aqueous ammonium chloride solution (1 ml), water (2 ml), ethyl acetate (5 ml), and
15 hexane (5 ml) were successively added, then the layers were separated. The aqueous layer was extracted with a mixed solvent, hexane-ethyl acetate (1:1, 5 mlx2). The organic layer and the extract were combined, successively washed with water (2 ml), saturated aqueous sodium
20 thiosulfate solution (1 ml), and brine (2 ml), dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=3/1 to 2/3) to obtain tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-
25 {{(2H₃)methoxy}imino}-7-oxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound 99a).

Step (2): Instead of the starting material, that is, the compound 29a, of Example 29, Step (2), the compound
30 99a was used for a similar procedure as in Example 29, Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) 80.87 (3H, t, J = 7.3Hz), 1.14 -1.37 (2H, m), 1.57 -1.77 (2H, m), 2.67 (1H, dd, J = 8.7, 14.3Hz),
2.96 (1H, dd, J = 5.0, 14.3Hz), 3.07 (1H, dd, J = 12.4,
35 12.4Hz), 3.11 -3.20 (1H, m), 3.80 (3H, s), 3.81 -3.89 (1H, m), 4.52 (1H, d, J = 16.3Hz), 4.63 (1H, dt, J = 7.8,

7.8Hz), 4.82 (1H, d, J = 16.3Hz), 6.43 (1H, br.s), 6.45 (1H, dd, J = 1.5, 8.3Hz), 6.65 (1H, d, J = 1.5Hz), 7.00 (1H, d, J = 8.8Hz), 7.27 (1H, dd, J = 2.7, 8.8Hz), 7.31 (1H, d, J = 2.7Hz), 7.65 (1H, d, J = 8.3Hz), 9.43 (1H, d, J = 7.8Hz)

MS: 549(M+H)⁺

0279

Example 100: 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-

10 {[(²H₅)ethoxy]imino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 100)

Instead of the reaction agent, that is, iodo(²H₃)methane, of Example 99, Step (1), iodo(²H₅)ethane was used for a similar procedure as in Example 99, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J = 7.3Hz), 1.14 -1.36 (2H, m), 1.55 -1.79 (2H, m), 2.66 (1H, dd, J = 8.7, 14.4Hz), 2.96 (1H, dd, J = 5.1, 14.4Hz), 3.04 (1H, dd, J = 11.8, 11.8Hz), 3.09 -3.19 (1H, m), 3.80 (3H, s), 3.81 -3.90 (1H, m), 4.50 (1H, d, J = 16.3Hz), 4.63 (1H, dt, J = 7.7, 7.7Hz), 4.80 (1H, d, J = 16.3Hz), 6.31 (1H, br.s), 6.45 (1H, dd, J = 1.6, 8.3Hz), 6.65 (1H, d, J = 1.6Hz), 7.00 (1H, d, J = 8.8Hz), 7.26 (1H, dd, J = 2.7, 8.8Hz), 7.31 (1H, d, J = 2.7Hz), 7.66 (1H, d, J = 8.3Hz), 9.44 (1H, d, J = 7.7Hz)

MS: 565(M+H)⁺

0280

Reference Example 61: tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S61)

Step (1): To the compound S25a obtained by the method described at Reference Example 25, Step (1) (2.69 g) and the compound S140C described in WO 06-059801A, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (3.50 g) in an acetonitrile (60 ml) solution, potassium tert-butoxide in

a 1M tetrahydrofuran solution (0.46 ml) was added under ice cooling, and the mixture was stirred at that temperature for 30 minutes. To the reaction solution, saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The extract was combined, washed with brine, dried over anhydrous sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate=1/1 to 0/1) to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3,7-dioxo-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S61a) (2.49 g).

Step (2): To the compound S61a obtained at Step (1) (4.09 g) in a tetrahydrofuran (21 ml) solution, Lawesson's reagent was added under ice cooling (1.16 g), and the mixture was stirred at that temperature for 16 hours. To the reaction mixture, ethyl acetate and saturated aqueous sodium hydrogencarbonate solution were added, and the layers were separated. The organic layer was successively washed with a sodium hydrogencarbonate aqueous solution and brine, dried over sodium sulfate, then concentrated to obtain the title compound (4.28 g). ¹H-NMR (CDCl₃) δ 0.94 (3H, t, J = 7.3Hz), 1.29 -1.44 (2H, m), 1.56 (9H, s), 1.68 -1.89 (2H, m), 2.35 (1H, dd, J = 9.7, 13.8Hz), 3.11 (1H, dd, J = 4.5, 13.8Hz), 3.14 -3.27 (2H, m), 3.36 -3.47 (1H, m), 3.67 (6H, s), 3.75 (3H, s), 3.86 (3H, s), 4.84 (1H, d, J = 16.8Hz), 4.90 -4.99 (2H, m), 5.07 (1H, d, J = 14.2Hz), 5.57 (1H, d, J = 16.8Hz), 6.10 (2H, s), 6.75 (1H, d, J = 8.6Hz), 6.77 (1H, d, J = 2.7Hz), 7.19 (1H, dd, J= 2.7, 8.6Hz), 7.58 (1H, dd, J = 1.6, 8.1Hz), 7.68 (1H, d, J = 8.1Hz), 7.73 (1H, d, J = 1.6Hz), 9.55 (1H, d, J = 6.9Hz)

0281

Example 101: 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoic acid

hydrochloride (compound 101)

Step (1): The compound S61 obtained at Reference Example 61 (3.94 g) was dissolved in tetrahydrofuran (40 ml) and methanol (40 ml), the mixture was ice cooled, and
5 then O-ethyl hydroxylamine hydrochloride (1.21 g), triethylamine (1.72 ml), and mercury acetate (3.17 g) were successively added. The mixture was stirred at that temperature for 1 hour. Further, O-ethyl hydroxylamine hydrochloride (0.24 g), triethylamine (0.34 ml), and
10 mercury acetate (0.63 g) were successively added, and the mixture was stirred at 30 minutes. The insolubles were filtered out, then the filtrate was concentrated. To the residue, ethyl acetate (30 ml), saturated aqueous ammonium chloride solution (20 ml), and water (10 ml)
15 were added, and the layers were separated. The organic layer was successively washed with aqueous ammonium chloride solution and brine, dried over anhydrous sodium sulfate, then concentrated to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound 101a)
20 (4.19 g).

Step (2): To the compound 101a obtained at Step (1) (4.18 g), 4M hydrochloric acid in ethyl acetate solution
25 (40 ml) was added, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was ice cooled and stirred for 30 minutes, then diethyl ether (0.5 ml) was added to the solution. The mixture was further stirred for 4.5 hours. The precipitated crystals
30 were collected by filtration to obtain the title compound (2.78 g) as a colorless crystals.

¹H-NMR (DMSO-d₆) δ0.89 (3H, t, J = 7.3Hz), 1.16 (3H, t, J = 7.0Hz), 1.21 -1.41 (2H, m), 1.69 -1.90 (2H, m), 2.70 (1H, dd, J = 9.1, 14.3Hz), 3.00 (1H, dd, J = 4.5,
35 14.3Hz), 3.13 -3.34 (2H, m), 3.80 (3H, s), 3.85 -3.95 (1H, m), 3.87 (2H, q, J = 7.0Hz), 4.65 -4.90 (3H, m), 7.03 (1H, d, J = 8.8Hz), 7.29 (1H, dd, J = 2.7, 8.8Hz),

7.35 (1H, d, J = 2.7Hz), 7.74 (1H, dd, J = 1.6, 8.1Hz),
7.83 (1H, d, J = 8.1Hz), 7.98 (1H, d, J = 1.6Hz), 9.39
(1H, d, J = 6.9Hz)

0282

5 Example 102: 2-amino-4-[(1R)-1-([(6R)-6-(5-chloro-2-
methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-
yl]carbonyl)amino)butyl]benzoic acid (compound 102)

To the compound 101 (2.76 g) in an ethyl acetate (32
ml) and acetic acid (16 ml) suspension, zinc powder (2.88
10 g) was added under ice cooling, and the mixture was
stirred at that temperature for 20 minutes and at room
temperature for 4 hours. The reaction mixture was
filtered by a glass filter spread with Celite®, then the
residue was washed with ethyl acetate (50 ml). The
15 filtrate and the washings were combined, then the mixture
was successively washed with saturated aqueous ammonium
chloride solution and brine, dried over sodium sulfate,
then concentrated. The residue was purified by flash
column chromatography (silica gel, hexane/ethyl
20 acetate/methanol=6/6/1) to obtain the title compound (2.5
g).

¹H-NMR (CD₃OD) δ0.94 (3H, t, J = 7.3Hz), 1.18 (3H, t, J =
7.1Hz), 1.26 -1.46 (2H, m), 1.66 -1.84 (2H, m), 2.72 (1H,
dd, J = 8.3, 13.9Hz), 3.11 (1H, dd, J = 5.7, 13.9Hz),
25 3.18 (1H, dd, J = 12.2, 12.2Hz), 3.78 -3.87 (1H, m), 3.84
(3H, s), 3.88 -3.94 (2H, m), 4.36 (1H, d, J = 16.4Hz),
4.72 (1H, dt, J = 7.7, 7.7Hz), 4.99 (1H, d, J = 16.4Hz),
6.48 (1H, dd, J = 1.8, 8.5Hz), 6.64 (1H, d, J = 1.8Hz),
6.93 (1H, d, J = 8.5Hz), 7.20 (1H, dd, J = 2.6, 8.5Hz),
30 7.24 (1H, d, J = 2.6Hz), 7.76 (1H, d, J = 8.5Hz), 9.68
(1H, d, J = 7.7Hz)

0283

Example 103: 2-amino-4-[(1R)-1-([(6R)-6-(5-chloro-2-
methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-
35 yl]carbonyl)amino)butyl]benzoic acid di hydrochloride
(compound 103)

To the compound 102 (1.10 g) in an acetonitrile (44

ml) solution, a 4M hydrochloric acid in ethyl acetate solution (1.5 ml) was added, and the mixture was stirred at room temperature for 5 hours. The precipitated crystals were collected by filtration to obtain the title compound (1.03 g) as a colorless crystal.

¹H-NMR (DMSO-d₆) δ0.88 (3H, t, J = 7.0Hz), 1.17 (3H, t, J = 7.0Hz), 1.19 -1.36 (2H, m), 1.59 -1.80 (2H, m), 2.69 (1H, dd, J = 9.3, 14.2Hz), 2.98 (1H, dd, J = 4.5, 14.2Hz), 3.14 -3.37 (2H, m), 3.80 (3H, s), 3.87 -3.96 (1H, m), 3.88 (2H, q, J = 7.0Hz), 4.61 (1H, dt, J = 7.7, 7.7Hz), 4.74 (1H, d, J = 16.6Hz), 4.90 (1H, d, J = 16.6Hz), 6.49 (1H, dd, J = 1.6, 8.5Hz), 6.69 (1H, d, J = 1.6Hz), 7.02 (1H, d, J = 8.8Hz), 7.28 (1H, dd, J = 2.7, 8.8Hz), 7.34 (1H, d, J = 2.7Hz), 7.66 (1H, d, J = 8.5Hz), 9.34 (1H, d, J = 7.7Hz)

MS: 560 (M+H)⁺

0284

Reference Example 62: 6-methylene-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione (compound S62)

Step (1): To ethyl 2-(bromomethyl)acrylate (104.4 g) in an acetonitrile (900 ml) solution, di-tert-butyl imino dicarboxylate (122.4 g) and potassium carbonate was added, and the mixture was stirred at room temperature for 2 days. The reaction solution was concentrated in vacuo. To the residue, ethyl acetate (1.4 liter) and water (700 ml) were added, and the layers were separated. The organic layer was washed with water (350 ml), dried over sodium sulfate, then concentrated to obtain ethyl 2-[[di(tert-butoxycarbonyl)amino]methyl]acrylate (compound S62a) as a crude product (182.7 g).

Step (2): To the compound S62a crude product obtained at Step (1) (182.0 g) in a methanol (1 liter) solution, 2M aqueous sodium hydroxide solution (552 ml) was slowly added, then the mixture was stirred at room temperature for 1.5 hours. The reaction solution was concentrated in vacuo. To the residue, chloroform (500 ml) and water (500 ml) were added, then saturated aqueous

potassium hydrogensulfate solution (280 ml) was slowly added. To the aqueous mixture obtained, chloroform (300 ml) was added, and the layers were separated. The aqueous layer was extracted with chloroform (300 ml). The organic layer and the extract were combined, then the mixture was washed with brine (300 ml), dried over sodium sulfate, and concentrated to obtain 2-([di(tert-butoxycarbonyl)amino)methyl)acrylic acid (compound S62b) as a crude product (171.8 g).

Step (3): To the compound S62b crude product obtained at Step (2) (171.0 g) in a dichloromethane (1.2 liter) solution, glycine ethylester hydrochloride (94.4 g), 1-hydroxybenzotriazole (94.4 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (131.9 g), and triethylamine (94.2 ml) were successively added, and the mixture was stirred at room temperature for 4 hours. To the reaction mixture, water (1 liter), saturated aqueous sodium hydrogencarbonate solution (1.29 liter), and chloroform (1 liter) were successively added, and the layers were separated. The organic layer was successively washed with water (1 liter), aqueous potassium hydrogensulfate solution (1 liter), aqueous sodium hydrogencarbonate solution (1.6 liter), and brine (500 ml), dried over sodium sulfate, and then concentrated to obtain ethyl 2-(2-([di(tert-butoxycarbonyl)amino)methyl)acrylamide) acetate (compound S62c) as a crude product (108.32 g).

Step (4): To the compound S62c crude product obtained at Step (3) (118.0 g) in an ethanol (1015 ml) solution, methanesulfonic acid (60 ml) was added, and the mixture was stirred at 40°C for 17 hours. The reaction solution was ice cooled, ethanol (252 ml) was added, and further triethylamine (129 ml) was slowly added. Further, to the reaction solution, 2,4,6-trimethoxybenzaldehyde (52.7 g) and sodium triacetoxymethylborohydride (113.3 g) were successively added under ice cooling, then the mixture was stirred at 40°C for 1.5 hours. The reaction solution

was concentrated in vacuo. To the residue, chloroform (1.4 liter) and water (500 ml) was added, further saturated aqueous sodium hydrogencarbonate solution (1.2 liter) was slowly added. The layers were separated, then
5 the organic layer was successively washed with aqueous sodium hydrogencarbonate solution (600 ml) and brine (500 ml), dried over sodium sulfate, then concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate=1/0 to 1/1) to obtain ethyl 2-
10 (2-[(2,4,6-trimethoxybenzyl)amino]methyl)acrylamide acetate (compound S62d) (50.4 g) as a light yellow crystals.

¹H-NMR (CDCl₃) δ 1.27 (3H, t, J = 7.1Hz), 3.42 (2H, br.s), 3.79 (2H, s), 3.79 (6H, s), 3.82 (3H, s), 4.09 (2H, d, J = 5.3Hz), 4.19 (2H, q, J = 7.1Hz), 5.34 -5.37 (1H, m),
15 6.13 (2H, s), 6.15 (1H, d, J= 2.0Hz), 9.96 (1H, t, J = 5.3Hz)

Step (5): To the compound S62d obtained at Step (4) (50.0 g) in a methanol (164 ml) solution, 4 M aqueous
20 sodium hydroxide solution (40.5 ml) was added, and the mixture was stirred at room temperature for 14 hours. The reaction solution was ice cooled, saturated aqueous potassium hydrogensulfate solution was slowly added to adjust pH to 4.9, then the mixture was concentrated in
25 vacuo. To the residue, acetonitrile (200 ml) was added and concentrated in vacuo. The operation was repeated four times. To the residue thus obtained, acetonitrile (1 liter), 1-hydroxybenztriazole (18.4 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
30 (26.1 g) were successively added, and the mixture was stirred at room temperature for 2 days. The reaction solution was concentrated in vacuo, and chloroform (1 liter) and water (470 ml) were added to the residue, then saturated aqueous sodium hydrogencarbonate solution (600
35 ml) was slowly added. The layers were separated, then the organic layer was washed with brine, and then concentrated. The residue was purified by column

chromatography (silica gel, chloroform/methanol=96/4 to 95/5) to obtain the title compound (28.0 g) as a light yellow crystals.

¹H-NMR (DMSO-d₆) δ 3.72 (6H, s), 3.78 (3H, s), 3.85 (2H, d, J = 5.2Hz), 3.98 (2H, s), 4.43 (2H, s), 4.87 (1H, m), 5.84 (1H, d, J = 2.4Hz), 6.20 (2H, s), 8.02 (1H, t, J = 5.2Hz)

MS: 321(M+H)⁺

0285

10 Reference Example 63: 6-[4-chloro-3-(trifluoromethyl)benzyl]-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione (compound S63)

To a mixture of the compound S62 (250 mg), hydroxy(cyclooctadiene) rhodium (I) dimer (18 mg), 4-chloro-3-(trifluoromethyl)phenylboronic acid (262 mg), 15 and powdered potassium hydroxide (44 mg), a 1,2-dimethoxymethane-water (6:1) mixed solvent (2.1 ml) was added in an argon atmosphere, and the mixture was stirred at room temperature for 16 hours. The insolubles were 20 filtered out, and the filtrate was diluted with ethyl acetate, then this was successively washed with water, saturated aqueous sodium hydrogencarbonate solution, and brine. The organic layer was dried over sodium sulfate, and then concentrated. The residue was purified by flash 25 column chromatography (silica gel, hexane/ethyl acetate/methanol=4/4/1) to obtain the title compound (94.2 mg) as a light yellow crystals.

¹H-NMR (CDCl₃) δ 2.23 -2.42 (1H, m), 2.50 (1H, dd, J = 10.3, 13.9Hz), 2.94 (1H, dd, J = 4.9, 15.3Hz), 3.22 (1H, dd, J = 3.7, 13.9Hz), 3.41 (1H, dd, J = 12.4, 15.3Hz), 3.63 (6H, s), 3.70 (1H, dd, J = 7.7, 15.4Hz), 3.84 (3H, s), 4.22 (1H, d, J = 13.8Hz), 4.23 (1H, dd, J = 3.2, 15.4Hz), 4.87 (1H, d, J = 13.8Hz), 5.98 (2H, s), 6.03-6.15 (1H, m), 7.03 (1H, dd, J = 1.9, 8.2Hz), 7.32 (1H, d, J = 1.9Hz), 7.35 (1H, d, J = 8.2Hz)

MS: 501(M+H)⁺

0286

Reference Example 64: 6-(4,5-difluoro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione (compound S64)

Instead of the reaction agent, that is, 4-chloro-3-(trifluoromethyl)phenylboronic acid, of Reference Example 63, 4,5-difluoro-2-methoxyphenylboronic acid was used for a similar procedure as in Reference Example 63 to obtain the title compound.

¹H-NMR (CDCl₃) δ 2.31 -2.42 (1H, m), 2.50 (1H, dd, J = 10.6, 13.8Hz), 2.91 (1H, dd, J = 4.7, 15.3Hz), 3.07 (1H, dd, J = 3.7, 13.8Hz), 3.37 (1H, dd, J = 12.6, 15.3Hz), 3.66 (6H, s), 3.67 -3.76 (1H, m), 3.71 (3H, s), 3.83 (3H, s), 4.21 -4.26 (2H, m), 4.83 (1H, d, J = 13.8Hz), 5.94 -6.00 (1H, m), 5.99 (2H, s), 6.59 (1H, dd, J = 6.9, 12.2Hz), 6.68 (1H, dd, J = 8.9, 10.6Hz)

MS: 465(M+H)⁺

0287

Reference Example 65: 6-(5-fluoro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione (compound S65)

Instead of the reaction agent, that is, 4-chloro-3-(trifluoromethyl)phenylboronic acid, of Reference Example 63, 5-fluoro-2-methoxyphenylboronic acid was used for a similar procedure as in Reference Example 63 to obtain the title compound.

¹H-NMR (CDCl₃) δ 2.36 -2.49 (1H, m), 2.58 (1H, dd, J = 10.8, 13.8Hz), 2.95 (1H, dd, J = 4.9, 15.4Hz), 3.08 (1H, dd, J = 3.7, 13.8Hz), 3.38 (1H, dd, J = 12.6, 15.4Hz), 3.64 (6H, s), 3.67 -3.75 (1H, m), 3.72 (3H, s), 3.83 (3H, s), 4.25 (1H, dd, J = 4.1, 15.4Hz), 4.26 (1H, d, J = 13.4Hz), 4.82 (1H, d, J = 13.4Hz), 5.90 -6.05 (1H, m), 5.99 (2H, s), 6.59 (1H, dd, J = 2.9, 8.9Hz), 6.70 (1H, dd, J = 4.5, 8.9Hz), 6.87 (1H, ddd, J = 2.9, 8.9, 8.9Hz)

MS: 447(M+H)⁺

0288

Reference Example 66: 6-(5-chloro-2-fluorobenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione

(compound S66)

Instead of the reaction agent, that is, 4-chloro-3-(trifluoromethyl)phenylboronic acid, of Reference Example 63, 5-chloro-2-fluorophenylboronic acid was used for a similar procedure as in Reference Example 63 to obtain the title compound.

¹H-NMR (CDCl₃) δ 2.30 -2.45 (1H, m), 2.58 (1H, dd, J = 10.3, 14.0Hz), 3.00 (1H, dd, J = 4.9, 15.4Hz), 3.05 -3.14 (1H, m), 3.43 (1H, dd, J = 12.6, 15.4Hz), 3.66 (6H, s), 3.72 (1H, d, J = 7.9, 15.8Hz), 3.84 (3H, s), 4.25 (1H, dd, J = 3.7, 15.8Hz), 4.27 (1H, d, J = 13.8Hz), 4.86 (1H, d, J = 13.8Hz), 5.95 -6.01 (1H, m), 6.00 (2H, s), 6.91 (1H, dd, J = 8.8, 8.8Hz), 6.97 (1H, dd, J = 2.4, 6.5Hz), 7.16 (1H, ddd, J = 2.4, 4.3, 8.8Hz)

MS: 451 (M+H)⁺

0289

Reference Example 67: (6R)-6-(5-chloro-2-hydroxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione
(compound S67)

Step (1): To (2R)-3-[(tert-butoxycarbonyl)amino]-2-(5-chloro-2-methoxybenzyl)propanoic acid (20.15 g), which can be obtained by the method described in WO 06-059801A, Reference Example 151, Step (1) and Step (2), in a dichloromethane (180 ml) solution, boron tribromide (44.78 g) in a dichloromethane (150 ml) solution was slowly added dropwise under ice cooling, then the mixture was stirred at room temperature for 3 hours. The reaction solution was again ice cooled, then 2M aqueous sodium hydroxide solution (358 ml) was slowly added dropwise. The layers were separated, and the aqueous layer was washed with dichloromethane (90 ml). To the aqueous layer, tetrahydrofuran (200 ml) and di-tert-butyl-dicarbonate (28.65 g) were added, and the mixture was stirred at room temperature for 16 hours. To the reaction solution, N,N-dimethylethylenediamine (0.72 g) was added, and the mixture was stirred at 35°C for 2 hours, then saturated aqueous potassium hydrogensulfate solution (270

ml) was slowly added dropwise. To the mixture, ethyl acetate (225 ml) was added, and the layers were separated, then the aqueous layer was extracted with ethyl acetate (50 ml). The organic layer and the extract
5 were combined and successively washed with water (90 ml) and brine (90 ml), dried over magnesium sulfate, then concentrated to obtain (2R)-3-[(tert-butoxycarbonyl)amino]-2-[2-(tert-butoxycarbonyl)oxy-5-chlorobenzyl]propanoic acid (compound S67a) as a crude
10 product (19.4 g).

Step (2): To the compound S67a crude product obtained at Step (1) (19.4 g) in a dichloromethane (180 ml) solution, glycine ethylester hydrochloride (7.54 g), triethylamine (7.53 ml), 1-hydroxybenzotriazole (6.09 g),
15 and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12.95 g) were successively added, and the mixture was stirred at 35°C for 1.5 hours. The reaction solution was concentrated, the residue was diluted with ethyl acetate (250 ml) and saturated aqueous sodium
20 hydrogencarbonate solution (100 ml), and the layers were separated. The organic layer was successively washed with water (100 ml), saturated aqueous potassium hydrogensulfate (100 ml), brine (90 ml), saturated aqueous sodium hydrogencarbonate solution (50 ml), and
25 brine (50 ml), dried over magnesium sulfate, then was concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate=4/1 to 1/1) to obtain ethyl (2R)-2-{3-[(tert-butoxycarbonyl)amino]-2-[5-chloro-2-(tert-butoxycarbonyl)oxybenzyl] propanamide} acetate (15.7 g)
30 (compound S67b) as a colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ 1.26 (3H, t, $J = 7.1\text{Hz}$), 1.42 (9H, s), 1.57 (9H, s), 2.60 -3.03 (3H, m), 3.24 -3.47 (2H, m), 3.70 -3.82 (1H, m), 3.99 (1H, dd, $J = 5.7, 18.3\text{Hz}$), 4.18
35 (2H, q, $J = 7.1\text{Hz}$), 5.16 (1H, br.s), 6.13 (1H, br.s), 6.98 -7.08 (1H, m), 7.15 -7.24 (2H, m)

MS: 415 ($\text{M-COO}^t\text{Bu}$) $^+$

Step (3): To the compound S67b obtained at Step (2) (15.7 g) in an ethanol (160 ml) solution, methanesulfonic acid (9.6 ml) was added, and the mixture was stirred at 40°C for 6 hours. The reaction mixture was allowed to cool down to room temperature, then was ice cooled, and triethylamine (15.2 g) was added dropwise. To the reaction solution, 2,4,6-trimethoxybenzaldehyde (5.99 g) and sodium triacetoxyborohydride (9.71 g) were successively added under ice cooling, and the mixture was stirred at room temperature for 3.5 hours. The reaction solution was concentrated, ethyl acetate (240 ml) and saturated aqueous sodium hydrogencarbonate solution (136 ml) were added to the residue, and the layers were separated. The organic layer was washed with brine, then dried over magnesium sulfate, and concentrated to obtain ethyl (2R)-2-[(5-chloro-hydroxybenzyl)-3-[(2,4,6-trimethoxybenzyl) amino]propanamide}acetate (compound S67c) as a crude product (16.6 g) as a yellow crystals.

Step (4): To the compound S67c crude product obtained at Step (3) (15.6 g), 2M aqueous sodium hydroxide solution (38.5 ml) and water (38.5 ml) were added, and the mixture was stirred at room temperature for 4 hours. To the reaction solution, 2M hydrochloric acid (36.5 ml) was added, and the precipitated crystals were collected by filtration and dried to obtain (2R)-2-[(5-chloro-hydroxybenzyl)-3-[(2,4,6-trimethoxybenzyl)amino] propanamide}acetic acid (compound S67d) as a crude product (13.5 g) as a yellow solid.

Step (5): To a mixture of the compound S67d crude product obtained at Step (4) (13.5 g), 1-hydroxybenztriazole (4.7 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.33 g), N,N-dimethylformamide (350 ml) and acetonitrile (350 ml) were successively added, and the mixture was stirred at 40°C for 21 hours. The reaction solution was concentrated. To the residue, ethyl acetate (450 ml) and water (300 ml) were added, and the layers were separated.

The organic layer was successively washed with aqueous potassium hydrogensulfate solution (150 ml), water (150 ml), saturated aqueous sodium hydrogencarbonate solution (150 ml), and brine (150 ml), dried over magnesium sulfate, then concentrated. The residue was purified by column chromatography (silica gel, dichloromethane/methanol=1/0 to 14/1) to obtain the title compound (5.8 g).

¹H-NMR (CDCl₃) δ 2.29 (1H, dd, J = 4.7, 14.4Hz), 2.33 - 2.42 (1H, m), 2.86 -2.97 (1H, m), 3.28 (1H, dd, J = 4.5, 15.4Hz), 3.53 (1H, dd, J = 11.8, 15.4Hz), 3.70 -3.88 (1H, m), 3.73 (6H, s), 3.78 (3H, s), 4.24 (1H, dd, J = 3.7, 15.8Hz), 4.50 (1H, d, J = 13.8Hz), 4.79 (1H, d, J = 13.8Hz), 6.00 (2H, s), 6.39 (1H, br.s), 6.75 (1H, d, J = 2.6Hz), 6.79 (1H, d, J = 8.7Hz), 7.07 (1H, dd, J = 2.6, 8.7Hz)

MS: 449(M+H)⁺

0290

Reference Example 68: (6R)-6-(5-chloro-2-cyanobenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (compound S68)

Step (1): To the compound S67 obtained in Reference Example 67 (100 mg) in an N,N-dimethylformamide (1 ml) solution, p-nitrophenyl trifluoromethanesulfonic acid (66 mg) and potassium carbonate (68 mg) were successively added, and the mixture was stirred at room temperature for 2 hours. The reaction solution was diluted with toluene and was successively washed with water, saturated aqueous sodium hydrogencarbonate solution, water, and brine. The organic layer was dried over sodium sulfate, then concentrated to obtain (6R)-6-[5-chloro-2-(trifluoromethanesulfonyl)oxybenzyl]-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (compound S68a) as a crude product (135 mg).

Step (2): To a mixture of the compound S68a crude product obtained in Step (1) (135 mg) and zinc cyanide (47 mg), N,N-dimethylformamide (1 ml) was added. After

the inside of the reaction system was made an argon atmosphere, tetrakis(triphenylphosphine) palladium (26 mg) was added, and the mixture was stirred at 100°C for 1 hour. The reaction solution was diluted with toluene, then the insolubles were filtered out. The filtrate was successively washed with saturated aqueous sodium hydrogencarbonate solution, water, and brine, dried over sodium sulfate, then concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate/methanol=6/6/1) to obtain the title compound (17 mg).

¹H-NMR (CDCl₃) δ 2.39 -2.47 (1H, m), 2.77 (1H, dd, J = 9.8, 14.1Hz), 3.03 (1H, dd, J = 4.7, 15.3Hz), 3.32 (1H, dd, J = 5.3, 14.1Hz), 3.52 (1H, dd, J = 12.3, 15.3Hz), 3.68 (6H, s), 3.74 (1H, d, J = 7.8, 15.7Hz), 3.84 (3H, s), 4.22 -4.66 (1H, m), 4.25 (1H, d, J = 13.7Hz), 4.88 (1H, d, J = 13.7Hz), 5.95 -6.01 (1H, m), 6.00 (2H, s), 7.13 (1H, d, J = 2.0Hz), 7.31 (1H, dd, J = 2.0, 8.3Hz), 7.49 (1H, d, J = 8.3Hz)

MS: 458 (M+H)⁺

0291

Reference Example 69: (6S)-6-(5-chloro-2-hydroxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione (compound S69)

Instead of the starting material, that is, (2R)-3-[(tert-butoxycarbonyl)amino]-2-(5-chloro-2-methoxybenzyl)propanoic acid, of Reference Example 67, Step (1), (2S)-3-[(tert-butoxycarbonyl)amino]-2-(5-chloro-2-methoxybenzyl)propanoic acid, which can be obtained by the method described in WO 06-059801A, Reference Example 152, Step (1) and Step (2), was used for a similar procedure as in Reference Example 67 to obtain the title compound.

¹H-NMR (CDCl₃) δ 2.29 (1H, dd, J = 4.7, 14.4Hz), 2.33 - 2.42 (1H, m), 2.86 -2.97 (1H, m), 3.28 (1H, dd, J = 4.5, 15.4Hz), 3.53 (1H, dd, J = 11.8, 15.4Hz), 3.70 -3.88 (1H,

m), 3.73 (6H, s), 3.78 (3H, s), 4.24 (1H, dd, J = 3.7, 15.8Hz), 4.50 (1H, d, J = 13.8Hz), 4.79 (1H, d, J = 13.8Hz), 6.00 (2H, s), 6.39 (1H, br.s), 6.75 (1H, d, J = 2.6Hz), 6.79 (1H, d, J = 8.7Hz), 7.07 (1H, dd, J = 2.6, 8.7Hz)

MS: 449(M+H)⁺

0292

Reference Example 70: (6S)-6-(5-chloro-2-cyanobenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione
(compound S70)

Instead of the starting material, that is, the compound S67, of Reference Example 68, Step (1), the compound S69 was used for a similar procedure as in Reference Example 68, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (CDCl₃) δ 2.39 -2.47 (1H, m), 2.77 (1H, dd, J = 9.8, 14.1Hz), 3.03 (1H, dd, J = 4.7, 15.3Hz), 3.32 (1H, dd, J = 5.3, 14.1Hz), 3.52 (1H, dd, J = 12.3, 15.3Hz), 3.68 (6H, s), 3.74 (1H, d, J = 7.8, 15.7Hz), 3.84 (3H, s), 4.22 -4.66 (1H, m), 4.25 (1H, d, J = 13.7Hz), 4.88 (1H, d, J = 13.7Hz), 5.95 -6.01 (1H, m), 6.00 (2H, s), 7.13 (1H, d, J = 2.0Hz), 7.31 (1H, dd, J = 2.0, 8.3Hz), 7.49 (1H, d, J = 8.3Hz)

MS: 458(M+H)⁺

0293

Reference Example 71: tert-butyl 4-[(1R)-1-({[(6R)-6-[4-chloro-3-(trifluoromethyl)benzyl]-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S71)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, Step (2), the compound S63 was used, and instead of the reaction agent, that is, the compound S19, the compound S25a was used for a similar procedure as in Reference Example 20, Step (2) to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-[4-chloro-3-(trifluoromethyl)benzyl]-

3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S71a) and tert-butyl 4-[(1R)-1-([[(6S)-6-[4-chloro-3-(trifluoromethyl)benzyl]-3,7-dioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S71b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S71a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 837(M+H)⁺

0294

Example 104: 2-amino-4-[(1R)-1-([[(6R)-6-[4-chloro-3-(trifluoromethyl)benzyl]-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]benzoic acid (compound 104)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S71 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J = 7.3Hz), 1.12 (3H, t, J = 7.0Hz), 1.16 -1.37 (2H, m), 1.57 -1.80 (2H, m), 2.71 (1H, dd, J = 8.0, 14.2Hz), 3.02 -3.24 (3H, m), 3.77 -3.87 (2H, m), 3.88 -4.02 (1H, m), 4.50 (1H, d, J = 16.2Hz), 4.60 (1H, dt, J = 7.7, 7.7Hz), 4.78 (1H, d, J = 16.2Hz), 6.28 (1H, br.s), 6.39 (1H, dd, J = 1.6, 8.3Hz), 6.63 (1H, d, J = 1.6Hz), 7.55 -7.71 (3H, m), 7.82 (1H, d, J = 1.5Hz), 9.41 (1H, d, J = 7.7Hz)

MS: 598(M+H)⁺

0295

Reference Example 72: tert-butyl 4-[(1R)-1-([[(6S)-6-[4-chloro-3-(trifluoromethyl)benzyl]-7-oxo-3-thioxo-4-(2,4,6-trimethoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S72)

Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S71b was used for a similar procedure as in Reference Example 22 to obtain the title compound.

5 MS: 837(M+H)⁺
0296

10 Example 105: 2-amino-4-[(1R)-1-([[(6S)-6-[4-chloro-3-(trifluoromethyl) benzyl]-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl] benzoic acid
(compound 105)

15 Instead of the starting material, that is, the compound S31, of Example 29, the compound S72 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J = 7.3Hz), 1.09 (3H, t, J = 7.0Hz), 1.12 -1.33 (2H, m), 1.55 -1.76 (2H, m), 2.65 -
20 2.70 (1H, dd, J = 8.4, 14.1Hz), 3.06 (1H, dd, J = 12.5, 12.5Hz), 3.15 (1H, dd, J = 5.6, 14.1Hz), 3.16 -3.25 (1H, m), 3.72 -3.86 (2H, m), 3.90 -4.05 (1H, m), 4.52 (1H, d, J = 16.3Hz), 4.61 (1H, dt, J = 7.4, 7.8Hz), 4.81 (1H, d, J = 16.3Hz), 6.43 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz),
25 7.60 -7.73 (3H, m), 7.82 (1H, d, J = 1.4Hz), 9.40 (1H, d, J = 7.8Hz)

MS: 598(M+H)⁺
0297

30 Reference Example 73: tert-butyl 4-[(1R)-1-([[(6R)-6-(4,5-difluoro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate
(compound S73)

35 Step (1): Instead of the starting material, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, Step (2), the compound S64 was used, and instead of the reaction agent, that is, the compound S19, the compound

S25a was used for a same procedure as in Reference Example 20, Step (2) to obtain tert-butyl 4-[(1R)-1-([[(6R)-6-(4,5-difluoro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]-2-nitrobenzoate (compound S73a) and tert-butyl 4-[(1R)-1-([[(6S)-6-(4,5-difluoro-2-methoxybenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]-2-nitrobenzoate (compound S73b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S73a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 801(M+H)⁺

0298

Example 106: 2-amino-4-[(1R)-1-([[(6R)-6-(4,5-difluoro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino) butyl]benzoic acid (compound 106)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S73 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J = 7.3Hz), 1.12 (3H, t, J = 7.0Hz), 1.15 -1.35 (2H, m), 1.58 -1.78 (2H, m), 2.65 (1H, dd, J = 8.7, 14.5Hz), 2.92 (1H, dd, J = 5.1, 14.5Hz), 3.06 (1H, dd, J = 12.2, 12.2Hz), 3.11 -3.20 (1H, m), 3.73 -3.88 (3H, m), 3.79 (3H, s), 4.47 (1H, d, J = 16.3Hz), 4.60 (1H, dt, J = 7.2, 7.7Hz), 4.78 (1H, d, J = 16.3Hz), 6.27 (1H, br.s), 6.42 (1H, dd, J = 1.6, 8.4Hz), 6.64 (1H, d, J = 1.6Hz), 7.13 (1H, dd, J = 7.0, 12.9Hz), 7.35 (1H, dd, J = 9.3, 11.4Hz), 7.64 (1H, d, J = 8.4Hz), 9.42 (1H, d, J = 7.7Hz)

MS: 562(M+H)⁺

0299

Reference Example 74: tert-butyl 4-[(1R)-1-([[(6S)-6-(4,5-difluoro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-

diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate
(compound S74)

Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S73b was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 801(M+H)⁺

0300

Example 107: 2-amino-4-[(1R)-1-({[(6S)-6-(4,5-difluoro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]benzoic acid (compound 107)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S74 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J = 7.2Hz), 1.09 (3H, t, J = 7.0Hz), 1.14 -1.34 (2H, m), 1.57 -1.77 (2H, m), 2.64 (1H, dd, 8.9, 14.4Hz), 2.93 (1H, dd, J = 5.2, 14.4Hz), 3.04 (1H, dd, 12.8, 12.8Hz), 3.09-3.21 (1H, m), 3.71 - 3.91 (3H, m), 3.79 (3H, s), 4.49 (1H, d, J = 16.4Hz), 4.62 (1H, dt, J = 7.8, 7.8Hz), 4.80 (1H, d, J = 16.4Hz), 6.44 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz), 7.13 (1H, dd, J = 7.1, 13.0Hz), 7.35 (1H, dd, J = 9.3, 11.5Hz), 7.65 (1H, d, J = 8.3Hz), 9.42 (1H, d, J = 7.8Hz)

MS: 562(M+H)⁺

0301

Reference Example 75: tert-butyl 4-[(1R)-1-({[(6R)-6-(5-fluoro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S75)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, Step (2), the compound S65 was used, and instead of the reaction agent, that is, the compound S19,

the compound S25a was used for a similar procedure as in Reference Example 20, Step (2) to obtain tert-butyl 4-[(1R)-1-([[(6R)-3,7-dioxo-6-(5-fluoro-2-methoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S75a) and tert-butyl 4-[(1R)-1-([[(6S)-3,7-dioxo-6-(5-fluoro-2-methoxybenzyl)-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S75b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S75a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 783(M+H)⁺

0302

Example 108: 2-amino-4-[(1R)-1-([[(6R)-3-(ethoxyimino)-6-(5-fluoro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]benzoic acid (compound 108)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S75 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.88 (3H, t, J = 7.3Hz), 1.12 (3H, t, J = 7.0Hz), 1.15 -1.37 (2H, m), 1.58 -1.78 (2H, m), 2.68 (1H, dd, J = 8.9, 14.4Hz), 2.96 (1H, dd, J = 5.0, 14.4Hz), 3.07 (1H, dd, J = 12.7, 12.7Hz), 3.13 -3.21 (1H, m), 3.79 (3H, s), 3.79 -3.86 (3H, m), 4.48 (1H, d, J = 16.3Hz), 4.60 (1H, dt, J = 7.3, 7.7Hz), 4.78 (1H, d, J = 16.3Hz), 6.42 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz), 6.97 (1H, dd, J = 4.6, 8.9Hz), 7.04 (1H, ddd, J = 3.0, 8.9, 8.9Hz), 7.12 (1H, dd, J = 3.0, 9.3Hz), 7.64 (1H, d, J = 8.3Hz), 9.44 (1H, d, J = 7.7Hz)

MS: 544(M+H)⁺

0303

Example 109: 2-amino-4-[(1R)-1-([[(6R)-3-[(3,5-difluorophenoxy)imino]-6-(5-fluoro-2-methoxybenzyl)-7-

oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl] benzoic acid
(compound 109)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S75 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-(3,5-difluorophenyl) hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2) to obtain the title compound.

¹H-NMR (CDCl₃) δ0.93 (3H, t, J = 7.3Hz), 1.27 -1.45 (2H, m), 1.59 -1.85 (2H, m), 2.68 (1H, dd, J = 8.2, 13.9Hz), 3.21 (1H, dd, J = 5.4, 13.9Hz), 3.33 (1H, dd, J = 12.8, 12.8Hz), 3.44 -3.55 (1H, m), 3.82 -3.85 (1H, m), 3.83 (3H, s), 4.23 (1H, d, J = 16.6Hz), 4.75 (1H, dt, J = 7.4, 7.2Hz), 5.35 (1H, d, J = 16.6Hz), 5.46 (1H, br.s), 6.34 - 6.43 (1H, m), 6.57 -6.73 (4H, m), 6.80 (1H, dd, J = 4.0, 8.8Hz), 6.89 -6.98 (2H, m), 7.85 (1H, d, J = 8.0Hz), 9.52 (1H, d, J = 7.2Hz)

MS: 628(M+H)⁺

0304

Reference Example 76: tert-butyl 4-[(1R)-1-({[(6S)-6-(5-fluoro-2-methoxybenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S76)

Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S75b was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 783(M+H)⁺

0305

Example 110: 2-amino-4-[(1R)-1-({[(6S)-3-(ethoxyimino)-6-(5-fluoro-2-methoxybenzyl)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 110)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S76 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl) hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar

procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J = 7.2Hz), 1.09 (3H, t, J = 7.0Hz), 1.13 -1.36 (2H, m), 1.57 -1.77 (2H, m), 2.67 (1H, dd, J = 8.3, 14.4Hz), 2.96 (1H, dd, J = 5.1, 14.4Hz), 3.06 (1H, dd, J = 11.7, 11.7Hz), 3.11 -3.20 (1H, m), 3.73 -3.91 (3H, m), 3.78 (3H, s), 4.52 (1H, d, J = 16.4Hz), 4.58 -4.67 (1H, m), 4.82 (1H, d, J = 16.4Hz), 6.44 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz), 6.98 (1H, dd, J = 5.0, 9.2Hz), 7.04 (1H, ddd, J = 3.6, 9.2, 9.2Hz), 7.13 (1H, dd, J = 3.1, 9.2Hz), 7.65 (1H, d, J = 8.3Hz), 9.43 (1H, d, J = 7.7Hz)

MS: 544 (M+H)⁺

0306

Reference Example 77: tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-fluorobenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S77)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepan-2,5-dione, of Reference Example 20, Step (2), the compound S66 was used, and instead of the reaction agent, that is, the compound S19, the compound S25a was used for a similar procedure as in Reference Example 20, Step (2) to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-fluorobenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S77a) and tert-butyl 4-[(1R)-1-({[(6S)-6-(5-chloro-2-fluorobenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate (compound S77b).

Step (2): Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S77a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 787 (M+H)⁺

0307

Example 111: 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-fluorobenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-

yl}carbonyl}amino)butyl}benzoic acid (compound 111)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S77 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethylhydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.87 (3H, t, J = 7.3Hz), 1.12 (3H, t, J = 7.0Hz), 1.16 -1.34 (2H, m), 1.58 -1.79 (2H, m), 2.70 (1H, dd, J = 8.8, 14.5Hz), 2.99 -3.27 (3H, m), 3.80 -3.86 (2H, m), 3.87 -3.96 (1H, m), 4.53 (1H, d, J = 16.3Hz), 4.60 (1H, dt, J = 7.2, 7.5Hz), 4.79 (1H, d, J = 16.3Hz), 6.42 (1H, dd, J = 1.6, 8.4Hz), 6.64 (1H, d, J = 1.6Hz), 7.24 (1H, t, J = 9.1Hz), 7.35 (1H, ddd, J = 2.7, 4.4, 9.1Hz), 7.53 (1H, dd, J = 2.7, 6.5Hz), 7.64 (1H, d, J = 8.4Hz), 9.39 (1H, d, J = 7.5Hz)

MS: 548 (M+H)⁺

0308

Example 112: 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-fluorobenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl}carbonyl}amino] butyl}benzoic acid (compound 112)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S77 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-(3,5-difluorophenyl) hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (CDCl₃) δ0.93 (3H, t, J = 7.2Hz), 1.18 -1.48 (2H, m), 1.68 -1.88 (2H, m), 2.75 (1H, dd, J = 7.9, 14.4Hz), 3.23 (1H, dd, J = 5.7, 14.4Hz), 3.38 (1H, dd, J = 12.4, 12.4Hz), 3.48 -3.57 (1H, m), 3.62 -3.75 (1H, m), 4.23 (1H, d, J = 16.7Hz), 4.75 (1H, dt, J = 7.1, 7.4Hz), 5.39 (1H, d, J = 16.7Hz), 5.48 (1H, s), 6.39 (1H, dt, J = 2.4, 8.9Hz), 6.55 -6.62 (2H, m), 6.64 -6.75 (2H, m), 7.02 (1H,

dd, J = 9.3, 9.3Hz), 7.20-7.29 (2H, m), 7.86 (1H, d, J = 8.2Hz), 9.43 (1H, d, J = 7.4Hz)

MS: 632 (M+H)⁺

0309

5 Reference Example 78: tert-butyl 4-[(1R)-1-([[(6S)-6-(5-chloro-2-fluorobenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]-2-nitrobenzoate (compound S77)

 Instead of the starting material, that is, the compound S21, of Reference Example 22, the compound S77b was used for a similar procedure as in Reference Example 10 22 to obtain the title compound.

MS: 787 (M+H)⁺

0310

15 Example 113: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-fluorobenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]benzoic acid (compound 113)

 Instead of the starting material, that is, the compound S31, of Example 29, the compound S78 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl 20 hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.86 (3H, t, J = 7.3Hz), 1.09 (3H, t, J = 7.0Hz), 1.15 -1.34 (2H, m), 1.57 -1.76 (2H, m), 2.68 (1H, dd, J = 8.3, 15.1Hz), 3.00 -3.14 (2H, m), 3.15 -3.26 (1H, m), 3.75 -3.85 (2H, m), 3.86 -4.00 (1H, m), 4.55 (1H, d, J = 16.4Hz), 4.62 (1H, dt, J = 7.4, 7.8Hz), 4.81 (1H, d, J = 16.4Hz), 6.44 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz), 7.24 (1H, dd, J = 9.0, 9.0 Hz), 7.35 (1H, ddd, J = 2.8, 4.5, 9.0Hz), 7.54 (1H, dd, J = 2.8, 6.5Hz), 7.65 (1H, d, J = 8.3Hz), 9.38 (1H, d, J = 7.8Hz)

MS: 548 (M+H)⁺

0311

35 Reference Example 79: tert-butyl 4-[(1R)-1-([[(6R)-6-(5-chloro-2-cyanobenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]-2-nitrobenzoate (compound S79)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, Step (2), the compound S68 was used, and
5 instead of the reaction agent, that is, the compound S19, the compound S25a was used for a similar procedure as in Reference Example 20, Step (2) to obtain tert-butyl 4-[(1R)-1-({[(6R)-6-(5-chloro-2-cyanobenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]-2-nitrobenzoate
10 (compound S79a).

Step (2): Instead of the starting material of Reference Example 22, that is, the compound S21, the compound S79a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

15 MS: 794 (M+H)⁺

0312

Example 114: 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-cyanobenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid (compound 114)

20 Instead of the starting material, that is, the compound S31, of Example 29, the compound S79 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar
25 procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (DMSO-d₆) 80.87 (3H, t, J = 7.3Hz), 1.13 (3H, t, J = 7.0Hz), 1.16 -1.35 (2H, m), 1.56 -1.81 (2H, m), 2.87 (1H, dd, J = 8.0, 14.8Hz), 3.15 (1H, dd, J = 11.8, 11.8Hz), 3.22 -3.25 (1H, m), 3.27 (1H, dd, J = 6.7, 14.8Hz), 3.76 -3.89 (2H, m), 4.01 -4.13 (1H, m), 4.55 (1H, d, J = 16.4Hz), 4.60 (1H, dt, J = 7.7, 7.7Hz), 4.79 (1H, d, J = 16.4Hz), 6.40 (1H, dd, J = 1.6, 8.4Hz), 6.63 (1H, d, J = 1.6Hz), 7.54 (1H, dd, J = 2.1, 8.4Hz), 7.63 (1H, d, J = 8.4Hz), 7.77 (1H, d, J = 2.1Hz), 7.86 (1H, d, J = 8.4Hz), 9.34 (1H, d, J = 7.7Hz)

35 MS: 555 (M+H)⁺

0313

Example 115: 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-cyanobenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino] butyl}benzoic acid

5 (compound 115)

Instead of the starting material, that is, the compound S31, of Example 29, the compound S79 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-(3,5-difluorophenyl)hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2), to obtain the title compound.

¹H-NMR (CDCl₃) δ0.93 (3H, t, J = 7.3Hz), 1.26 -1.47 (2H, m), 1.68 -1.87 (2H, m), 2.93 (1H, dd, J = 6.5, 14.2Hz), 3.41 -3.51 (2H, m), 3.55 -3.64 (1H, m), 3.73-3.82 (1H, m), 4.21 (1H, d, J = 16.8Hz), 4.74 (1H, dt, J = 7.2, 7.4Hz), 5.41 (1H, d, J = 16.8Hz), 5.50 (1H, s), 6.40 (1H, dt, J = 2.3, 8.4Hz), 6.53 -6.60 (2H, m), 6.71 (2H, dd, J = 2.5, 8.4Hz), 7.39 (1H, dd, J = 2.0, 8.4Hz), 7.47 (1H, d, J = 2.0Hz), 7.62 (1H, d, J = 8.4Hz), 7.85 (1H, d, J = 8.7Hz), 9.34 (1H, d, J = 7.4Hz)

MS: 639(M+H)⁺

0314

Reference Example 80: tert-butyl 4-[(1R)-1-[(6S)-6-(5-chloro-2-cyanobenzyl)-7-oxo-3-thioxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S80)

Step (1): Instead of the starting material, that is, (6R)-6-(5-chloro-2-methoxybenzyl)-1-(2,4,6-trimethoxybenzyl)-1,4-diazepane-2,5-dione, of Reference Example 20, Step (2), the compound S70 was used, and instead of the reaction agent, that is, the compound S19, the compound S25a was used for a similar procedure as in Reference Example 20, Step (2), to obtain tert-butyl 4-[(1R)-1-[(6S)-6-(5-chloro-2-cyanobenzyl)-3,7-dioxo-1,4-diazepan-1-yl]carbonyl)amino)butyl]-2-nitrobenzoate (compound S80a).

Step (2): Instead of the starting material of

Reference Example 22, that is, the compound S21, the compound S80a was used for a similar procedure as in Reference Example 22 to obtain the title compound.

MS: 794 (M+H)⁺

5 0315

Example 116: 2-amino-4-[(1R)-1-([[(6S)-6-(5-chloro-2-cyanobenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl]amino)butyl]benzoic acid (compound 116)

10 Instead of the starting material, that is, the compound S31, of Example 29, the compound S80 was used, and instead of the reaction agent, that is, O-(4-fluorophenyl)hydroxylamine hydrochloride, O-ethyl hydroxylamine hydrochloride was used for a similar procedure as in Example 29, Step (1) and Step (2), to
15 obtain the title compound.

¹H-NMR (DMSO-d₆) δ0.85 (3H, t, J = 7.2Hz), 1.10 (3H, t, J = 7.0Hz), 1.13 -1.33 (2H, m), 1.55 -1.76 (2H, m), 2.87 (1H, dd, J = 7.7, 14.8Hz), 3.15 (1H, dd, J = 12.0, 12.0Hz), 3.18 -3.25 (1H, m), 3.29 (1H, dd, J = 6.1, 14.8Hz), 3.74 -3.86 (2H, m), 4.03 -4.15 (1H, m), 4.55 (1H, d, J = 16.3Hz), 4.60 (1H, dt, J = 7.7, 7.7Hz), 4.83 (1H, d, J = 16.3Hz), 6.44 (1H, dd, J = 1.6, 8.3Hz), 6.64 (1H, d, J = 1.6Hz), 7.54 (1H, dd, J = 2.1, 8.3Hz), 7.65 (1H, d, J = 8.3Hz), 7.78 (1H, d, J = 2.1Hz), 7.87 (1H, d, J = 8.3Hz), 9.34 (1H, d, J = 7.7Hz)

25 MS: 555 (M+H)⁺

 0316

 The chemical structures of the compounds of the Examples are shown in Table I.

30 0317

Table I

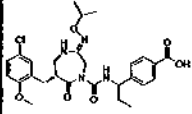
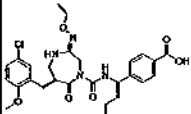
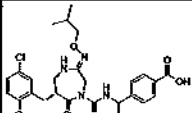
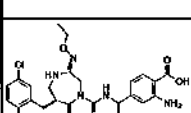
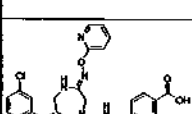
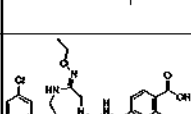
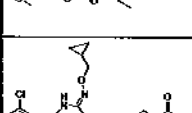
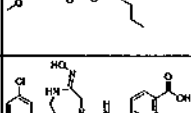
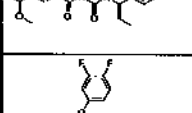
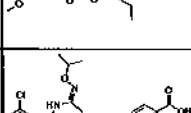
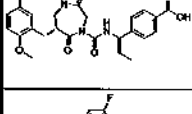
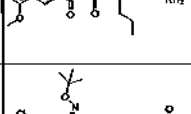
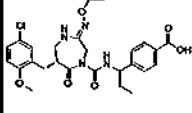
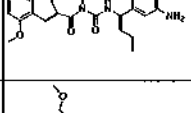
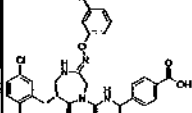
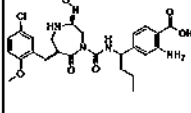
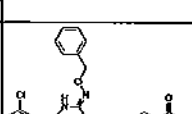
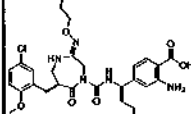
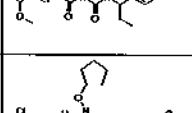
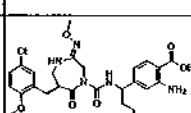
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5	1		11	
	2		12	
10	3		13	
	4		14	
15	5		15	
	6		16	
20	7		17	
	8		18	
25	9		19	
	10		20	
30				
35				

Table I (continued)

Compound No.	Structure	Compound No.	Structure
21		31	
22		32	
23		33	
24		34	
25		35	
26		36	
27		37	
28		38	
29		39	
30		40	

Table I (continued)

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Compound No.	Structure
41	
42	
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Compound No.	Structure
51	
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Table I (continued)

Compound No.	Structure
61	
62	
63	
64	
65	
66	
67	
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70	

Compound No.	Structure
71	
72	
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78	
79	
80	

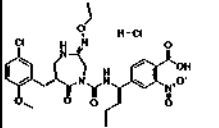
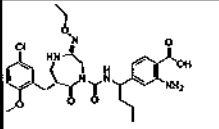
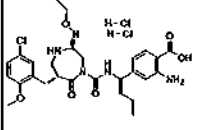
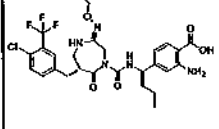
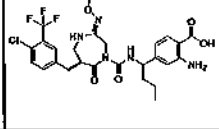
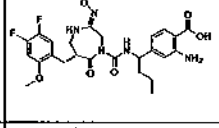
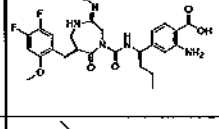
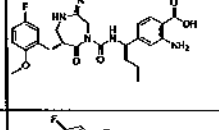
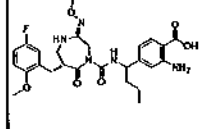
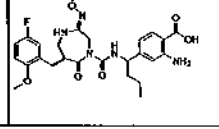
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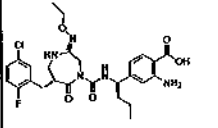
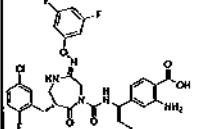
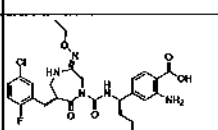
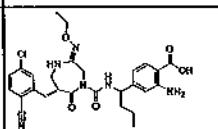
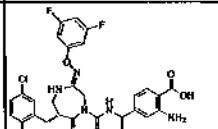
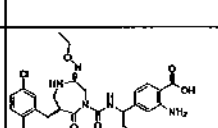
Compound No.	Structure
81	
82	
83	
84	
85	
86	
87	
88	
89	
90	

Compound No.	Structure
91	
92	
93	
94	
95	
96	
97	
98	
99	
100	

0322

Table I (continued)

Compound No.	Structure
101	
102	
103	
104	
105	
106	
107	
108	
109	
110	

Compound No.	Structure
111	
112	
113	
114	
115	
116	

Test Example 1: Measurement of Inhibitory Activity of
Test Compound for Human Chymase

The inhibitory activity of the compounds of the present invention for recombinant human chymase was measured by the method of Pasztor et al. (Pasztor et al., Acta. Biol. Hung. 42: 285-95, 1991). That is, recombinant human chymase was diluted to an appropriate concentration by a 50 mM tris-hydrochloride buffer (pH 7.5), 1M sodium chloride solution, and 0.01% (v/v) Triton X-100 to obtain an enzyme solution. A 10 mM dimethyl sulfoxide (hereinafter referred to as DMSO) solution of Suc-Ala-Ala-Pro-Phe-MCA (Peptide Institute) was diluted 20-fold at the time of use by 50 mM tris-hydrochloride buffer (pH 7.5), 1M sodium chloride solution and 0.01% (v/v) Triton X-100 to obtain the substrate solution. 75 μ l of the enzyme solution was mixed with 5 μ l of the test compound in a DMSO solution, and incubated for 10 minutes. Then 20 μ l of the substrate solution was added to the mixture and reacted for a further 10 minutes at room temperature. The reaction was stopped by adding 50 μ l of 30% (v/v) acetic acid. The intensity of the fluorescence (Ex 380 nm, Em 460 nm) of the fluorescent substance MCA produced by the degradation of the substrate was measured by a fluorescent photometer (Fluoroscanner II, Labsystems Japan). Simultaneously, 5 μ l of DMSO was added to a reaction instead of the test compound, and was used as a blank. The inhibitory activity for chymase was calculated based on the value of the blank. Further, the ratio of inhibition and the 50% inhibition concentration (IC_{50} value) were calculated. The IC_{50} values of representative compounds are shown in Table II.

Table II

	Tested compound	IC ₅₀ value (μM)
1	Compound 3	0.03
2	Compound 12	0.02
3	Compound 14	0.03
4	Compound 15	0.03
5	Compound 18	0.02
6	Compound 20	0.03
7	Compound 22	0.04
8	Compound 26	0.05
9	Compound 27	0.02
10	Compound 29	0.01
11	Compound 30	0.004
12	Compound 31	0.01
13	Compound 34	0.03
14	Compound 37	0.05
15	Compound 40	0.01
16	Compound 41	0.003
17	Compound 42	0.02
18	Compound 44	0.02
19	Compound 49	0.03
20	Compound 53	0.04
21	Compound 58	0.02
22	Compound 64	0.03
23	Compound 67	0.05
24	Compound 73	0.03
25	Compound 76	0.009
26	Compound 88	0.06
27	Compound 96	0.007
28	Compound 103	0.02
29	Compound 108	0.03
30	Compound 113	0.04

0325

5 Test Example 2: Effect of Test Compounds on the Late-
phase skin reaction (at 24 hours after challenge) of TNCB-
induced biphasic dermatitis in mice.

10 Preparation of IgE solution for sensitization
containing anti-TNP mouse IgE, sensitization, and
induction of dermatitis were performed with reference to
the method of Nagai et al (Nagai et al., Biol Pharm Bull.
18: 239-45, 1995). That is, IGELb4 cells (ATCC-TIB141)
were suspended in a culture medium (RPMI1640 with 10%
FBS) and adjusted to a concentration of 0.5×10^5 cells/ml.

The prepared cells were incubated at 37°C in 5% CO₂ for 72 hours, and the culture supernatant was used as the IgE solution for sensitization. The IgE solution containing anti-TNP mouse IgE was administered in an amount of 1.0 ml to 7-week old female BALB/c mice (Charles River Japan) intravenously for sensitization. Dermatitis was induced after about 24 hours from sensitization by application of 1% TNCB dissolved in acetone/olive oil (1:9) to both sides of the right ear of the mice (10 µl/side, total 20 µl). As a control, acetone/olive oil (1:9) was applied to sensitized mice by a similar method (control group). Further, to consider the effect of application of TNCB, non-sensitized mice were applied with 1% TNCB dissolved in acetone/olive oil (1:9) by a similar method (non-sensitized+TNCB applied group). The test compound was suspended in distilled water containing 0.5% hydroxypropylcellulose (hereinafter abbreviated as "0.5% HPC-distilled water") and orally administered at a dosage of 1 or 0.5 mg/kg at 1 hour before induction of dermatitis (compound group). Further, as a control, instead of the suspension of test compound, 0.5% HPC-distilled water was administered in the same way (vehicle group).

0326

Ear thickness was measured before TNCB application and 24 hours after TNCB application by a microgauge (Mitsutoyo), and the amount of increase of ear thickness was evaluated by subtracting ear thickness before TNCB application from the ear thickness at 24 hours after application with TNCB. The effect of the test compound was judged by calculating the inhibition ratio (%) according to the following calculation formula.

0327

Inhibition ratio (%)=

$$\frac{\{(\text{Increase of vehicle group}) - (\text{Increase of control group})\} - \{(\text{Increase of compound group}) - (\text{Increase of control group})\}}{\{(\text{Increase of vehicle group}) - (\text{Increase of control group})\} - \{(\text{Increase of non-sensitized+TNCB applied group}) - (\text{Increase of control group})\}} \times 100$$

5
$$\frac{\{(\text{Increase of vehicle group}) - (\text{Increase of control group})\} - \{(\text{Increase of non-sensitized+TNCB applied group}) - (\text{Increase of control group})\}}{\{(\text{Increase of vehicle group}) - (\text{Increase of control group})\} - \{(\text{Increase of non-sensitized+TNCB applied group}) - (\text{Increase of control group})\}} \times 100$$

0328

10 Due to application of TNCB, earedema (late-phase reaction) was observed after 24 hours. As a result of oral administration of the test compounds, each test compound remarkably inhibited the late-phase skin reaction. For example, when the compound 3, compound 12, compound 64, and compound 76 were administered orally by
15 a dosage of 1 mg/kg, the inhibition ratio of the late-phase reaction were respectively 71.0%, 64.0%, 74.2%, and 85.7%, while when the compound 20, compound 34, and compound 53 were administered orally by a dosage of 0.5 mg/kg, the inhibition ratio of the late-phase reaction
20 were respectively 115.0%, 135.0%, and 91.2%.

Industrial Applicability

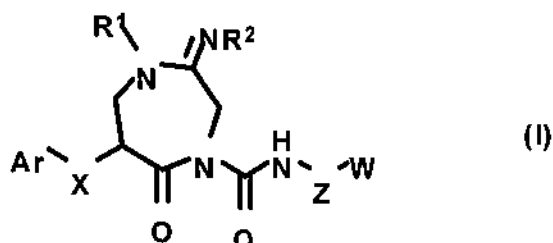
0329

25 The compound of formula (I) of the present invention has a chymase inhibitory activity, is superior in stability in blood plasma and in vivo pharmacokinetics, and is useful as a pharmaceutical for the prevention and/or treatment of diseases such as bronchial asthma, chronic obstructive pulmonary disease, urticaria, atopic
30 dermatitis, allergic conjunctivitis, rhinitis, rheumatoid arthritis, food allergies, colitis, allergic enteritis, mastocytosis, scleroderma, heart failure, cardiac hypertrophy, hypertension, arrhythmia, atherosclerosis, abdominal aortic aneurysm, myocardial infarction,
35 restenosis after PTCA, restenosis after bypass graft surgery, ischemic peripheral circulatory disorders, hyperaldosteronism, diabetes, diabetic retinopathy, diabetic nephropathy, nephritis, glomerulosclerosis,

renal insufficiency, solid tumor, fibrosis, postoperative adhesion, cicatrix, glaucoma, and ocular hypertension.

CLAIMS

1. A compound, or a salt or solvate thereof having the formula (I):



5

wherein, Ar indicates (1) a C₆ to C₁₄ aromatic hydrocarbon group, (2) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom, or (3) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring,

15 where the above groups (1) to (3) of Ar are unsubstituted or substituted with 1 to 5 groups selected from:

- (i) a halogen atom,
- (ii) nitro,
- 20 (iii) cyano,
- (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms,
- (v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms,
- 25 (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms,
- (vii) C₃ to C₆ cycloalkyl,
- (viii) hydroxyl,
- (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, mono- or di-C₁ to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆
- 30

- alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl, mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl, carboxyl, and C₁ to C₆ alkoxy carbonyl, or substituted with 1 to 13 deuterium atom
- 5 (x) C₁ to C₅ alkylenedioxy,
(xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, mono- or di-C₁ to C₆ alkylamino, C₁ to C₆ alkoxy, mono- or di-C₁ to C₆ alkylcarbamoyl, mono- or di-C₇ to C₁₆ aralkylcarbamoyl,
- 10 mono- or di-C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl, carboxyl, and C₁ to C₆ alkoxy carbonyl, or substituted with 1 to 13 deuterium atom
- (xii) amino,
(xiii) mono-C₁ to C₆ alkylamino,
- 15 (xiv) di-C₁ to C₆ alkylamino,
(xv) 5- to 6-membered cyclic amino,
(xvi) C₁ to C₆ alkylcarbonyl,
(xvii) carboxyl,
(xviii) C₁ to C₆ alkoxy carbonyl,
- 20 (xix) carbamoyl,
(xx) thiocarbamoyl,
(xxi) mono-C₁ to C₆ alkylcarbamoyl,
(xxii) di-C₁ to C₆ alkylcarbamoyl,
(xxiii) 5- to 6-membered cyclic aminocarbonyl,
- 25 (xxiv) sulfo,
(xxv) C₁ to C₆ alkylsulfonyl,
(xxvi) C₁ to C₆ alkoxy carbonylamino,
(xxvii) C₁ to C₆ alkylcarbonylamino,
(xxviii) mono- or di-C₁ to C₆ alkylaminocarbonylamino,
- 30 (xxix) aminosulfonyl, and
(xxx) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxxi) 1 to 9 deuterium atoms,
- X indicates (1) a connecting bond, (2) linear or branched C₁ to C₆ alkylene unsubstituted, or substituted with 1 to 12 deuterium atoms, (3) an oxygen atom, (4) NR³, where R³ indicates a hydrogen atom or a C₁ to C₆ alkyl group, or
- 35 (5) -S(O)_m-, where m indicates an integer of 0 to 2,

Z indicates (1) a connecting bond or (2) CR^4R^5 , where R^4 and R^5 are, independently,

(A) a hydrogen atom,

(B) a deuterium atom,

5 (C) C_1 to C_6 alkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) carboxyl, (ii) C_1 to C_6 alkoxy carbonyl, (iii) phenyl, (iv) hydroxyl, (v) C_1 to C_6 alkoxy, (vi) a halogen atom, and (vii) C_3 to C_6 cycloalkyl, or substituted with (viii) 1 to
10 13 deuterium atoms,

(D) C_3 to C_6 cycloalkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom and (ii) an alkyl group unsubstituted, or substituted with 1 to 3 halogen atoms or unsubstituted,
15 or substituted, with (iii) 1 to 11 deuterium atoms,

(E) $COOR^6$ where R^6 indicates a hydrogen atom or C_1 to C_6 alkyl, or

(F) $CONR^7R^8$ where R^7 and R^8 are, independently,

(a) hydrogen atom,

20 (b) C_1 to C_6 alkyl unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C_3 to C_6 cycloalkyl, (iii) carboxyl, (iv) C_1 to C_6 alkoxy carbonyl, (v) C_1 to C_6 alkyl carbonyl, (vi) carbamoyl, (vii) mono- C_1 to C_6 alkyl carbamoyl, (viii)
25 di- C_1 to C_6 alkyl carbamoyl, (ix) C_6 to C_{12} aryl, and (x) C_1 to C_{10} heteroaryl,

(c) C_6 to C_{14} aromatic hydrocarbon group,

(d) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen
30 atom, sulfur atom, and oxygen atom, other than a carbon atom, or

(e) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C_6 to C_{14} aromatic hydrocarbon ring,

35 where each of the groups (c) to (e) is unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (ii)

nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vii) C₃ to C₆ cycloalkyl, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (x) C₁ to C₅ alkylenedioxy, (xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 halogen atoms, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkylcarbonyl, (xvii) carboxyl, (xviii) C₁ to C₆ alkoxy carbonyl, (xix) carbamoyl, (xx) thiocarbamoyl, (xxi) mono-C₁ to C₆ alkylcarbamoyl, (xxii) di-C₁ to C₆ alkylcarbamoyl, (xxiii) C₆ to C₁₀ arylcarbamoyl, (xxiv) C₁ to C₁₀ heteroarylcarbamoyl, (xxv) sulfo, (xxvi) C₁ to C₆ alkylsulfonyl, (xxvii) aminosulfonyl, and (xxviii) mono- or di-C₁ to C₆ alkylaminosulfonylamino, or substituted with (xxix) 1 to 9 deuterium atoms,

W indicates (1) a hydrogen atom, (2) a C₆ to C₁₄ aromatic hydrocarbon group, (3) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom, and an oxygen atom, other than a carbon atom, (4) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring, or (5) deuterium atom,

where each of the groups (2) to (4) of the above W is unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, amino, C₁ to C₆ alkoxy carbonyl, C₁ to C₆ alkoxy carbonylamino, and carboxyl, (v) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vii) C₃ to C₆ cycloalkyl, (viii)

hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, hydroxyl, C₁ to C₆ alkoxy, amino and mono- or di-C₁ to C₆ alkylamino, (x) C₁ to C₅ alkylenedioxy, (xi) C₁ to C₆ alkylthio unsubstituted, or substituted with 1 to 3 groups selected from a halogen atom, hydroxyl, C₁ to C₆ alkoxy, amino, and mono- or di-C₁ to C₆ alkylamino, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkyl-carbonyl, (xvii) carboxyl, (xviii) C₁ to C₆ alkoxy-carbonyl unsubstituted, or substituted with a halogen atom, (xix) C₇ to C₁₆ aralkyloxycarbonyl unsubstituted, or substituted with a halogen atom, (xx) carbamoyl, (xxi) mono-C₁ to C₆ alkylcarbamoyl unsubstituted, or substituted with 1 to 3 groups which are selected from a halogen atom, hydroxyl, carboxyl, C₁ to C₆ alkoxy, amino, and mono- or di-C₁ to C₆ alkylamino, (xxii) di-C₁ to C₆ alkylcarbamoyl unsubstituted, or substituted with hydroxyl, (xxiii) 5- to 6-membered cyclic aminocarbonyl unsubstituted, or substituted with C₁ to C₆ alkoxy-carbonyl, (xxiv) C₆ to C₁₀ arylcarbamoyl, (xxv) C₁ to C₁₀ heteroarylcarbamoyl, (xxvi) C₇ to C₁₆ aralkylcarbamoyl, (xxvii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkylcarbamoyl, (xxviii) N-C₁ to C₆ alkyl-N-C₆ to C₁₂ arylcarbamoyl, (xxix) C₃ to C₆ cycloalkylcarbamoyl, (xxx) sulfo, (xxxi) C₁ to C₆ alkylsulfonyl, (xxxii) C₁ to C₆ alkylsulfonylamino, (xxxiii) C₆ to C₁₂ arylsulfonylamino unsubstituted, or substituted with C₁ to C₆ alkyl, (xxxiv) C₁ to C₁₀ heteroarylsulfonylamino, (xxxv) C₁ to C₆ alkoxy-carbonylamino, (xxxvi) C₁ to C₆ alkylcarbonylamino, (xxxvii) mono- or di-C₁ to C₆ alkylaminocarbonylamino, (xxxviii) C₆ to C₁₂ aryl, (xxxix) C₁ to C₁₀ heteroaryl, (xl) C₆ to C₁₀ aryloxy, (xli) C₁ to C₁₀ heteroaryloxy, (xlii) C₇ to C₁₆ aralkyloxy, (xliii) C₁ to C₁₀ heteroaryl-C₁ to C₆ alkyl, (xliv) aminosulfonyl, (xlv) mono- or di-C₁ to C₆ alkylaminosulfonyl, (xlvi) C₇ to C₁₆ aralkyloxycarbamoyl, and (xlvii) C₁ to C₁₀ heteroaryl-C₁ to

C₆ alkyloxycarbamoyl, or substituted with (xlviii) 1 to 9 deuterium atoms,

R¹ indicates

- (1) a hydrogen atom,
- 5 (2) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl or substituted with (iii) 1 to 13 deuterium atoms,
- (3) C₂ to C₆ alkenyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl or
- 10 substituted with (iii) 1 to 11 deuterium atoms,
- (4) C₂ to C₆ alkynyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 9 deuterium atoms, or
- (5) C₃ to C₆ cycloalkyl unsubstituted, or substituted with
- 15 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 11 deuterium atoms,

R² indicates (1) OR⁹ or (2) NR¹⁰R¹¹

where, R⁹, R¹⁰, and R¹¹ independently indicate

- (A) a hydrogen atom,
- 20 (B) C₁ to C₆ alkyl,
- (C) C₂ to C₆ alkenyl,
- (D) C₂ to C₆ alkynyl,
- (E) C₃ to C₆ cycloalkyl
- (F) C₆ to C₁₄ aromatic hydrocarbon group,
- 25 (G) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom, or
- (H) a bicyclic or tricyclic aromatic group formed by
- 30 condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring,

where each of the groups of the above (B) to (E) is unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy

35 unsubstituted, or substituted with 1 to 3 halogen atoms, (v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆

- alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, (x) C₁ to C₆ alkoxy carbonyl, (xi) C₁ to C₆ alkyl carbonyl, (xii) carbamoyl, (xiii) mono-C₁ to C₆ alkyl carbamoyl, (xiv) di-C₁ to C₆ alkyl carbamoyl, (xv) C₆ to C₁₂ aryl, and (xvi) C₁ to C₁₀ heteroaryl, or substituted with (xvii) 1 to 13 deuterium atoms,
- further, each of the groups of the above (F) to (H) unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, (xii) C₁ to C₆ alkyl carbonyl, (xiii) carboxyl, (xiv) C₁ to C₆ alkoxy carbonyl, (xv) carbamoyl, (xvi) mono-C₁ to C₆ alkyl carbamoyl, (xvii) di-C₁ to C₆ alkyl carbamoyl, (xviii) C₁ to C₆ alkyl sulfonyl, (xix) aminosulfonyl, and (xx) mono- or di-C₁ to C₆ alkyl aminosulfonyl, or substituted with (xxi) 1 to 9 deuterium atoms, or
- R¹ and R² may form 5- or 6-member heterocyclic ring together with the atoms they are bonded with,
- where the above 5- or 6-member heterocyclic ring is unsubstituted, or substituted with 1 to 3 groups selected from
- (A) a halogen atom
 - (B) oxo
 - (C) hydroxyl
 - (D) C₁ to C₆ alkyl,
 - (E) C₂ to C₆ alkenyl,
 - (F) C₂ to C₆ alkynyl,
 - (G) C₃ to C₆ cycloalkyl
 - (H) C₆ to C₁₄ aromatic hydrocarbon group,
 - (I) 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen

atom, sulfur atom, and oxygen atom, other than a carbon atom, and

(J) a bicyclic or tricyclic aromatic group formed by condensation of the above aromatic heterocyclic group and a C₆ to C₁₄ aromatic hydrocarbon ring, or substituted with (K) 1 to 6 deuterium atoms,

where each of the groups of the above (D) to (G) is unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆ alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, (x) C₁ to C₆ alkoxycarbonyl, (xi) C₁ to C₆ alkylcarbonyl, (xii) carbamoyl, (xiii) mono-C₁ to C₆ alkylcarbamoyl, (xiv) di-C₁ to C₆ alkylcarbamoyl, (xv) C₆ to C₁₂ aryl and (xvi) C₁ to C₁₀ heteroaryl, or substituted with (xvii) 1 to 13 deuterium atoms,

each of the groups of the above (H) to (J) is unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (v) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, (xii) C₁ to C₆ alkylcarbonyl, (xiii) carboxyl, (xiv) C₁ to C₆ alkoxycarbonyl, (xv) carbamoyl, (xvi) mono-C₁ to C₆ alkylcarbamoyl, (xvii) di-C₁ to C₆ alkylcarbamoyl, (xviii) C₁ to C₆ alkylsulfonyl, (xix) aminosulfonyl, and (xx) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxi) 1 to 9 deuterium atoms.

2. A compound, or a salt or solvate thereof as claimed in claim 1, wherein, in the formula (I), X indicates a linear or branched C₁ to C₆ alkylene and Ar is

a C₆ to C₁₄ aromatic hydrocarbon group.

3. A compound, or a salt or solvate thereof as claimed in claim 1 or 2, wherein, in the formula (I), Ar is a phenyl group, of which Ar group is unsubstituted, or substituted with 1 to 5 groups which are selected from the group consisting of (i) a halogen atom, (ii) nitro, (iii) cyano, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms or substituted with 1 to 13 deuterium atoms, and (xxxi) a deuterium atom.

4. A compound, or a salt or solvate thereof as claimed in any one of claims 1 to 3, wherein, in the formula (I), W is (1) a C₆ to C₁₄ aromatic hydrocarbon group or (2) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom.

5. A compound, or a salt or solvate thereof as claimed in claim 4, wherein, in the formula (I), Z is (1) a connecting bond or (2) CR⁴R⁵, wherein R⁴ and R⁵ independently are

- (A) a hydrogen atom,
- (B) a deuterium atom,
- (C) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) carboxyl, (ii) C₁ to C₆ alkoxy carbonyl, (iii) phenyl, (iv) hydroxyl, (v) C₁ to C₆ alkoxy, (vi) a halogen atom, and (vii) C₃ to C₆ cycloalkyl, or substituted with (viii) 1 to 13 deuterium atoms, or
- (D) C₃ to C₆ cycloalkyl unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom and (ii) an alkyl group unsubstituted, or substituted with 1 to 3 halogen atoms, or substituted with (iii) 1 to 11 deuterium atoms.

6. A compound, or a salt or solvate thereof as claimed in any one of claims 1 to 3, wherein, in the

formula (I), W is a hydrogen atom or deuterium atom.

7. A compound, or a salt or solvate thereof as claimed in claim 6, wherein, in the formula (I), Z is (1) a connecting bond or (2) CR^4R^5 , where R^4 and R^5

5 independently are

(A) a hydrogen atom,

(B) a deuterium atom,

(C) C_1 to C_6 alkyl unsubstituted, or substituted with 1
10 to 5 groups selected from the group consisting of (i) carboxyl, (ii) C_1 to C_6 alkoxy carbonyl, (iii) phenyl, (iv) hydroxyl, (v) C_1 to C_6 alkoxy, (vi) a halogen atom, and (vii) C_3 to C_6 cycloalkyl, or substituted with (viii) 1 to 13 deuterium atoms,

(D) C_3 to C_6 cycloalkyl unsubstituted, or substituted
15 with 1 to 5 groups selected from the group consisting of (i) a halogen atom and (ii) an alkyl group unsubstituted, or substituted with 1 to 3 halogen atoms, or substituted with (iii) 1 to 11 deuterium atoms,

(E) $COOR^6$ where R^6 indicates a hydrogen atom or C_1 to C_6
20 alkyl, or

(F) $CONR^7R^8$ where R^7 and R^8 respectively independently are

(a) a hydrogen atom,

(b) C_1 to C_6 alkyl unsubstituted, or substituted
with 1 to 3 groups selected from the group consisting of
25 (i) a halogen atom, (ii) C_3 to C_6 cycloalkyl, (iii) carboxyl, (iv) C_1 to C_6 alkoxy carbonyl, (v) C_1 to C_6 alkyl carbonyl, (vi) carbamoyl, (vii) mono- C_1 to C_6 alkyl carbamoyl, (viii) di- C_1 to C_6 alkyl carbamoyl, (ix) C_6 to C_{12} aryl, and (x) C_1 to C_{10} heteroaryl,

30 (c) a C_6 to C_{14} aromatic hydrocarbon cyclic group,
or

(d) a 5- to 8-membered aromatic heterocyclic group
including 1 to 4 hetero atoms selected from a nitrogen
atom, sulfur atom, and oxygen atom, other than a carbon
35 atom,

where the above groups (c) to (d) are unsubstituted,
or substituted with 1 to 5 groups selected from the group

consisting of (i) a halogen atom, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) hydroxyl, (ix) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (xii) amino, (xiii) mono-C₁ to C₆ alkylamino, (xiv) di-C₁ to C₆ alkylamino, (xv) 5- to 6-membered cyclic amino, (xvi) C₁ to C₆ alkylcarbonyl, (xvii) carboxyl, (xxvii) aminosulfonyl, and (xxviii) mono- or di-C₁ to C₆ alkylaminosulfonyl, or substituted with (xxix) 1 to 9 deuterium atoms.

8. A compound, or a salt or solvate thereof as claimed in any one of claims 1 to 7, wherein, in the formula (I), R¹ is (1) a hydrogen atom or (2) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom or (ii) C₃ to C₆ cycloalkyl, or substituted with (iii) 1 to 13 deuterium atoms, and R² indicates (1) OR⁹ or (2) NR¹⁰R¹¹

where R⁹, R¹⁰, and R¹¹ independently are

- (A) a hydrogen atom,
- (B) C₁ to C₆ alkyl,
- (C) C₂ to C₆ alkenyl,
- (E) C₃ to C₆ cycloalkyl
- (F) C₆ to C₁₄ aromatic hydrocarbon group, or
- (G) a 5- to 8-membered aromatic heterocyclic group including 1 to 4 hetero atoms selected from a nitrogen atom, sulfur atom, and oxygen atom, other than a carbon atom,

where each group of the above (B) to (E) is unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of (i) a halogen atom, (ii) C₃ to C₆ cycloalkyl, (iii) hydroxyl, (iv) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (v) amino, (vi) mono-C₁ to C₆ alkylamino, (vii) di-C₁ to C₆ alkylamino, (viii) 5- to 6-membered cyclic amino, (ix) carboxyl, and (xv) C₆ to C₁₂ aryl, or substituted with (xvii) 1 to 13 deuterium atoms,

further, each group of the above (F) to (G) is

unsubstituted, or substituted with 1 to 5 groups selected from the group consisting of (i) a halogen atom, (iv) C₁ to C₆ alkyl unsubstituted, or substituted with 1 to 3 halogen atoms, (vi) hydroxyl, (vii) C₁ to C₆ alkoxy unsubstituted, or substituted with 1 to 3 halogen atoms, (viii) amino, (ix) mono-C₁ to C₆ alkylamino, (x) di-C₁ to C₆ alkylamino, (xi) 5- to 6-membered cyclic amino, and (xiii) carboxyl, or substituted with (xxi) 1 to 9 deuterium atoms.

9. A compound, or a salt or solvate thereof as claimed in any one of claims 1 to 7, wherein, in the formula (I), the heterocyclic ring which is formed by R¹ and R² together with the atoms they are bonded with is (1) imidazole, (2) triazole, (3) oxadiazole, or (4) oxadiazine, or partially saturated heterocyclic rings of the same, where (1) to (4) are unsubstituted, or substituted with 1 to 3 groups selected from the group consisting of

- (A) a halogen atom,
- (B) oxo,
- (C) hydroxyl,
- (D) C₁ to C₆ alkyl and
- (K) deuterium atoms.

10. A compound or a salt or solvate thereof as claimed in claim 1, wherein the compound is

(1) 4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(pyridin-2-yloxy)imino]-1,4-diazepan-1-yl]carbonyl)amino]propyl]benzoic acid,

(2) 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]butyl]benzoic acid,

(3) 2-amino-4-[(1R)-1-[(6S)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-[(2,2,2-trifluoroethoxy)imino]-1,4-diazepan-1-yl]carbonyl)amino]butyl] benzoic acid,

(4) 2-amino-4-[(1R)-1-[(6R)-6-(5-chloro-2-methoxybenzyl)-3-[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl)amino]ethyl] benzoic acid,

- (5) 2-amino-4-[(1R)-1-({[(6S)-6-(5-chloro-2-methoxybenzyl)-3-(methoxyimino)-4-methyl-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl] benzoic acid,
- (6) (4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-
5 [(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl}amino) ethyl]phenyl)acetic acid,
- (7) 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-
[(3,5-difluorophenoxy)imino]-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)methyl] benzoic acid,
- 10 (8) {4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-yl]carbonyl}amino)propyl]phenyl}acetic acid,
- (9) 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-7-oxo-3-(phenoxyimino)-1,4-diazepan-1-
15 yl]carbonyl}amino)propyl]benzoic acid, or
- (10) 2-amino-4-[(1R)-1-({[(6R)-6-(5-chloro-2-methoxybenzyl)-3-(ethoxyimino)-7-oxo-1,4-diazepan-1-yl]carbonyl}amino)butyl]benzoic acid

11. A pharmaceutical composition comprising a
20 compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt or solvate thereof.

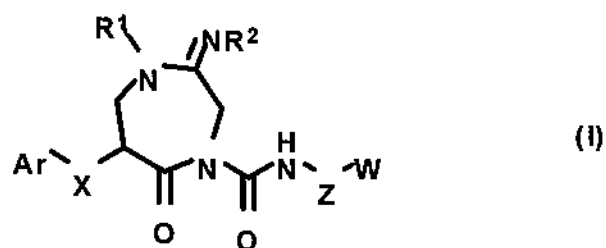
12. A pharmaceutical composition as claimed in claim 11 for the prevention or treatment of a disease, in which chymase is involved, selected from the group
25 consisting of bronchial asthma, chronic obstructive pulmonary disease, urticaria, atopic dermatitis, allergic conjunctivitis, rhinitis, rheumatoid arthritis, food allergies, colitis, allergic enteritis, mastocytosis, scleroderma, heart failure, cardiac hypertrophy,
30 hypertension, arrhythmia, atherosclerosis, abdominal aortic aneurysm, myocardial infarction, restenosis after PTCA, restenosis after bypass graft surgery, ischemic peripheral circulatory disorders, hyperaldosteronism, diabetes, diabetic retinopathy, diabetic nephropathy,
35 nephritis, glomerulosclerosis, renal insufficiency, solid tumor, fibrosis, postoperative adhesion, cicatrix, glaucoma, and ocular hypertension.

13. A pharmaceutical composition as claimed in claim 11 for the prevention or treatment of a disease, in which chymase is involved, selected from the group consisting of bronchial asthma, urticaria, atopic dermatitis, allergic conjunctivitis, allergic enteritis, colitis, abdominal aortic aneurysm, diabetic nephropathy, nephritis, and cicatrix.

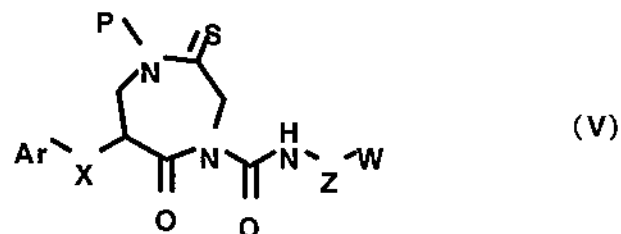
14. A pharmaceutical composition as claimed in claim 11 for the prevention or treatment of atopic dermatitis or allergic conjunctivitis.

15. A chymase inhibitor comprising, as a compound or a salt or solvates thereof according to any one of claims 1 to 10.

16. A method for producing a compound having the formula (I):



wherein Ar, W, X, Z, R¹, and R² are as defined in claim 1, comprising the steps of
1) reacting a compound (V):

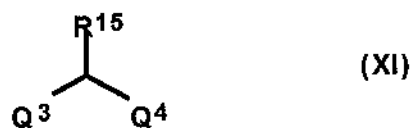


wherein Ar, W, X, and Z are as defined in claim 1, P

indicates a protective group of allyl, allyloxycarbonyl, 9-fluorenylmethylcarbonyl, C₁ to C₆ alkyloxycarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C₁ to C₆ alkylcarbonyl unsubstituted, or substituted with 1 to 3 halogen atoms, C₇ to C₁₆ aralkyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy or (iv) nitro, C₅ to C₁₆ arylcarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, C₇ to C₁₆ aralkyloxycarbonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, or C₅ to C₁₆ arylsulfonyl unsubstituted, or substituted with 1 to 3 of (i) a halogen atom, (ii) C₁ to C₆ alkyl, (iii) C₁ to C₆ alkoxy, or (iv) nitro, or indicates R¹, where R¹ is as defined above, with

R²-NH₂, where R² is as defined in claim 1, or a salt thereof, and optionally, if necessary, performing a deprotection reaction,

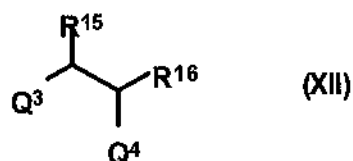
2) reacting the above compound (V) with R¹²-NH₂, where R¹² is OH or NHR¹¹ and R¹¹ is the same as defined in claim 1, or a salt thereof, then subsequently reacting the resulting product with the compound (XI):



25

wherein Q³ and Q⁴ independently indicate a halogen atom, C₆ to C₁₀ arylsulfonyloxy unsubstituted, or substituted with 1 to 3 halogen atoms, C₁ to C₄ alkylsulfonyloxy unsubstituted, or substituted with 1 to 3 halogen atoms, or C₆ to C₁₀ aryloxy unsubstituted, or substituted with 1 to 3 halogen atoms or nitro, and R¹⁵ indicates a hydrogen atom or oxo,

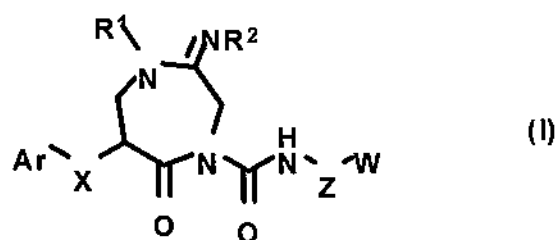
or with the compound (XII):



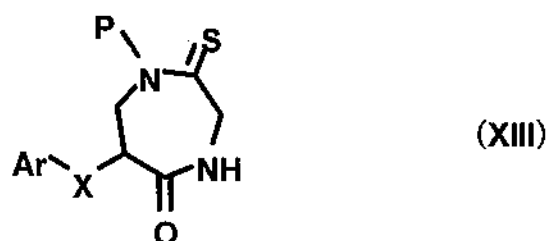
wherein Q^3 and Q^4 are as defined above, and R^{15} and R^{16} independently indicate a hydrogen atom or oxo, so as to perform a cyclization reaction and, optionally, performing a deprotection reaction, or

3) reacting the above compound (V) with $R^{13}-NH_2$, where R^{13} is OR^{14} , $NR^{11}R^{14}$ or a C_2 to C_6 alkyl group substituted with two C_1 to C_6 alkoxy, R^{11} is as defined in claim 1, and R^{14} is formyl, C_1 to C_6 alkylcarbonyl, C_2 to C_6 alkenylcarbonyl, C_2 to C_6 alkynylcarbonyl, C_3 to C_6 cycloalkylcarbonyl, C_6 to C_{14} arylcarbonyl, C_1 to C_{10} heteroarylcarbonyl, or C_1 to C_6 alkoxy carbonyl, or its salt, then subsequently performing a cyclization reaction and, if necessary, performing a deprotection reaction.

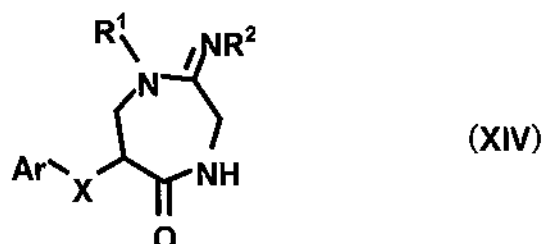
17. A method for producing a compound having the formula (I):



where Ar, W, X, Z, R^1 , and R^2 are as defined in claim 1, comprising the steps of obtaining from the compound (XIII):



where Ar and X are as defined in claim 1, and P is defined as in claim 16, the compound (XIV):



5

where Ar, X, R¹, and R² are as defined in claim 1, then subsequently

1) reacting the above compound (XIV) and compound (X):

10 O=C=N-Z-W (X)

where W and Z are as defined in claim 1, and optionally performing a deprotection reaction, or

2) reacting the above compound (XIV) and compound (VIII):

15 Q¹Q²C=O

where Q¹ and Q² independently indicate a halogen atom or C₆ to C₁₀ aryloxy unsubstituted, or substituted with 1 to 3 of a halogen atom or nitro,

then reacting the resultant product with the compound (IX):

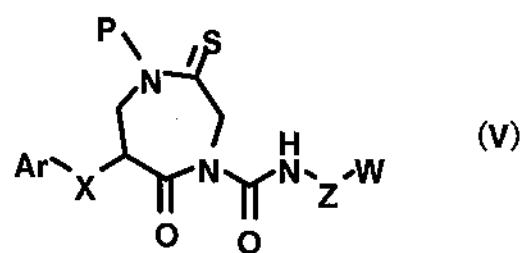
20

H₂N-Z-W

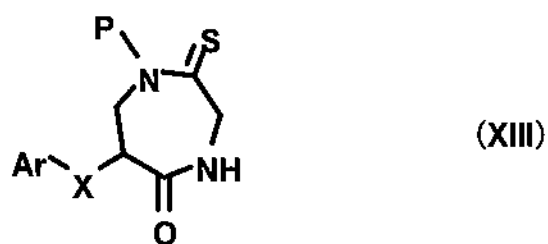
where, W and Z are as defined above, and, optionally performing a deprotection reaction.

18. A compound or a salt thereof having the formula

25 (V):



where Ar, W, X, and Z are as defined in claim 1 and
P is as defined in claim 16, or
5 the formula (XIII):



where Ar, X, and P are as defined above,
or its salt.