

[DESCRIPTION]

[Title of Invention]

3-PHENYLPROPYLAMINE DERIVATIVE

[Technical Field]

5 [0001]

The present invention relates to a novel compound having SF-1 antagonist activity, a polyfunctional molecule containing a moiety corresponding to the compound, particularly an SF-1 degrader, and a pharmaceutical composition etc. containing

10 same.

[Background Art]

[0002]

Steroidogenic factor 1 (also to be referred to as "SF1" or "SF-1") is a nuclear receptor expressed in adrenal cortex, gonad, hypothalamus, and pituitary gland, and is a molecule important for the development of adrenal gland and gonad (Non Patent Literature 1). Since adrenal tumor develops in mice overexpressing SF-1 (Non-Patent Literature 2) and there have been reports of overexpression of SF-1 protein in

20 adrenocortical carcinoma tissue (Non-Patent Literature 3), it is believed that SF-1 contributes to the development and progression of adrenal tumors. On the other hand, it has been shown that SF-1 controls the expression of steroid hormone synthases such as CYP11A1 and CYP17A1 in the adrenal cortex and

25 testis, and induces the production of steroid hormones such as androgen and the like (Non Patent Literatures 4, 5). Androgen is important for the development and growth of prostate cancer. Although the progression of prostate cancer can be suppressed by hormonal therapy such as castration and the like in the

30 early stages of treatment, it progresses to castration-resistant prostate cancer, which is resistant to hormonal therapy. The growth of castration-resistant prostate cancer is known to depend on androgens derived from the adrenal gland (Non Patent Literature 6).

35 [0003]

On the other hand, in recent years, the usefulness of a heterobifunctional molecule, which binds a part that binds to a target protein and a part that recruits an endogenous effector molecule via a linker, has been reported. Heterobifunctional molecules bring a target protein and an endogenous effector molecule into physical proximity, thereby causing a change in the target protein and exerting a desired effect (Non Patent Literature 7).

[0004]

As one of the techniques that utilize such heterobifunctional molecules, Targeted Protein Degradation (TPD) is known. TPD is a technology that induces the degradation of a target protein. It uses a heterobifunctional molecule in which a binder portion that binds to a target protein and a binder portion that binds to an E3 ligase are linked by a linker to induce formation of a complex between the target protein and E3 ligase in cells, and induces ubiquitination and degradation of the target protein, thereby exhibiting strong physiological activity. More than 600 types of E3 ligases have been identified, but only a limited number of them are used in TPD and, in particular, cereblon (CRBN) and Von Hippel-Lindau (VHL) can be mentioned (Non Patent Literature 8). Particularly, binder moieties that bind to CRBN (also called "CRBN ligand") are widely used in TPD, and the diverse structures and usefulness thereof have been reported (Patent Literatures 1-9, Non Patent Literature 9). Although various proteins have been reported as targets in TPD, a targeted protein degrader targeting SF-1 has not been reported so far.

[Citation List]

[Patent Literature]

[0005]

[Patent Literature 1]

WO 2017/197051

[Patent Literature 2]

WO 2018/237026

[Patent Literature 3]
 WO 2019/060693

[Patent Literature 4]
 WO 2019/060742

5 [Patent Literature 5]
 WO 2019/099868

[Patent Literature 6]
 WO 2019/199816

[Patent Literature 7]
 10 WO 2020/210630

[Patent Literature 8]
 WO 2022/081927

[Patent Literature 9]
 WO 2022/081928

15 [Non Patent Literature]
 [0006]

[Non Patent Literature 1]
 Parker KL, Schimmer BP, Steroidogenic factor 1: a key
 determinant of endocrine development and function. *Endocr Rev.*,
 20 1997; 18: 361-77.

[Non Patent Literature 2]
 Doghman M, Karpova T, Rodrigues GA, et al., Increased
 steroidogenic factor-1 dosage triggers adrenocortical cell
 proliferation and cancer. *Mol Endocrinol.*, 2007; 21: 2968-87.

25 [Non Patent Literature 3]
 Sbiera S, Schnull S, Assie G, et al., High Diagnostic and
 Prognostic Value of Steroidogenic Factor-1 Expression in
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[Non Patent Literature 4]
 30 Relav L, Doghman-Bouguerra M, Ruggiero C, Muzzi JCD,
 Figueiredo BC, Lalli E, Steroidogenic Factor 1, a Goldilocks
 Transcription Factor from Adrenocortical Organogenesis to
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[Non Patent Literature 5]
 35 Lin L, Achermann J, C: Steroidogenic Factor-1 (SF-1, Ad4BP,

NR5A1) and Disorders of Testis Development. Sex Dev., 2008; 2: 200-209.

[Non Patent Literature 6]

Attard G, Sarker D, Reid A, Molife R, Parker C, de Bono JS,
5 Improving the outcome of patients with castration-resistant
prostate cancer through rational drug development. Br J
Cancer., 2006 9; 95: 767-74.

[Non Patent Literature 7]

Liwen Hua, et al., Beyond Proteolysis-Targeting Chimeric
10 Molecules: Designing Heterobifunctional Molecules Based on
Functional Effectors. J. Med. Chem., 2022; 65: 8091-8112.

[Non Patent Literature 8]

Chaoguo Cao, et al. Chemistries of bifunctional PROTAC
degraders. Chem. Soc. Rev., 2022: 51: 7066-7114.

15 [Non Patent Literature 9]

Alexander Kazantsev and Mikhail Krasavin, Ligands for
cereblon: 2017-2021 patent overview. Expert Opinion on
Therapeutic Patents. 2022; 32: 2: 171-190.

[Summary of Invention]

20 [Technical Problem]

[0007]

A problem of the present invention is to provide a novel
compound having SF-1 antagonist activity, and a polyfunctional
molecule containing a moiety corresponding to the compound,
25 particularly SF-1 degrader. A further problem of the present
invention is to provide a composition for inhibiting SF-1, a
composition for inducing degradation of SF-1, or a
pharmaceutical composition containing the compound or
polyfunctional molecule. Another problem of the present
30 invention is to provide a method for treating diseases
(particularly, cancers such as castration-resistant prostate
cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-
sensitive prostate cancer, breast cancer and the like,
Cushing's syndrome or primary aldosteronism) including
35 administering the compound or polyfunctional molecule. A still

another problem of the present invention is to provide an intermediate that can be used in the production of the compound or polyfunctional molecule.

[Solution to Problem]

5 [0008]

The present inventors have conducted intensive studies and found that 3-phenylpropylamine derivative compounds represented by the following formula (1) and the like have SF-1 antagonist activity, and that polyfunctional molecules
10 containing a moiety corresponding to the compound represented by the formula (1) or the like can degrade SF-1 protein, and can inhibit proliferation of tumor cells, which resulted in the completion of the present invention.

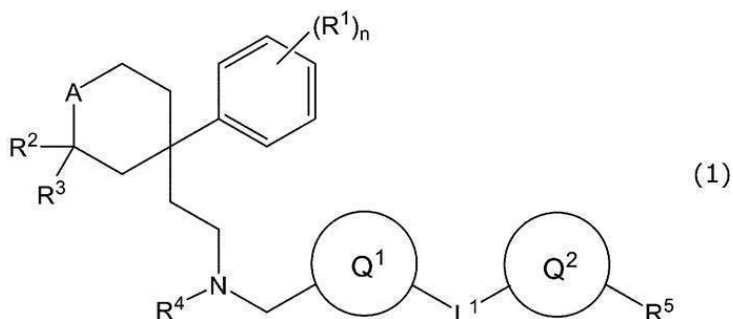
That is, the present invention relates to the following.

15 [1]

A compound represented by the following formula (1):

[0009]

[Chem. 1]



20 [0010]

wherein

A is -O-, -S-, -NR^a-, or -CR^bR^c-,

wherein

R^a is hydrogen or C₁₋₃ alkyl,

25 R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and

the aforementioned alkyl is unsubstituted or substituted by 1 to 3 halogens,

each R¹ in the number of n is independently halogen,

hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

wherein

5 the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens, the aforementioned cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen,

10 unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, or C₂₋₆ alkenyl,

wherein

the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,

R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅ alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl), C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,

wherein

the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

the aforementioned aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

30 the aforementioned heteroaryl and heterocycloalkyl have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-

membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic
5 heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, and heterocycloalkene ring are each
independently unsubstituted or substituted by 1 to 3 groups
selected from the group consisting of halogen, unsubstituted
C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

10 the aforementioned aromatic heterocycle,
heterocycloalkane ring, and heterocycloalkene ring have 1 or 2
hetero atoms selected from oxygen, nitrogen, and sulfur as ring
member atoms,

L¹ is a single bond, -O-, -S-, -NH-, C₁₋₃ alkylene, C₂₋₃
15 alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -
OC(=O)-,

wherein

the aforementioned alkylene and alkenylene are each
independently unsubstituted or substituted by 1 to 3 halogens,

20 ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3-
to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane
25 ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic
heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, heterocycloalkene ring, spirocycloalkane
30 ring, and spiroheterocycloalkane ring are each independently
unsubstituted or substituted by 1 to 3 groups selected from the
group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃
haloalkyl, and

the aforementioned aromatic heterocycle,
35 heterocycloalkane ring, heterocycloalkene ring, and

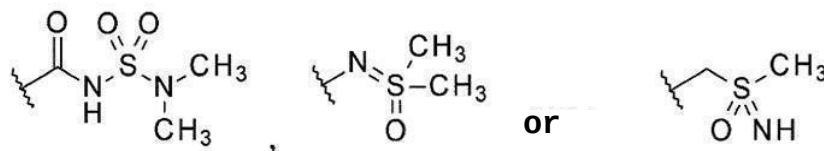
spiroheterocycloalkane ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R⁵ is C₁₋₆ alkyl, carboxy, hydroxy, or

a group represented by the following formula:

5 [0011]

[Chem. 2]



[0012]

wherein

10 the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 or 2 groups selected from the group consisting of carboxy, hydroxy, and -O-C₁₋₆ alkyl, and

n is an integer of 0 to 3, or a pharmaceutically acceptable salt thereof.

15 [2]

The compound according to [1] or a pharmaceutically acceptable salt thereof, wherein A is -O- or -CR^bR^c-.

[3]

The compound according to [1] or [2] or a
20 pharmaceutically acceptable salt thereof, wherein

each R¹ in the number of n is independently halogen, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, or 3- to 7-membered heterocycloalkyl,

wherein the aforementioned heterocycloalkyl has 1 or 2
25 nitrogen atoms as ring member atoms.

[4]

The compound according to any one of [1] to [3] or a pharmaceutically acceptable salt thereof, wherein

R² and R³ are each independently hydrogen or C₁₋₆ alkyl.

30 [5]

The compound according to any one of [1] to [4] or a pharmaceutically acceptable salt thereof, wherein

R⁴ is C₁₋₆ alkyl, -C(=O)-R^d, or 6- to 12-membered heteroaryl,

wherein

the aforementioned R^d is C₁₋₆ alkyl,

5 the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3 halogens or C₃₋₇ cycloalkyl, and

the aforementioned heteroaryl has 1 or 2 nitrogen atoms as ring member atoms.

[6]

10 The compound according to any one of [1] to [5] or a pharmaceutically acceptable salt thereof, wherein

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, or a C₃₋₇

15 cycloalkene ring, and the aforementioned aromatic heterocycle has 1 or 2 nitrogen atoms as ring member atoms.

[7]

The compound according to any one of [1] to [6] or a pharmaceutically acceptable salt thereof, wherein

20 L¹ is a single bond, -O-, C₁₋₃ alkylene, or -C(=O)-.

[8]

The compound according to any one of [1] to [7] or a pharmaceutically acceptable salt thereof, wherein

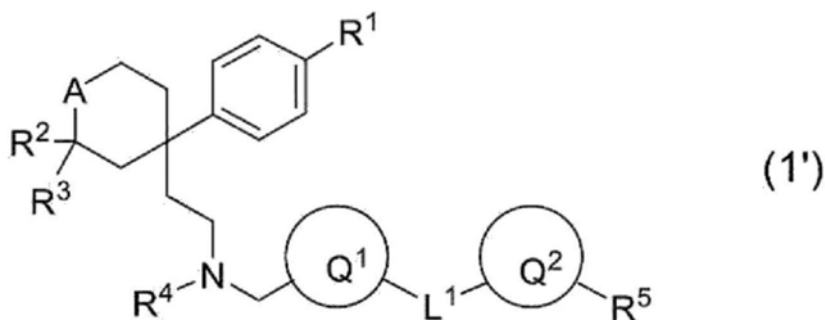
25 ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 5- to 12-membered spiroheterocycloalkane ring, and the aforementioned heterocycloalkane ring and spiroheterocycloalkane ring have 1 or 2 nitrogen atoms as ring member atoms.

30 [9]

A compound represented by the following formula (1'):

[0013]

[Chem. 3]



[0014]

wherein

A is -O- or -CF₂-,

5 R¹ is halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom,

R² and R³ are each independently hydrogen or C₁₋₆ alkyl,

10 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen),

15 ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring,

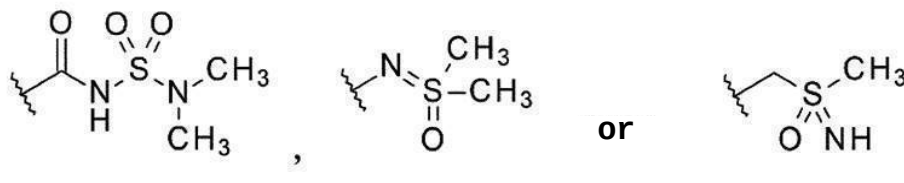
L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,

20 ring Q² is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring optionally substituted by one halogen, a piperidine ring, or a 7-azaspiro[3.5]nonane ring, and

25 R⁵ is C₁₋₆ alkyl optionally having 1 or 2 groups selected from the group consisting of carboxy, hydroxy, and -O-C₁₋₆ alkyl, carboxy, hydroxy, or a group represented by the following formula:

[0015]

[Chem. 4]



[0016]

5 or a pharmaceutically acceptable salt thereof.

[10]

The compound according to [9] or a pharmaceutically acceptable salt thereof, wherein

A is -O-,

10 R² is methyl,

R³ is methyl,

R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, or 6-membered heteroaryl having 1 or 2 nitrogen atoms
15 as ring member atoms (the heteroaryl is optionally substituted by one halogen),

ring Q¹ is a benzene ring optionally having one group selected from the group consisting of halogen and C₁₋₃ alkyl, or a pyridine ring,

20 L¹ is a single bond, -O-, or -C(=O)-, and

ring Q² is a benzene ring, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring.

[11]

The compound according to [9] or [10] or a
25 pharmaceutically acceptable salt thereof, wherein

R¹ is methoxy, and

R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl.

[12]

Any one compound selected from the following group:

30 trans-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)cyclohexanecarboxylic acid,

2-[4-(4-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenoxy)phenyl]propanoic acid,
{trans-4-[(5-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
5 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}pyridin-2-yl)oxy]cyclohexyl}acetic
acid,
[trans-4-(4-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
10 dimethylpropyl)amino]methyl}phenoxy)cyclohexyl]acetic acid,
(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
carboxylic acid,
15 [(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methanol, and
tert-butyl 4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
20 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
4-yl]methyl}piperazine-1-carboxylate,
or a pharmaceutically acceptable salt thereof.

[13]

25 A polyfunctional molecule comprising a moiety
corresponding to the compound or a pharmaceutically acceptable
salt thereof according to any one of [1] to [12].

[14]

The polyfunctional molecule according to [13], further
30 comprising another functional moiety, wherein the moiety
corresponding to the aforementioned compound or a
pharmaceutically acceptable salt thereof is linked to the other
functional moiety directly or is linked via a linker at any
position in R⁵.

35 [15]

The polyfunctional molecule according to [14], wherein
said other functional moiety is an E3 ligase-binding
moiety, an autophagy-recruiting moiety, a lysosome-recruiting
moiety, a kinase-recruiting moiety, a phosphatase-recruiting
5 moiety, a glycosyltransferase-recruiting moiety, an
acetyltransferase-recruiting moiety, or ADC.

[16]

The polyfunctional molecule according to [14], wherein
said other functional moiety is an E3 ligase-binding
10 moiety.

[17]

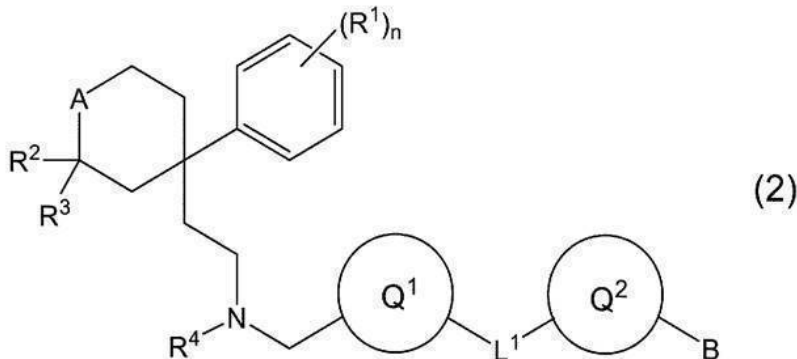
The polyfunctional molecule according to [16], wherein
the E3 ligase-binding moiety is a cereblon (CRBN)-binding
moiety.

15 [18]

A compound represented by the following formula (2):

[0017]

[Chem. 5]



20 [0018]

wherein

A is $-O-$, $-S-$, $-NR^a-$, or $-CR^bR^c-$,

wherein

R^a is hydrogen or C_{1-3} alkyl,

25 R^b and R^c are each independently hydrogen, halogen, or C_{1-3} alkyl, and

the aforementioned alkyl is unsubstituted or substituted
by 1 to 3 halogens,

each R^1 in the number of n is independently halogen,

hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

wherein

5 the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens, the aforementioned cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen,

10 unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, or C₂₋₆ alkenyl,

wherein

the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,

R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅ alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl), C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,

wherein

the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

the aforementioned aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

30 the aforementioned heteroaryl and heterocycloalkyl have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-

membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic
5 heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, and heterocycloalkene ring are each
independently unsubstituted or substituted by 1 to 3 groups
selected from the group consisting of halogen, unsubstituted
C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

10 the aforementioned aromatic heterocycle,
heterocycloalkane ring, and heterocycloalkene ring have 1 or 2
hetero atoms selected from oxygen, nitrogen, and sulfur as ring
member atoms,

L¹ is a single bond, -O-, -S-, -NH-, C₁₋₃ alkylene, C₂₋₃
15 alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -
OC(=O)-,

wherein

the aforementioned alkylene and alkenylene are each
independently unsubstituted or substituted by 1 to 3 halogens,

20 ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3-
to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane
25 ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic
heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, heterocycloalkene ring, spirocycloalkane
30 ring, and spiroheterocycloalkane ring are each independently
unsubstituted or substituted by 1 to 3 groups selected from the
group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃
haloalkyl, and

the aforementioned aromatic heterocycle,
35 heterocycloalkane ring, heterocycloalkene ring, and

spiroheterocycloalkane ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

B is $-L^2-L^3-L^4-R^6$,

L^2 is a single bond, C_{1-6} alkylene, $-C(=O)-$, $-C(=O)NH-$, $-(CH_2)_k-C(=O)NH-$ (k indicates an integer of 1 to 3), or $-NHC(=O)-$,

L^3 is a single bond, C_{1-6} alkylene, C_{3-6} cycloalkylene, piperazinediyl, piperazin-2-onediyl, piperidinediyl, pyrrolidinediyl, azetidinediyl, or 3-oxa-9-azabicyclo[3.3.1]nonanediyl,

L^4 is a single bond, $-NH-$, $-N(-R^7)-$ (R^7 indicates C_{1-6} alkyl), $-CH_2-$, or $-C(=O)-$, and

R^6 is an E3 ligase-binding moiety, an autophagy-recruiting moiety, a lysosome-recruiting moiety, a kinase-recruiting moiety, a phosphatase-recruiting moiety, a glycosyltransferase-recruiting moiety, an acetyltransferase-recruiting moiety, or ADC, and

n is an integer of 0 to 3, or a pharmaceutically acceptable salt thereof.

[19]

The compound according to [18] or a pharmaceutically acceptable salt thereof, wherein A is $-O-$ or $-CR^bR^c-$.

[20]

The compound according to [18] or [19] or a pharmaceutically acceptable salt thereof, wherein

each R^1 in the number of n is independently halogen, $-O-C_{1-6}$ alkyl, $-N(H)-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, or 3- to 7-membered heterocycloalkyl, and the aforementioned heterocycloalkyl has 1 or 2 nitrogen atoms as ring member atoms.

[21]

The compound according to any one of [18] to [20] or a pharmaceutically acceptable salt thereof, wherein

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl.

[22]

The compound according to any one of [18] to [21] or a

pharmaceutically acceptable salt thereof, wherein

R^4 is C_{1-6} alkyl, $-C(=O)-R^d$, or 6- to 12-membered heteroaryl,

wherein

5 the aforementioned R^d is C_{1-6} alkyl,

the aforementioned C_{1-6} alkyl is unsubstituted or substituted by 1 to 3 halogens or C_{3-7} cycloalkyl, and

the aforementioned heteroaryl has 1 or 2 nitrogen atoms as ring member atoms.

10 [23]

The compound according to any one of [18] to [22] or a pharmaceutically acceptable salt thereof, wherein

ring Q^1 is a C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
15 aromatic heterocycle, a C_{3-7} cycloalkane ring, or a C_{3-7} cycloalkene ring, and the aforementioned aromatic heterocycle has 1 or 2 nitrogen atoms as ring member atoms.

[24]

The compound according to any one of [18] to [23] or a
20 pharmaceutically acceptable salt thereof, wherein

L^1 is a single bond, $-O-$, C_{1-3} alkylene, or $-C(=O)-$.

[25]

The compound according to any one of [18] to [24] or a pharmaceutically acceptable salt thereof, wherein

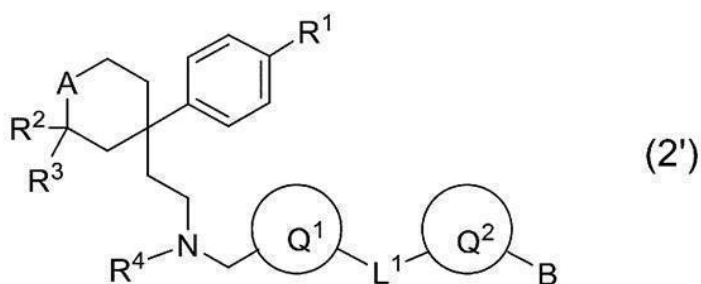
25 ring Q^2 is a C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a C_{3-7} cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C_{3-7} cycloalkene ring, or a 5- to 12-membered spiroheterocycloalkane ring, and the aforementioned heterocycloalkane ring and spiroheterocycloalkane ring have 1
30 or 2 nitrogen atoms as ring member atoms.

[26]

A compound represented by the following formula (2'):

[0019]

[Chem. 6]



[0020]

wherein

A is -O- or -CF₂-,

5 R¹ is halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom,

R² and R³ are each independently hydrogen or C₁₋₆ alkyl,

10 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl, or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is
15 optionally substituted by one halogen),

ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇
20 cycloalkane ring, or a C₄₋₇ cycloalkene ring,

L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,

ring Q² is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring optionally substituted by one halogen, a piperidine ring, or a
25 7-azaspiro[3.5]nonane ring,

B is -L²-L³-L⁴-R⁶,

L² is a single bond, C₁₋₆ alkylene, -C(=O)-, -C(=O)NH-, - (CH₂)_k-C(=O)NH- (k indicates an integer of 1 to 3), or - NHC(=O)-,

30 L³ is a single bond, C₁₋₆ alkylene, C₃₋₆ cycloalkylene,

piperazinediyl, piperazin-2-onediyl, piperidinediyl,
pyrrolidinediyl, azetidinediyl, or 3-oxa-9-
azabicyclo[3.3.1]nonanediyl,

L⁴ is a single bond, -NH-, -N(-R⁷)- (R⁷ indicates C₁₋₆
5 alkyl), -CH₂-, or -C(=O)-, and

R⁶ is an E3 ligase-binding moiety, an autophagy-
recruiting moiety, a lysosome-recruiting moiety, a kinase-
recruiting moiety, a phosphatase-recruiting moiety, a
glycosyltransferase-recruiting moiety, an acetyltransferase-
10 recruiting moiety, or ADC, or a pharmaceutically acceptable
salt thereof.

[27]

The compound according to any one of [18] to [26] or a
pharmaceutically acceptable salt thereof, wherein R⁶ is an E3
15 ligase-binding moiety.

[28]

The compound according to [27] or a pharmaceutically
acceptable salt thereof, wherein the E3 ligase-binding moiety
is a cereblon (CRBN)-binding moiety.

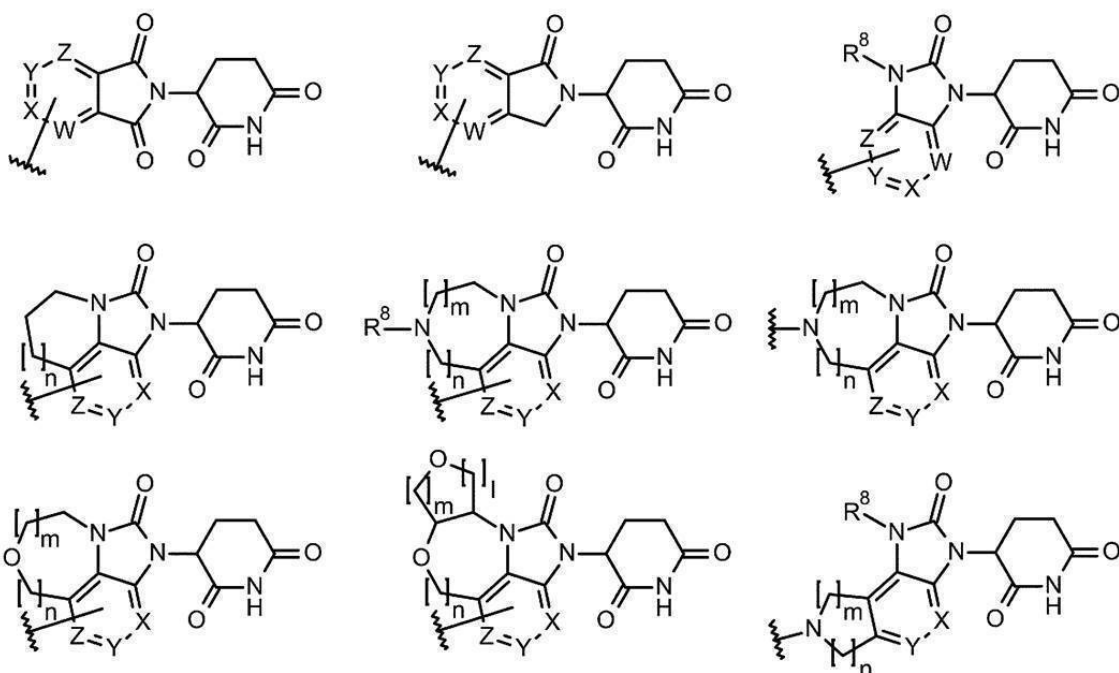
20 [29]

The compound according to any one of [18] to [28] or a
pharmaceutically acceptable salt thereof, wherein

R⁶ is any group selected from the following formulas:

[0021]

25 [Chem. 7]



[0022]

wherein,

R^8 is hydrogen or C_{1-6} alkyl,

5 W , X , Y , and Z indicate each independently a nitrogen atom or a carbon atom optionally having one group selected from the group consisting of halogen, C_{1-6} alkyl, and $-O-C_{1-6}$ alkyl, l , m , and n are each independently an integer of 0 to 3, and

10 a wavy line indicates the bonding position with L^4 .

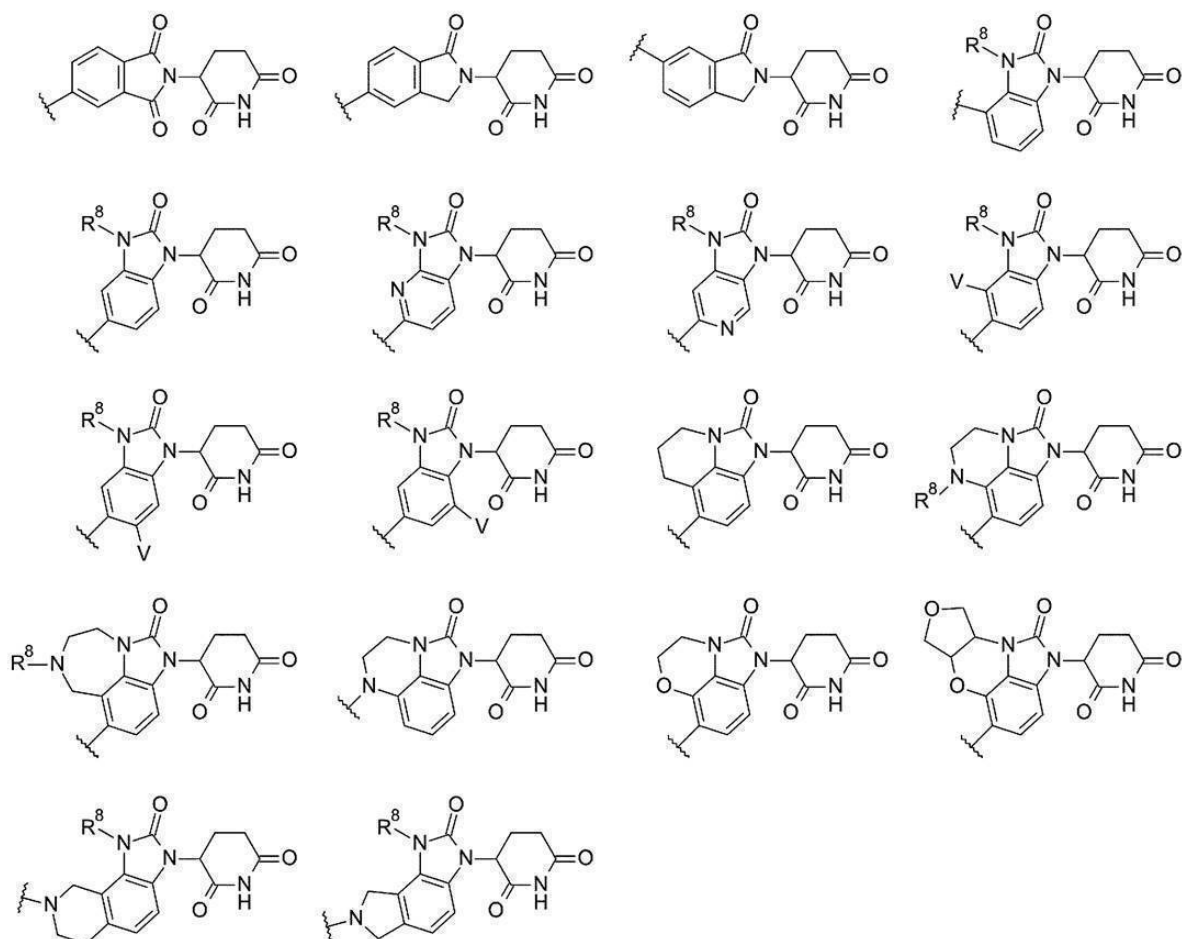
[30]

The compound according to [29] or a pharmaceutically acceptable salt thereof, wherein

R^6 is any group selected from the following formulas:

15 [0023]

[Chem. 8]



[0024]

wherein

R^8 is hydrogen or C_{1-6} alkyl,

5 V is halogen, and

a wavy line indicates the bonding position with L^4 .

[31]

The compound according to any one of [18] to [30] or a pharmaceutically acceptable salt thereof, wherein

10 R^1 is $-O-C_{1-6}$ alkyl optionally substituted by 1 to 3 halogens,

R^4 is C_{1-6} alkyl optionally substituted by 1 to 3 halogens or C_{3-6} cycloalkylmethyl optionally substituted by one trifluoromethyl,

15 ring Q^1 is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C_{1-6} alkyl, a 9- to 10-membered bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C_{4-7} cycloalkane ring, or

a C₄₋₇ cycloalkene ring, and

L¹ is a single bond or -O-.

[32]

The compound according to any one of [18] to [31] or a
5 pharmaceutically acceptable salt thereof, wherein

A is -O-,

R² is methyl, and

R³ is methyl.

[33]

10 The compound according to any one of [18] to [32] or a
pharmaceutically acceptable salt thereof, wherein

R¹ is methoxy, and

R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl.

[34]

15 The compound according to any one of [18] to [33] or a
pharmaceutically acceptable salt thereof, wherein

ring Q¹ is a benzene ring optionally having one halogen,

L¹ is a single bond, and

ring Q² is a cyclohexene ring.

20 [35]

Any one compound selected from the following group:

3-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
25 yl)methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-
1H-benzimidazol-1-yl}piperidine-2,6-dione,

(3R)-3-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-
30 4-yl)methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-
dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione,

(3S)-3-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-
35 4-yl)methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-

dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione,
 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
 5 yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 (3R)-3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 10 4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 (3S)-3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 15 4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
 20 2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl}piperidin-4-
 yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 yl}piperidine-2,6-dione,
 (3R)-3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
 25 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
 2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl}piperidin-4-
 yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 yl}piperidine-2,6-dione,
 (3S)-3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
 30 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
 2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl}piperidin-4-
 yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 yl}piperidine-2,6-dione,
 35 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-

dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione,

5 (3R)-3-{7-[4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione, and

10 (3S)-3-{7-[4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione,

15 or a pharmaceutically acceptable salt thereof.

[35-2]

Any one compound selected from the following group:

(3RS)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-

20 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3R)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-

25 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3S)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-

30 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-

35 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-

4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3R)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3S)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3R)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3S)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione,
(3R)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-

4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione, and
 (3S)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

[36]

10 3-{7-[4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
 15 benzenesulfonate.

[36-2]

3-{7-[4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
 20 monobenzenesulfonate.

[36-3]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
 25 benzenesulfonate.

30 [36-4]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
 35

monobenzenesulfonate.

[36-5]

A crystal of 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione benzenesulfonate, the crystal having peaks at diffraction angles (2θ) of 2.15 ± 0.2 , 8.30 ± 0.2 ,
10 10.29 ± 0.2 , 14.75 ± 0.2 , 17.19 ± 0.2 , 20.00 ± 0.2 , 21.34 ± 0.2 , 22.68 ± 0.2 , 23.77 ± 0.2 , and 25.23 ± 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray ($\lambda = 1.54$ angstroms).

[36-6]

15 A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
20 benzenesulfonate, the crystal having peaks at diffraction angles (2θ) of 2.15 ± 0.2 , 8.30 ± 0.2 , 10.29 ± 0.2 , 14.75 ± 0.2 , 17.19 ± 0.2 , 20.00 ± 0.2 , 21.34 ± 0.2 , 22.68 ± 0.2 , 23.77 ± 0.2 , and 25.23 ± 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray ($\lambda = 1.54$ angstroms).

25 [37] 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
30 ethanesulfonate.

[37-2]

3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
35

imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
monoethanesulfonate.

[37-3]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-
5 2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
ethanesulfonate.

10 [37-4]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
15 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
monoethanesulfonate.

[37-5]

A crystal of 3-{7-[4-{[(4R)-4'-{[{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
20 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-
yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-
1(2H)-yl}piperidine-2,6-dione ethanesulfonate, the crystal
having peaks at diffraction angles (2 θ) of 2.21 $\pm$ 0.2, 12.04 $\pm$ 0.2,
25 14.87 $\pm$ 0.2, 17.69 $\pm$ 0.2, 18.93 $\pm$ 0.2, 20.41 $\pm$ 0.2, 22.42 $\pm$ 0.2,
23.19 $\pm$ 0.2, 24.13 $\pm$ 0.2, and 27.98 $\pm$ 0.2 in a powder X-ray
diffraction pattern obtained by irradiation with copper K α ray
(λ =1.54 angstroms).

[37-6]

30 A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-
4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione
35 ethanesulfonate, the crystal having peaks at diffraction angles

(2 θ) of 2.21 $\pm$ 0.2, 12.04 $\pm$ 0.2, 14.87 $\pm$ 0.2, 17.69 $\pm$ 0.2, 18.93 $\pm$ 0.2, 20.41 $\pm$ 0.2, 22.42 $\pm$ 0.2, 23.19 $\pm$ 0.2, 24.13 $\pm$ 0.2, and 27.98 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray (λ =1.54 angstroms).

5 [38]

3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione 10-camphorsulfonate.

[38-2]

3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione mono-10-camphorsulfonate.

[38-3]

20 (3RS)-3-[7-({1-[(4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione 10-

25 camphorsulfonate.

[38-4]

(3RS)-3-[7-({1-[(4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione mono-10-camphorsulfonate.

[38-5]

A crystal of 3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

35 (4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

yl}ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
 2,3,4,5-tetrahydro[biphenyl]-4-yl}carbonyl}piperidin-4-
 yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 yl}piperidine-2,6-dione 10-camphorsulfonate, the crystal having
 5 peaks at diffraction angles (2θ) of 3.89 ± 0.2 , 6.81 ± 0.2 ,
 7.68 ± 0.2 , 8.20 ± 0.2 , 10.28 ± 0.2 , 13.15 ± 0.2 , 15.97 ± 0.2 , 16.81 ± 0.2 ,
 18.58 ± 0.2 , and 23.56 ± 0.2 in a powder X-ray diffraction pattern
 obtained by irradiation with copper K α ray ($\lambda=1.54$ angstroms).
 [38-6]

10 A crystal of (3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-
 [(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl}ethyl}(3,3,3-
 trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-
 tetrahydro[1,1'-biphenyl]-4-carbonyl}piperidin-4-yl)amino)-2-
 oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 15 yl}piperidine-2,6-dione 10-camphorsulfonate, the crystal having
 peaks at diffraction angles (2θ) of 3.89 ± 0.2 , 6.81 ± 0.2 ,
 7.68 ± 0.2 , 8.20 ± 0.2 , 10.28 ± 0.2 , 13.15 ± 0.2 , 15.97 ± 0.2 , 16.81 ± 0.2 ,
 18.58 ± 0.2 , and 23.56 ± 0.2 in a powder X-ray diffraction pattern
 obtained by irradiation with copper K α ray ($\lambda=1.54$ angstroms).
 20 [39]

3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl}ethyl}(3,3,3-trifluoro-2,2-
 dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
 yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
 25 imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
 ethanesulfonate.
 [39-2]

3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl}ethyl}(3,3,3-trifluoro-2,2-
 30 dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
 yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
 monoethanesulfonate.
 [39-3]

35 (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-

2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
5 ethanesulfonate.

[39-4]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
10 monoethanesulfonate.

[39-5]

A crystal of 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazine-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione ethanesulfonate, the crystal
15 having peaks at diffraction angles (2 θ) of 2.27 $\pm$ 0.2, 8.18 $\pm$ 0.2, 9.88 $\pm$ 0.2, 13.09 $\pm$ 0.2, 14.57 $\pm$ 0.2, 15.80 $\pm$ 0.2, 16.91 $\pm$ 0.2, 17.77 $\pm$ 0.2, 18.87 $\pm$ 0.2, and 20.14 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray (λ =1.54 angstroms).

25 [39-6]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
30 ethanesulfonate ethanesulfonate, the crystal having peaks at diffraction angles (2 θ) of 2.27 $\pm$ 0.2, 8.18 $\pm$ 0.2, 9.88 $\pm$ 0.2, 13.09 $\pm$ 0.2, 14.57 $\pm$ 0.2, 15.80 $\pm$ 0.2, 16.91 $\pm$ 0.2, 17.77 $\pm$ 0.2, 18.87 $\pm$ 0.2, and 20.14 $\pm$ 0.2 in a powder X-ray diffraction pattern
35 obtained by irradiation with copper K α ray (λ =1.54 angstroms).

[40]

3-{7-[(4-{ [(4R) -4' -{ [{2-[(4R) -4- (4-Methoxyphenyl) -2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-
dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
5 yl]methyl}piperazin-1-yl) carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
salicylate.

[40-2]

3-{7-[(4-{ [(4R) -4' -{ [{2-[(4R) -4- (4-Methoxyphenyl) -2,2-
10 dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-
dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methyl}piperazin-1-yl) carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
monosalicylate.

15 [40-3]

(3RS)-3-[7-(4-{ [(4R) -4' -{ [{2-[(4R) -4- (4-Methoxyphenyl) -
2,2-dimethyloxan-4-yl]ethyl} (3,3,3-trifluoro-2,2-
dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
20 imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
salicylate.

[40-4]

(3RS)-3-[7-(4-{ [(4R) -4' -{ [{2-[(4R) -4- (4-Methoxyphenyl) -
2,2-dimethyloxan-4-yl]ethyl} (3,3,3-trifluoro-2,2-
25 dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
monosalicylate.

[40-5]

30 A crystal of 3-{7-[(4-{ [(4R) -4' -{ [{2-[(4R) -4- (4-
methoxyphenyl) -2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-
yl) carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-
35 1(2H)-yl}piperidine-2,6-dione salicylate, the crystal having

peaks at diffraction angles (2θ) of 2.20 ± 0.2 , 4.34 ± 0.2 ,
 9.45 ± 0.2 , 10.97 ± 0.2 , 13.23 ± 0.2 , 16.98 ± 0.2 , 18.09 ± 0.2 ,
 20.20 ± 0.2 , 21.32 ± 0.2 , and 25.19 ± 0.2 in a powder X-ray
diffraction pattern obtained by irradiation with copper K α ray
5 ($\lambda=1.54$ angstroms).

[40-6]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
10 biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-
4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
salicylate, the crystal having peaks at diffraction angles (2θ)
of 2.20 ± 0.2 , 4.34 ± 0.2 , 9.45 ± 0.2 , 10.97 ± 0.2 , 13.23 ± 0.2 ,
 16.98 ± 0.2 , 18.09 ± 0.2 , 20.20 ± 0.2 , 21.32 ± 0.2 , and 25.19 ± 0.2 in a
15 powder X-ray diffraction pattern obtained by irradiation with
copper K α ray ($\lambda=1.54$ angstroms).

[41]

3-{7-[4-{[(4R)-4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
20 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
benzenesulfonate.

[41-2]

25 3-{7-[4-{[(4R)-4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione
30 monobenzenesulfonate.

[41-3]

(3RS)-3-[7-(4-{[(4R)-4'-{[2-[(4R)-4-(4-Methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
35 4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-

imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate.

[41-4]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione monobenzenesulfonate.

10 [41-5]

A crystal of 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione benzenesulfonate, the crystal having peaks at diffraction angles (2θ) of 2.19±0.2, 8.87±0.2, 10.86±0.2, 12.55±0.2, 13.05±0.2, 14.99±0.2, 17.84±0.2, 20.62±0.2, 21.43±0.2, and 25.27±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms).

[41-6]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate, having peaks at diffraction angles (2θ) of 2.19±0.2, 8.87±0.2, 10.86±0.2, 12.55±0.2, 13.05±0.2, 14.99±0.2, 17.84±0.2, 20.62±0.2, 21.43±0.2, and 25.27±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms).

[42]

3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-

dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione 10-camphorsulfonate.

5 [42-2]

3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione mono-10-camphorsulfonate.

[42-3]

(3RS)-3-[7-(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione 10-camphorsulfonate.

[42-4]

(3RS)-3-[7-(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione mono-10-camphorsulfonate.

[42-5]

A crystal of 3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione 10-camphorsulfonate, having peaks at diffraction angles (2 θ) of 2.20 $\pm$ 0.2, 7.82 $\pm$ 0.2, 11.05 $\pm$ 0.2, 12.42 $\pm$ 0.2, 13.34 $\pm$ 0.2, 15.23 $\pm$ 0.2, 16.49 $\pm$ 0.2, 17.86 $\pm$ 0.2, 20.15 $\pm$ 0.2, and 24.36 $\pm$ 0.2 in a powder X-ray diffraction pattern

obtained by irradiation with copper K α ray ($\lambda=1.54$
angstroms) crystal.

[42-6]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[2-[(4R)-4-(4-
5 methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-
4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
10 10-camphorsulfonate, having peaks at diffraction angles (2 θ) of
2.20 $\pm$ 0.2, 7.82 $\pm$ 0.2, 11.05 $\pm$ 0.2, 12.42 $\pm$ 0.2, 13.34 $\pm$ 0.2, 15.23 $\pm$ 0.2,
16.49 $\pm$ 0.2, 17.86 $\pm$ 0.2, 20.15 $\pm$ 0.2, and 24.36 $\pm$ 0.2 in a powder X-
ray diffraction pattern obtained by irradiation with copper K α
ray ($\lambda=1.54$ angstroms) crystal.

[43]

15 A composition for inhibiting Steroidogenic Factor 1,
comprising the compound or a pharmaceutically acceptable salt
thereof according to any one of [1] to [12], the polyfunctional
molecule according to any one of [13] to [17], or the compound
or a pharmaceutically acceptable salt thereof, or the crystal
20 thereof according to any one of [18] to [42-6].

[44]

A composition for inducing degradation of Steroidogenic
Factor 1, comprising the polyfunctional molecule according to
any one of [13] to [17] or the compound or a pharmaceutically
25 acceptable salt thereof, or the crystal thereof according to
any one of [18] to [42-6].

[45]

A pharmaceutical composition comprising the compound or a
pharmaceutically acceptable salt thereof according to any one
30 of [1] to [12], the polyfunctional molecule according to any
one of [13] to [17], or the compound or a pharmaceutically
acceptable salt thereof, or the crystal thereof according to
any one of [18] to [42-6].

[46]

35 The pharmaceutical composition according to [45], which

is for the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.

5 [46-2]

The pharmaceutical composition according to [45], which is for the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, Cushing's syndrome, or primary aldosteronism.

10 [47]

A method for treating castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism, comprising administering an effective
15 amount of the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [12], the polyfunctional molecule according to any one of [13] to [17], or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of [18] to [42-6] to a subject in
20 need of a treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.

[47-2]

25 A method for treating castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, Cushing's syndrome, or primary aldosteronism, comprising administering an effective amount of the compound or a pharmaceutically acceptable salt thereof
30 according to any one of [1] to [12], the polyfunctional molecule according to any one of [13] to [17], or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of [18] to [42-6] to a subject in need of a treatment of castration-resistant prostate cancer,
35 adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive

prostate cancer, Cushing's syndrome, or primary aldosteronism.
[48]

The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [12], the polyfunctional
5 molecule according to any one of [13] to [17] or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of [18] to [42-6], which is for use in the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive
10 prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.
[48-2]

The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [12], the polyfunctional
15 molecule according to any one of [13] to [17] or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of [18] to [42-6], which is for use in the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive
20 prostate cancer, Cushing's syndrome, or primary aldosteronism.
[49]

Use of the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [12], the polyfunctional molecule according to any one of [13] to [17], or the compound
25 or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of [18] to [42-6] in the production of a medicament for the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer,
30 Cushing's syndrome, or primary aldosteronism.
[49-2]

Use of the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [12], the polyfunctional molecule according to any one of [13] to [17], or the compound
35 or a pharmaceutically acceptable salt thereof, or the crystal

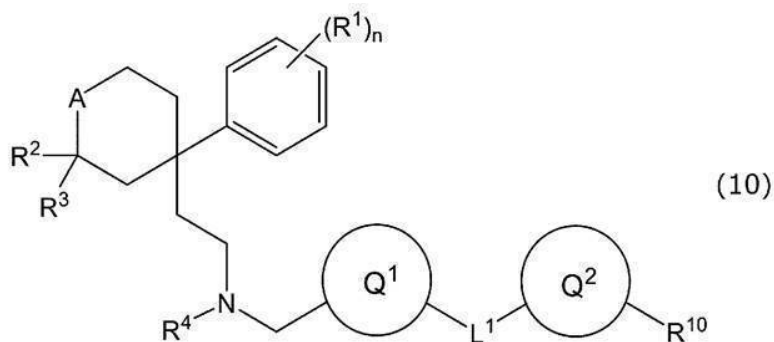
thereof according to any one of [18] to [42-6] in the
production of a medicament for the treatment of castration-
resistant prostate cancer, adrenocortical carcinoma, Leydig
cell tumor, hormone-sensitive prostate cancer, Cushing's
5 syndrome, or primary aldosteronism.

[50]

A compound represented by the following formula (10):

[0025]

[Chem. 9]



10

[0026]

wherein

A is -O-, -S-, -NR^a-, or -CR^bR^c-,

wherein

15 R^a is hydrogen or C₁₋₃ alkyl,

R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and

the aforementioned alkyl is unsubstituted or substituted
by 1 to 3 halogens,

20 each R¹ in the number of n is independently halogen,
hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃
alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered
heterocycloalkyl,

wherein

25 the aforementioned alkyl and alkenyl are each
independently unsubstituted or substituted by 1 to 3 halogens,
the aforementioned cycloalkyl and heterocycloalkyl are
each independently unsubstituted or substituted by 1 to 3
groups selected from the group consisting of halogen,

unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
the aforementioned heterocycloalkyl has 1 or 2 hetero
atoms selected from oxygen, nitrogen, and sulfur as ring member
atoms,
5 R² and R³ are each independently hydrogen, halogen, C₁₋₆
alkenyl, or C₂₋₆ alkenyl,
wherein
the aforementioned alkyl and alkenyl are each
independently unsubstituted or substituted by 1 to 3 halogens,
10 R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅
alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl),
C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,
wherein
the aforementioned C₁₋₆ alkyl is unsubstituted or
15 substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-
membered heterocycloalkyl,
the aforementioned aryl, heteroaryl, cycloalkyl, and
heterocycloalkyl are each independently unsubstituted or
substituted by 1 to 3 groups selected from the group consisting
20 of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
the aforementioned heteroaryl and heterocycloalkyl have 1
or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as
ring member atoms,
ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic
25 hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a
3- to 7-membered heterocycloalkene ring,
wherein
30 the aforementioned aromatic hydrocarbocycle, aromatic
heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, and heterocycloalkene ring are each
independently unsubstituted or substituted by 1 to 3 groups
selected from the group consisting of halogen, unsubstituted
35 C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned aromatic heterocycle,
heterocycloalkane ring and heterocycloalkene ring have 1 or 2
hetero atoms selected from oxygen, nitrogen, and sulfur as ring
member atoms,

5 L^1 is a single bond, -O-, -S-, -NH-, C_{1-3} alkylene, C_{2-3}
alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -
OC(=O)-,

wherein

the aforementioned alkylene and alkenylene are each
10 independently unsubstituted or substituted by 1 to 3 halogens,

ring Q^2 is a C_{6-12} monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C_{3-7} cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C_{3-7} cycloalkene ring, a 3-
15 to 7-membered heterocycloalkene ring, a C_{5-12} spirocycloalkane
ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic
heterocycle, cycloalkane ring, heterocycloalkane ring,
20 cycloalkene ring, heterocycloalkene ring, spirocycloalkane
ring, and spiroheterocycloalkane ring are each independently
unsubstituted or substituted by 1 to 3 groups selected from the
group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3}
haloalkyl, and

25 the aforementioned aromatic heterocycle,
heterocycloalkane ring, heterocycloalkene ring, and
spiroheterocycloalkane ring have 1 or 2 hetero atoms selected
from oxygen, nitrogen, and sulfur as ring member atoms,

R^{10} is C_{1-6} alkyl,

30 wherein

the aforementioned C_{1-6} alkyl is substituted by one or two
3- to 7-membered heterocycloalkyls,

the aforementioned heterocycloalkyl has 1 or 2 hetero
atoms selected from oxygen, nitrogen, and sulfur as ring member
35 atoms, and

the aforementioned heterocycloalkyl is unsubstituted or substituted by an amino-protecting group, and

n is an integer of 0 to 3, or a pharmaceutically acceptable salt thereof.

5 For example, when item numbers are indicated as a range, such as "[18] to [42-6]", and the range includes an item including a sub-number such as [36-3] or [42-4], the item including the sub-number is also included in the range.
[Advantageous Effects of Invention]

10 [0027]

Since a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention has SF-1 antagonist activity, it can be used as an SF-1 antagonist or an SF-1 inhibitor. In addition, since SF-1
15 is known to be involved in the development or progression of various diseases such as adrenocortical carcinoma and castration-resistant prostate cancer, the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention can be used in the treatment
20 of such diseases. In addition, since the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention has SF-1 antagonist activity, it can be used as a partial structure in a larger molecule (e.g., polyfunctional molecule) by combining with other
25 functional moieties.

In addition, since the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention specifically binds to SF-1, it can also be used as an SF-1 binder, and further can be used as an SF-1
30 binding moiety in a larger molecule (e.g., polyfunctional molecule) by combining a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention with other functional moieties. Among these, a polyfunctional molecule containing a
35 moiety corresponding to the compound represented by the formula

(1) or a pharmaceutically acceptable salt thereof of the present invention and an E3 ligase-binding moiety, particularly, a compound represented by the formula (2) or a pharmaceutically acceptable salt thereof, or the crystal of the present invention can degrade SF-1 protein and inhibit the proliferation of tumor cells, and thus can be used as an SF-1 inhibitor and an SF-1 degrader, as well as for the treatment of SF-1-related diseases such as adrenocortical carcinoma, castration-resistant prostate cancer, and the like.

10 [Brief Description of Drawings]

[0028]

[Fig. 1]

A powder X-ray diffraction pattern of the crystal obtained in Example CI1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

[Fig. 2]

A powder X-ray diffraction pattern of the crystal obtained in Example CJ1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

[Fig. 3]

25 A powder X-ray diffraction pattern of the crystal obtained in Example CK1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

30 [Fig. 4]

A powder X-ray diffraction pattern of the crystal obtained in Example CL1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

[Fig. 5]

A powder X-ray diffraction pattern of the crystal obtained in Example CM1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the
5 horizontal axis indicates the value of the diffraction angle 2θ .

[Fig. 6]

A powder X-ray diffraction pattern of the crystal obtained in Example CN1, in which the vertical axis indicates
10 the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

[Fig. 7]

A powder X-ray diffraction pattern of the crystal
15 obtained in Example CO1, in which the vertical axis indicates the diffraction intensity in counts/second (cps) and the horizontal axis indicates the value of the diffraction angle 2θ .

[Description of Embodiments]

20 [0029]

<1. Definitions>

Unless otherwise defined, all technical terms and scientific terms used in the present specification have the same meaning as generally understood by those of ordinary skill
25 in the art. If there is any discrepancy between the meaning of a term defined in the present specification and the meaning generally understood by those of ordinary skill in the art, the meaning defined in the present specification shall prevail. Preferred methods and materials are described below; however,
30 methods and materials similar or equivalent to those described in the present specification may be used for practicing or testing the present invention. All references cited in the present specification (including patent literatures and non-patent literatures) are incorporated herein in their entirety
35 by reference. The materials, methods, and examples disclosed in

the present specification are merely illustrative and are not intended for limitation.

[0030]

In the present specification, Steroidogenic factor 1
5 means the protein encoded by the NR5A1 gene, and may be sometimes abbreviated or synonymously referred to as SF-1, hSF-1, SF1, Ad4BP, AD4BP, ELP, FTZ1, TZF1, POF7, SPGF8, SRXX4, or SRXY3.

[0031]

10 In the present specification, "antagonist" means a substance that reduces, interferes with, or neutralizes the action, activity, or effect of another substance. Thus, in the present specification, "SF-1 antagonist" means a substance that reduces, interferes with, or neutralizes the action, activity,
15 or effect of SF-1.

[0032]

In the present specification, "halogen" means fluorine atom (F), chlorine atom (Cl), bromine atom (Br), or iodine atom (I).

20 [0033]

In the present specification, "alkyl" means linear or branched alkyl. In the present specification, "C₁₋₆ alkyl" means alkyl having 1 to 6 carbon atoms, and "C₁₋₃ alkyl" means alkyl having 1 to 3 carbon atoms. Examples of the "alkyl"
25 include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

[0034]

In the present specification, "alkylene" means linear or
30 branched alkylene. In the present specification, "C₁₋₆ alkylene" means alkylene having 1 to 6 carbon atoms, and "C₁₋₃ alkylene" means alkylene having 1 to 3 carbon atoms. Examples of the "alkylene" include, but are not limited to, methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-
35 butylene, t-butylene, n-pentylene, n-hexylene, and the like.

[0035]

In the present specification, "alkenyl" means linear or branched alkenyl. In the present specification, "C₂₋₆ alkenyl" means alkenyl having 2 to 6 carbon atoms, and "C₂₋₅ alkenyl" means alkenyl having 2 to 5 carbon atoms. Examples of the "alkenyl" include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, buta-2,3-dienyl, pentenyl, hexenyl, and the like.

[0036]

10 In the present specification, "alkenylene" means linear or branched alkenylene. In the present specification, "C₂₋₃ alkenylene" means alkenylene having 2 or 3 carbon atoms. Examples of the "alkenylene" include, but are not limited to, ethenylene (vinylene), 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, buta-2,3-dienylene, pentenylene, hexenylene, and the like.

[0037]

In the present specification, "haloalkyl" means alkyl substituted by one or more halogens, and "C₁₋₃ haloalkyl" means C₁₋₃ alkyl substituted by one or more halogens. Examples of the "haloalkyl" include, but are not limited to, trifluoromethyl, difluoromethyl, monofluoromethyl, pentafluoroethyl, tetrafluoroethyl, monofluoroethyl, trifluoroethyl, trichloromethyl, and the like.

25 [0038]

In the present specification, "aromatic hydrocarbocycle" means a monocyclic or polycyclic hydrocarbocycle where at least one of the rings is an aromatic ring. In the present specification, "aryl" means a group derived from an aromatic hydrocarbocycle. "C₆₋₁₂ aryl" means aryl containing 6 to 12 carbon atoms as ring member atoms, "C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle" means monocyclic or bicyclic aromatic hydrocarbocycle containing 6 to 12 carbon atoms as ring member atoms. Examples of the "aromatic hydrocarbocycle" include, but are not limited to, benzene, indene, naphthalene, anthracene,

and the like. Examples of the "aryl" include, but are not limited to, phenyl, indenyl, naphthyl, anthryl, and the like.
[0039]

In the present specification, "aromatic heterocycle" means a monocyclic or polycyclic ring where at least one of the rings is an aromatic ring, which contains one or more heteroatoms selected from atoms other than carbon, such as nitrogen, oxygen, and sulfur, as ring member atoms. In the present specification, "heteroaryl" means a group derived from an aromatic heterocycle. The "6- to 12-membered heteroaryl" means heteroaryl consisting of 6 to 12 ring member atoms, and "6- to 12-membered monocyclic or bicyclic aromatic heterocycle" means a monocyclic or bicyclic aromatic heterocycle consisting of 6 to 12 ring member atoms. Examples of the "aromatic heterocycle" include, but are not limited to, thiophene, pyrrole, pyrazole, triazole, oxazole, oxadiazole, thiazole, pyridine, pyrimidine, pyridazine, pyrazine, quinoline, quinoxaline, benzothiophene, benzimidazole, benzotriazole, benzofuran, and the like. Examples of the "heteroaryl" include, but are not limited to, thienyl, pyrrolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, quinolyl, quinoxalyl, benzothiophenyl, benzimidazolyl, benzotriazolyl, benzofuranyl, and the like.

[0040]

In the present specification, examples of the "6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms" include pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and the like.

[0041]

In the present specification, examples of the "6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms" include, but are not limited to, 6-membered rings such as pyridine, pyrazine, pyrimidine, and pyridazine; 7-membered rings such as azepine,

1,2-diazepine, 1,3-diazepine, and 1,4-diazepine; 8-membered rings such as azocine; 9-membered rings such as azonine; 6/5-membered fused rings such as indole, isoindole, indazole, benzimidazole, and imidazopyridine (including imidazo[1,2-
5 alpyridine); and 6/6-membered fused rings such as quinoline, isoquinoline, quinazoline, quinoxaline, and cinnoline. In the present specification, examples of the "9- or 10-membered bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms" include, but are not limited to, 6/5-
10 membered fused rings such as indole, isoindole, indazole, benzimidazole, and imidazopyridine (including imidazo[1,2-alpyridine); and 6/6-membered fused rings such as quinoline, isoquinoline, quinazoline, quinoxaline, and cinnoline.
[0042]

15 In the present specification, "cycloalkane ring" means a hydrocarbon ring that does not contain an unsaturated bond. In the present specification, "cycloalkyl" means a monovalent group derived from a cycloalkane ring. The "cycloalkane ring" may be a monocyclic cycloalkane, a fused bicyclic cycloalkane,
20 a spiro ring, or a bridged cycloalkane in which two non-adjacent atoms of the ring are connected by an alkylene bridge of 1, 2, 3, or 4 carbon atoms. In the present specification, "C₃₋₇ cycloalkane ring" and "C₄₋₇ cycloalkane ring" mean cycloalkane rings having 3 to 7 and 4 to 7 carbon atoms,
25 respectively, "C₃₋₇ cycloalkyl" and "C₃₋₆ cycloalkyl" mean cycloalkyls having 3 to 7 and 3 to 6 carbon atoms, respectively, and "C₅₋₁₂ spirocycloalkane ring" means a spirocycloalkane ring having 5 to 12 carbon atoms. Examples of the "cycloalkane ring" include cyclobutane, cyclopentane,
30 cyclohexane, cycloheptane, and the like.

[0043]

In the present specification, "cycloalkylene" means a divalent group derived from a cycloalkane ring. In the present specification, "C₃₋₆ cycloalkylene" means cycloalkylene having 3
35 to 6 carbon atoms. Examples of the "cycloalkylene" include,

but are not limited to, cyclobutylene, cyclopentylene, cyclohexylene, and the like.

[0044]

In the present specification, "cycloalkene ring" means a hydrocarbocycle containing at least one carbon-carbon double bond. In the present specification, the "cycloalkene ring" may be a monocyclic cycloalkene, a fused bicyclic cycloalkene, or a bridged cycloalkene in which two non-adjacent atoms of the ring are connected by an alkylene bridge of 1, 2, 3, or 4 carbon atoms. In the present specification, the "C₃₋₇ cycloalkene ring" means a cycloalkene ring having 3 to 7 carbon atoms, and the "C₄₋₇ cycloalkene ring" means a cycloalkene ring having 4 to 7 carbon atoms. "Examples of the "cycloalkene ring" include, but are not limited to, cyclobutene, cyclobutadiene, cyclopentene, cyclopentadiene, cyclohexene, 1,3-cyclohexadiene, 1,4-cyclohexadiene, cycloheptene, 1,3-cycloheptadiene, 1,4-cycloheptadiene, cycloheptatriene, and the like.

[0045]

In the present specification, "heterocycloalkane ring" means a saturated ring containing one or more heteroatoms selected from atoms other than carbon, such as nitrogen, oxygen, and sulfur, as ring member atoms. In the present specification, "heterocycloalkyl" means a monovalent group derived from a heterocycloalkane ring. The "heterocycloalkane ring" may be a monocyclic heterocycloalkane, a fused bicyclic heterocycloalkane, a spiro ring, or a bridged heterocycloalkane in which two non-adjacent atoms of the ring are connected by an alkylene bridge of 1, 2, 3, or 4 carbon atoms. In the present specification, "3- to 7-membered heterocycloalkane ring" means a heterocycloalkane ring having 3 to 7 carbon atoms and heteroatoms in total as ring member atoms, "5- to 12-membered spiroheterocycloalkane ring" means a spiroheterocycloalkane ring having 5 to 12 carbon atoms and heteroatoms in total as ring member atoms, and "3- to 7-membered heterocycloalkyl" means a heterocycloalkyl having 3 to 7 carbon atoms and

heteroatoms in total as ring member atoms. Examples of the "heterocycloalkyl" include oxiranyl, thiiranyl, aziridinyl, oxetanyl, thietanyl, azetidiny, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, pyranyl, 5 tetrahydrothiopyranyl, thiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, thiomorpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-azaphosphinanyl, 1,4-diazepanyl, 10 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, chromanyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 15 1,3-pyrazolidin-1-yl, 7-oxa-1-aza-spiro[4,4]nonanyl, 3-azabicyclo[3.1.0]hexanyl, indolinyl, dihydroindolinyl, octahydro-1H-indolyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[4.1.0]heptanyl, 3,4-dihydro-2H-pyranyl, 1,2,3,4-tetrahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, tetrahydro-20 1H-benzo[d]azepinyl and the like.

[0046]

In the present specification, "heterocycloalkene ring" means a ring containing one or more heteroatoms selected from atoms other than carbon, such as nitrogen, oxygen, and sulfur, 25 and at least one double bond. The "heterocycloalkene ring" may be a monocyclic heterocycloalkene, a fused bicyclic heterocycloalkene, a spiro ring, or a bridged heterocycloalkene in which two non-adjacent atoms of the ring are connected by an alkylene bridge of 1, 2, 3, or 4 carbon atoms. In the present 30 specification, "3- to 7-membered heterocycloalkene ring" means a heterocycloalkene ring having 3 to 7 carbon atoms and heteroatoms in total as ring member atoms. Examples of the "heterocycloalkene ring" include, but are not limited to, imidazoline, tetrahydropyridine, dihydropyridine, pyran, 35 thiopyran, dihydropyran, dihydrofuran, dihydropyrazine,

octahydroquinoline, octahydroisoquinoline, dihydrothiophene, dihydropyrroline, and the like.

[0047]

In the present specification, unless otherwise specified,
5 as is clear to those of ordinary skill in the art, the symbol:

[0048]

[Chem. 10]



[0049]

10 means that it is bonded to the other side of the paper (α -configuration), and the symbol:

[0050]

[Chem. 11]



15 [0051]

means that it is bonded to the front side of the paper (β -configuration).

In addition, stereo symbols with an * (e.g. R*, S*, etc.) indicate the relative steric configuration of the asymmetric
20 center. The relative steric configuration is structurally represented by the symbols:

[0052]

[Chem. 12]



25 [0053]

[0054]

In the present specification, "pharmaceutically acceptable" means that it has no significant toxicity and can be used as a pharmaceutical composition. Therefore, in the
30 present specification, "pharmaceutically acceptable salt" means a salt that does not have significant toxicity and can be used as a pharmaceutical composition.

[0055]

In the present invention, "(3RS)-3-[5-(4-{[(4R)-4'-{[2-

[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione" means the same compound as "3-{5-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione".

[0056]

In the present invention, "(3R)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione" means the same compound as "(3R)-3-{5-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione".

[0057]

In the present invention, "(3S)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione" means the same compound as "(3S)-3-{5-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione".

[0058]

In the present invention, "(3RS)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-
5 oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
yl]piperidine-2,6-dione" means the same compound as "3-{7-[(4-
{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
10 yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".
[0059]

In the present invention, "(3R)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
15 trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-
oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
yl]piperidine-2,6-dione" means the same compound as "(3R)-3-{7-
[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
20 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".
[0060]

In the present invention, "(3S)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-
oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
30 yl]piperidine-2,6-dione" means the same compound as "(3S)-3-{7-
[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
35 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".

[0061]

In the present invention, "(3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione" means the same compound as "3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".

[0062]

In the present invention, "(3R)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione" means the same compound as "(3R)-3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".

[0063]

In the present invention, "(3S)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione" means the same compound as "(3S)-3-{7-[(1-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-

imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione".

[0064]

In the present invention, "(3RS)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
5 trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-
oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-
yl]piperidine-2,6-dione" means the same compound as "3-{7-[(4-
{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
10 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione".

[0065]

15 In the present invention, "(3R)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-
oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-
20 yl]piperidine-2,6-dione" means the same compound as "(3R)-3-{7-
[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-
25 imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione".

[0066]

In the present invention, "(3S)-3-[7-(4-{[(4R)-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-
trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-
30 tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-
oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-
yl]piperidine-2,6-dione" means the same compound as "(3S)-3-{7-
[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
35 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-

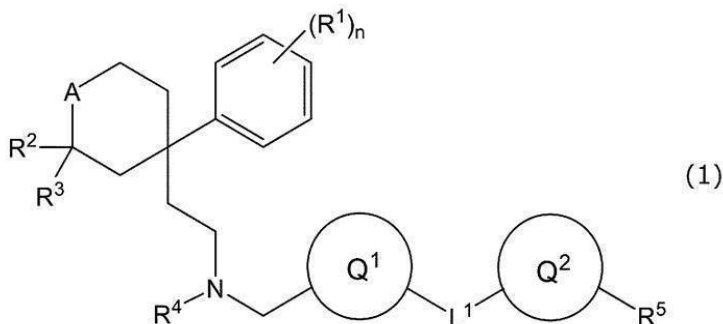
yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione".
[0067]

<2. SF-1 antagonist>

5 In one embodiment of the present invention, a compound represented by the following formula (1):

[0068]

[Chem. 13]



10 [0069]

wherein

A is -O-, -S-, -NR^a-, or -CR^bR^c-,

wherein

R^a is hydrogen or C₁₋₃ alkyl,

15 R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and

the aforementioned alkyl is unsubstituted or substituted by 1 to 3 halogens,

each R¹ in the number of n is independently halogen,

20 hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

wherein

the aforementioned alkyl and alkenyl are each

25 independently unsubstituted or substituted by 1 to 3 halogens,

the aforementioned cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, or C₂₋₆ alkenyl,

wherein

the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,

R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅ alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl), C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,

wherein

the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,

the aforementioned aryl, heteroaryl, cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned heteroaryl and heterocycloalkyl have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, and heterocycloalkene ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned aromatic heterocycle,

heterocycloalkane ring, and heterocycloalkene ring has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

L^1 is a single bond, -O-, -S-, -NH-, C_{1-3} alkylene, C_{2-3} alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -OC(=O)-,

wherein

the aforementioned alkylene and alkenylene are each independently unsubstituted or substituted by 1 to 3 halogens,

10 ring Q^2 is a C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C_{3-7} cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C_{3-7} cycloalkene ring, a 3- to 7-membered heterocycloalkene ring, a C_{5-12} spirocycloalkane
15 ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, heterocycloalkene ring, spirocycloalkane
20 ring, and spiroheterocycloalkane ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

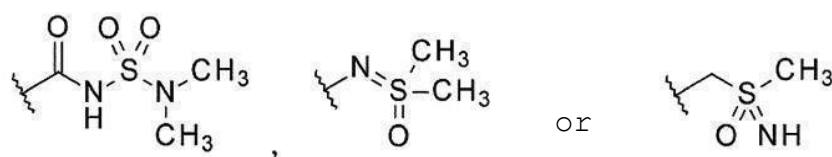
the aforementioned aromatic heterocycle,
25 heterocycloalkane ring, heterocycloalkene ring, and spiroheterocycloalkane ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R^5 is C_{1-6} alkyl, carboxy, hydroxy, or

a group represented by the following formula:

30 [0070]

[Chem. 14]



[0071]

wherein

the aforementioned C₁₋₆ alkyl is unsubstituted or substituted by 1 or 2 groups selected from the group consisting
5 of carboxy, hydroxy, and -O-C₁₋₆ alkyl, and

n is an integer of 0 to 3,

or a pharmaceutically acceptable salt thereof is provided.

[0072]

In one embodiment of the present invention, A in the
10 above-mentioned formula (1) is -O-, -S-, or -CR^bR^c-, preferably
-O- or -CR^bR^c-, more preferably -O- or -CF₂-, particularly
preferably -O-.

[0073]

In one embodiment of the present invention, R^a in the
15 above-mentioned formula (1) is hydrogen or C₁₋₂ alkyl,
preferably hydrogen or methyl, more preferably hydrogen.

[0074]

In one embodiment of the present invention, R^b and R^c in
the above-mentioned formula (1) are each independently hydrogen
20 or halogen, preferably halogen, more preferably F.

[0075]

In one embodiment of the present invention, each R¹ in
the number of n in the above-mentioned formula (1) is
independently halogen, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃
25 alkyl)₂ or 3- to 7-membered heterocycloalkyl (the
aforementioned heterocycloalkyl has 1 or 2 nitrogen atoms as
ring member atoms). In another embodiment of the present
invention, each R¹ in the number of n in the above-mentioned
formula (1) is independently halogen, -O-C₁₋₆ alkyl optionally
30 substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂
or 4- to 6-membered heterocycloalkyl having one nitrogen atom
as a ring member atom, preferably -O-C₁₋₆ alkyl optionally
substituted by 1 to 3 halogens, -N(C₁₋₃ alkyl)₂ or 4- to 6-
membered heterocycloalkyl having one nitrogen atom as a ring
35 member atom, more preferably -O-C₁₋₆ alkyl optionally

substituted by 1 to 3 halogens, further preferably -O-C₁₋₃ alkyl, most preferably methoxy.

[0076]

In one embodiment of the present invention, R² in the
5 above-mentioned formula (1) is hydrogen or C₁₋₆ alkyl,
preferably C₁₋₃ alkyl, more preferably methyl or ethyl, further
preferably methyl.

[0077]

In one embodiment of the present invention, R³ in the
10 above-mentioned formula (1) is hydrogen or C₁₋₆ alkyl,
preferably C₁₋₃ alkyl, more preferably methyl or ethyl, further
preferably methyl.

[0078]

In one embodiment of the present invention, R⁴ in the
15 above-mentioned formula (1) is C₁₋₆ alkyl which is unsubstituted
or substituted by C₃₋₇ cycloalkyl, -C(=O)-C₁₋₆ alkyl, or 6- to
12-membered heteroaryl (the aforementioned heteroaryl has 1 or
2 nitrogen atoms as ring member atoms). In another embodiment
of the present invention, R⁴ in the above-mentioned formula (1)
20 is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-
C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆
cycloalkylmethyl optionally substituted by one trifluoromethyl,
or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring
member atoms (the heteroaryl is optionally substituted by one
25 halogen), preferably C₁₋₆ alkyl optionally substituted by 1 to 3
halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3
halogens, or 6-membered heteroaryl having 1 or 2 nitrogen atoms
as ring member atoms (the heteroaryl is optionally substituted
by one halogen), more preferably 3,3,3-trifluoro-2,2-
30 dimethylpropyl, or -C(=O)-C₁₋₆ alkyl optionally substituted by 1
to 3 halogens, most preferably 3,3,3-trifluoro-2,2-
dimethylpropyl.

[0079]

In one embodiment of the present invention, ring Q¹ in
35 the above-mentioned formula (1) is a C₆₋₁₂ monocyclic or

bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle (the aromatic heterocycle has 1 or 2 nitrogen atoms as ring member atoms), a C₃₋₇ cycloalkane ring, or a C₃₋₇ cycloalkene ring. In another
5 embodiment of the present invention, ring Q¹ in the above-mentioned formula (1) is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms,
10 a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring, preferably a benzene ring optionally having one substituent selected from the group consisting of halogen and C₁₋₃ alkyl, or a pyridine ring, more preferably a benzene ring optionally having one substituent selected from the group consisting of halogen and
15 C₁₋₃ alkyl, particularly preferably a benzene ring.

[0080]

In one embodiment of the present invention, L¹ in the above-mentioned formula (1) is preferably a single bond, -O-, C₁₋₃ alkylene-, or -C(=O)-, more preferably a single bond, -O-,
20 -CH₂- or -C(=O)-, further preferably a single bond, -O-, or -C(=O)-, particularly preferably a single bond.

[0081]

In one embodiment of the present invention, ring Q² in the above-mentioned formula (1) is a C₆₋₁₂ monocyclic or
25 bicyclic aromatic hydrocarbocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring (the aforementioned heterocycloalkane ring has 1 or 2 nitrogen atoms as ring member atoms), a C₃₋₇ cycloalkene ring, or a 5- to 12-membered spiroheterocycloalkane ring (the aforementioned
30 spiroheterocycloalkane ring has 1 or 2 nitrogen atoms as ring member atoms). In another embodiment of the present invention, ring Q² in the above-mentioned formula (1) is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring optionally substituted by one halogen, a
35 piperidine ring, or a 7-azaspiro[3.5]nonane ring, preferably a

benzene ring, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring, further preferably a C₄₋₇ cycloalkene ring.

[0082]

In one embodiment of the present invention, R⁵ in the
5 above-mentioned formula (1) is preferably carboxy or C₁₋₆ alkyl optionally substituted by one or two groups selected from the group consisting of carboxy, hydroxy and -O-C₁₋₆ alkyl, more preferably carboxy or C₁₋₆ alkyl optionally substituted by one group selected from the group consisting of carboxy and
10 hydroxy, further preferably C₁₋₆ alkyl optionally substituted by one group selected from the group consisting of carboxy and hydroxy.

[0083]

In one embodiment of the present invention, a compound of
15 the above-mentioned formula (1) or a pharmaceutically acceptable salt thereof, wherein

A is -O-,

R² is methyl,

R³ is methyl,

20 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen),

25 ring Q¹ is a benzene ring optionally having one substituent selected from the group consisting of halogen and C₁₋₃ alkyl or a pyridine ring,

L¹ is a single bond, -O- or -C(=O)-, and

ring Q² is a benzene ring, a C₄₋₇ cycloalkane ring, or a
30 C₄₋₇ cycloalkene ring,
is provided.

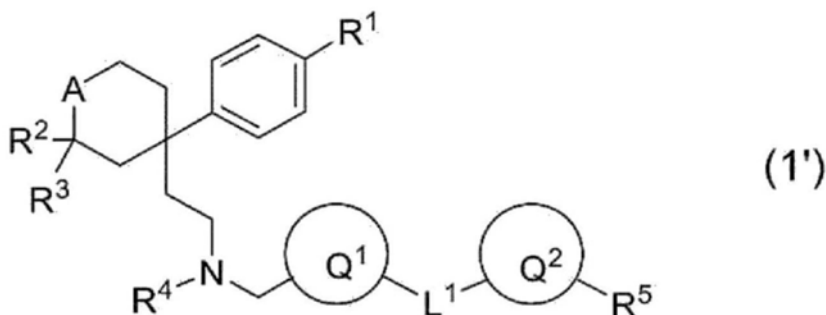
[0084]

In another embodiment of the present invention, a compound of the above-mentioned formula (1), wherein

35 R¹ is methoxy, and

R^4 is 3,3,3-trifluoro-2,2-dimethylpropyl,
or a pharmaceutically acceptable salt thereof is provided.
[0085]

In another embodiment of the present invention, a
5 compound represented by the formula (1) or a pharmaceutically
acceptable salt thereof is a compound represented by the
following formula (1') or a pharmaceutically acceptable salt
thereof. Therefore, in one embodiment of the present
invention, a compound of the following formula (1'):
10 [0086]
[Chem. 15]



[0087]
wherein
15 A is -O- or -CF₂-,
 R^1 is halogen, -O-C₁₋₆ alkyl optionally substituted by 1
to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-
membered heterocycloalkyl having one nitrogen atom as a ring
member atom,
20 R^2 and R^3 are each independently hydrogen or C₁₋₆ alkyl,
 R^4 is C₁₋₆ alkyl optionally substituted by 1 to 3
halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3
halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one
trifluoromethyl or 6-membered heteroaryl having 1 or 2 nitrogen
25 atoms as ring member atoms (the heteroaryl is optionally
substituted by one halogen),
ring Q¹ is a benzene ring optionally having 1 or 2 groups
selected from the group consisting of halogen and C₁₋₃ alkyl, a
6- to 12-membered monocyclic or bicyclic aromatic heterocycle

having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring,

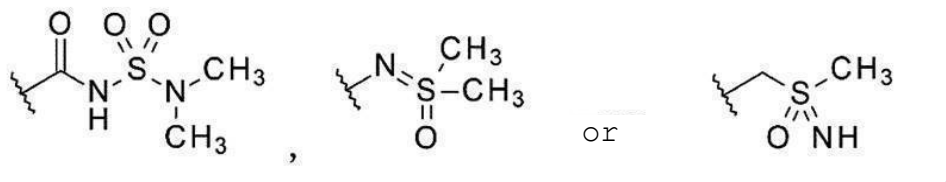
L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,

ring Q² is a benzene ring optionally substituted by one
5 halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring
optionally substituted by one halogen, a piperidine ring, or a
7-azaspiro[3.5]nonane ring, and

R⁵ is C₁₋₆ alkyl optionally having 1 or 2 groups selected
from the group consisting of carboxy, hydroxy and -O-C₁₋₆ alkyl,
10 carboxy, hydroxy, or a group represented by the following
formula:

[0088]

[Chem. 16]



15 [0089]

or a pharmaceutically acceptable salt thereof is provided.

[0090]

Since the formula (1') corresponds to a lower concept of
the formula (1), the definitions, explanations, preferred
20 embodiments, and the like of each group in the formula (1) in
the above all apply to each group in the formula (1'). Also,
in the present specification, when "a compound represented by
the formula (1)" is mentioned without any particular
reservation, this means a concept also including "a compound
25 represented by the formula (1')", in other words, "compounds
represented by the formula (1) and the formula (1')".

[0091]

In another embodiment of the present invention, a
compound of the above-mentioned formula (1') or a
30 pharmaceutically acceptable salt thereof, wherein

A is -O-,

R² is methyl,

R³ is methyl,

R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3
halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3
halogens or 6-membered heteroaryl having 1 or 2 nitrogen atoms
5 as ring member atoms (the heteroaryl is optionally substituted
by one halogen),

ring Q¹ is a benzene ring optionally having one
substituent selected from the group consisting of halogen and
C₁₋₃ alkyl or a pyridine ring,

10 L¹ is a single bond, -O- or -C(=O)-, and

ring Q² is a benzene ring, a C₄₋₇ cycloalkane ring, or a
C₄₋₇ cycloalkene ring,
is provided.

[0092]

15 In yet another embodiment of the present invention, a
compound of the above-mentioned formula (1') or a
pharmaceutically acceptable salt thereof, wherein

R¹ is methoxy, and

R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl,
20 is provided.

[0093]

In yet another embodiment of the present invention, any
one compound selected from the following group:

trans-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-
25 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}phenoxy)cyclohexanecarboxylic acid,
2-[4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}phenoxy)phenyl]propanoic acid,
30 {trans-4-[(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}pyridin-2-yl)oxy]cyclohexyl}acetic
acid,

[trans-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-
35 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-

dimethylpropyl) amino]methyl}phenoxy) cyclohexyl]acetic acid,
 (4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
 dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
 5 carboxylic acid,
 [(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
 dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
 yl]methanol, and
 10 tert-butyl 4'-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
 2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 4-yl]methyl}piperazine-1-carboxylate,
 or a pharmaceutically acceptable salt thereof is provided. All
 15 of these compounds correspond to the compounds represented by
 the aforementioned formula (1) and the formula (1') or
 pharmaceutical acceptable salts thereof.

[0094]

<3. Polyfunctional molecule>

20 As described above, since the compound represented by the
 formula (1) or a pharmaceutically acceptable salt thereof of
 the present invention has SF-1 antagonist activity, it can be
 used as a partial structure in a larger molecule (e.g.,
 polyfunctional molecule) by combining with other functional
 25 moieties. In particular, since the compound represented by the
 formula (1) or a pharmaceutically acceptable salt thereof of
 the present invention specifically binds to SF-1, it can also
 be used as an SF-1-binding moiety in a larger molecule (e.g.,
 polyfunctional molecule) by combining with other functional
 30 moieties.

[0095]

Therefore, in one embodiment of the present invention, a
 polyfunctional molecule containing the moiety corresponding to
 a compound represented by the above-mentioned formula (1) or a
 35 pharmaceutically acceptable salt thereof is provided.

[0096]

Since a compound represented by the formula (1) itself is a complete structure, when linking to other partial structure, it is necessary to remove a specific atom or atomic group from any position in the compound. For example, when a carboxy group present at the end of the compound represented by the formula (1) is linked to an amino group in other partial structure by dehydration condensation, the "part corresponding to the compound represented by the formula (1)" in the molecule after linking is structurally different from the compound represented by the formula (1) in that the "-OH" part of the carboxy group has been removed. In the present specification, a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof from which a specific atom or atomic group has been removed due to the linking reaction is referred to as a "moiety corresponding to a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof".

[0097]

The linking point when linking the compound represented by the formula (1) to other partial structure (e.g., E3 ligase-binding moiety or a linker portion for linking to the E3 ligase-binding moiety) is not particularly limited as long as it maintains the function of the compound represented by the formula (1), particularly SF-1 inhibitory activity and SF-1 binding activity, and preferably any position in R⁵.

Therefore, in one embodiment of the present invention, the polyfunctional molecule of the present invention has a moiety corresponding to a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof linked directly to other functional moiety at any position in R⁵ or linked via a linker. The any position in R⁵ is preferably a carboxy moiety or an amine moiety in R⁵.

[0098]

In the present invention, "polyfunctional molecule" means a molecule that includes a moiety having two or more specific

functions (functionalities). As described above, since the moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention has SF-1 antagonist activity and SF-1 binding activity, the polyfunctional molecule of the present invention includes at least one other functional moiety having a specific function. When one other functional moiety is involved, the polyfunctional molecule of the present invention is "a bifunctional molecule", and when 2, 3, or 4 other functional moieties are involved, the polyfunctional molecule of the present invention is a "trifunctional molecule", "tetrafunctional molecule", or "pentafunctional molecule", respectively. In one embodiment of the present invention, the polyfunctional molecule of the present invention is a bifunctional molecule, a trifunctional molecule, a tetrafunctional molecule, or a pentafunctional molecule, preferably a bifunctional molecule, a trifunctional molecule, or a tetrafunctional molecule, more preferably a bifunctional molecule or a trifunctional molecule, particularly preferably a bifunctional molecule. The other functional moiety may be a moiety having the same function as the moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof, or may be a moiety having a different function. Therefore, in one embodiment of the present invention, the polyfunctional molecule is a homopolyfunctional molecule, and in another embodiment, the polyfunctional molecule is a heteropolyfunctional molecule. In one embodiment of the present invention, the polyfunctional molecule of the present invention is preferably a heterobifunctional molecule or a heterotrifunctional molecule, more preferably a heterobifunctional molecule.

[0099]

The other functional moiety contained in the polyfunctional molecule of the present invention is not particularly limited, and is preferably one that is reasonably

expected to have a beneficial effect when linked to a moiety having SF-1 inhibitory/binding activity, such as enhancing or complementing the activity thereof. Examples of such other functional moiety include, but are not limited to, an E3
5 ligase-binding moiety (or E3 ligase-recruiting moiety), an autophagy-recruiting moiety, a lysosome-recruiting moiety, a kinase-recruiting moiety, a phosphatase-recruiting moiety, a glycosyltransferase-recruiting moiety, acetyltransferase-recruiting moiety, ADC, and the like. In addition, such other
10 functional moiety may be, for example, a substance that is useful exclusively in research applications, such as specific molecular markers and radioactive labels, or a functional substituent for making the compound of formula (1) into a prodrug.

15 [0100]

In the present invention, "binding moiety" (e.g., "E3 ligase-binding moiety") means a moiety that binds to a target (e.g., "E3 ligase"), and "recruitment moiety" (e.g., "E3 ligase-recruiting moiety") means a moiety that allows for the
20 recruitment of a target (e.g., "E3 ligase"). Since a moiety that binds to a target can be used to recruit the target, in one aspect of the present invention, "binding moiety" and "recruitment moiety" are used interchangeably.

[0101]

25 <4. E3 ligase-binding moiety>

In the present invention, "E3 ligase" (or "E3 ubiquitin ligase") means a protein that recruits a ubiquitin-loaded E2 ubiquitin-binding enzyme, recognizes a protein substrate, and assists or directly catalyzes the transfer of ubiquitin from
30 the E2 protein to the substrate. A polyfunctional molecule in which a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention is linked to an E3 ligase-binding moiety can induce degradation of SF-1. Therefore, in one embodiment
35 of the present invention, a polyfunctional molecule containing

a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention, and other functional moiety, wherein the moiety corresponding to the aforementioned compound or a
5 pharmaceutically acceptable salt thereof is linked directly to other functional moiety at any position in R⁵ or linked via a linker, and said other functional moiety is an E3 ligase-binding moiety, is provided. Without intending to be bound by theory, it is believed that when a polyfunctional molecule in
10 which a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention is linked to an E3 ligase-binding moiety is administered to a living body, the polyfunctional molecule recruits both SF-1 and E3 ligase to form a ternary complex
15 consisting of SF-1, E3 ligase, and the polyfunctional molecule, and places SF-1 and E3 ligase in close proximity to each other to ubiquitinate SF-1. Since ubiquitinated SF-1 is degraded by the endogenous proteasome system, the polyfunctional molecule of the present invention containing an E3 ligase-binding moiety
20 is considered to be able to induce specific degradation of SF-1.

[0102]

The technology of inducing degradation of a target protein using a heterobifunctional molecule in which a binder
25 portion that binds to a target protein (also called a Protein of Interest (POI)) and a binder portion that binds to an E3 ligase are linked via an appropriate linker is collectively called Targeted Protein Degradation (TPD). Many reports have been published regarding this technology as to the type of E3
30 ligase to be targeted, various E3 ligase-binding moieties suitable for recruiting the E3 ligase, linker structures suitable for linking the POI and the E3 ligase-binding moiety, technical theories for designing such linker structures, and the like (e.g., Patent Literatures 1-9, Non Patent Literatures
35 7-9). The present invention reports for the first time that

such TPD platform can target SF-1 and actually induce degradation, and in particular presents a novel POI-binding moiety in such a TPD platform.

[0103]

5 In the TPD platform, the POI-binding moiety and the E3 ligase-binding moiety each play a nearly independent and separate role, and therefore, when each block (part) that has been proven to function is combined, there is a high probability that the desired effect will be obtained.

10 Therefore, as the E3 ligase-binding moiety (or combination of ligase-binding moiety and linker portion) in the polyfunctional molecule of the present invention, any E3 ligase-binding moiety (or combination of ligase-binding moiety and linker portion) of any targeted protein degrader that has been confirmed to be

15 useful, for example, the E3 ligase-binding moiety (or combination of ligase-binding moiety and linker portion) disclosed in Patent Literatures 1-9, Non Patent Literatures 7-9 can be applied. In addition, the E3 ligase-binding moiety (or combination of ligase-binding moiety and linker portion) in a

20 heterobifunctional molecule such as ARV-471, ARV-110, CFT8634, CFT7455, CFT1946, ARV-766, AR-LDD, GT20029, NX-2127, HSK29116, BGB-16673, DT-2216, FHD-609, LNK01002, KT-474, KT-413, NX-5948, KT-333, CG001419, CFT8919 and the like, which has been reported to have been subjected to clinical trials or preclinical trials

25 can also be applied. In other words, when a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention is linked to an E3 ligase-binding moiety (or combination of ligase-binding moiety and linker portion) of any

30 targeted protein degrader that has heretofore been confirmed to be useful, for example, E3 ligase-binding moieties (or combinations of ligase-binding moiety and linker portion) disclosed in Patent Literatures 1-8, Non Patent Literatures 7-9 and the like or the E3 ligase-binding moiety (or combination of

35 ligase-binding moiety and linker portion) in a

heterobifunctional molecule such as ARV-471, ARV-110, CFT8634, CFT7455, CFT1946, ARV-766, AR-LDD, GT20029, NX-2127, HSK29116, BGB-16673, DT-2216, FHD-609, LNK01002, KT-474, KT-413, NX-5948, KT-333, CG001419, CFT8919 and the like, it can be reasonably
5 expected that a polyfunctional molecule (particularly heterobifunctional molecule) having the desired SF-1 degradation activity can be obtained, although the degree of activity may differ.

[0104]

10 600 or more kinds of E3 ligases have been identified to date, but only a limited number have been used in TPD platforms. The E3 ligase targeted by the polyfunctional molecule of the present invention is not particularly limited. In one embodiment of the present invention, the E3 ligase
15 targeted by the polyfunctional molecule of the present invention includes cereblon (CRBN), Von Hippel-Lindau (VHL), cellular inhibitor of apoptosis protein (cIAP), DDB1 and CUL4 associated factor 11 (DCAF11), DDB1 and CUL4 associated factor 15 (DCAF15), DDB1 and CUL4 associated factor 16 (DCAF16), Mouse
20 double minute 2 homolog (MDM2), Kelch-like ECH-associated protein 1 (KEAP1), RING finger protein 4 (RNF4), RING finger protein 114 (RNF114), Aryl hydrocarbon receptor (AhR), and Fem-1 homolog B (FEM1B), preferably CRBN, VHL, or cIAP, more preferably CRBN or VHL, further preferably CRBN. Therefore, in
25 one embodiment of the present invention, the E3 ligase-binding moiety is CRBN-binding moiety, VHL-binding moiety, cIAP-binding moiety, DCAF11-binding moiety, DCAF15-binding moiety, DCAF16-binding moiety, MDM2-binding moiety, KEAP1-binding moiety, RNF4-binding moiety, RNF114-binding moiety, AhR-binding moiety,
30 or FEM1B-binding moiety, preferably CRBN-binding moiety, VHL-binding moiety, or cIAP-binding moiety, more preferably CRBN-binding moiety or VHL-binding moiety, further preferably CRBN-binding moiety.

[0105]

35 As the "CRBN-binding moiety" in the present invention,

any compound moiety having any structure can be used without limitation as long as it exhibits the desired binding ability to CRBN. For example, the CRBN binding moieties disclosed in Patent Literatures 1-9 and Non Patent Literatures 7-9 can be exemplified. For example, thalidomide, and lenalidomide and pomalidomide which are derivatives thereof are known to exhibit binding ability to CRBN. Therefore, in one embodiment of the present invention, the CRBN-binding moiety is selected from thalidomide, lenalidomide, pomalidomide, thalidomide derivatives, lenalidomide derivatives, and pomalidomide derivatives. In the present invention, the "derivative" in the context of an E3 ligand-binding moiety means a molecule that has a structural difference from the parent molecule (E3 ligand-binding molecule), but maintains the intended binding activity to the target E3 ligase or has a higher binding activity to the target E3 ligase. As the targeted protein degrader containing a CRBN-binding moiety or proteolysis targeting chimera (PROTAC), compounds called ARV-471, ARV-110, CFT8634, CFT7455, CFT1946, AR-LDD, NX-2127, KT-413, NX-5948, CG001419, and CFT8919 have been subjected to clinical trials or preclinical trials. Therefore, in one embodiment of the present invention, the CRBN-binding moiety may be the CRBN-binding moiety in these compounds.

[0106]

In one embodiment of the present invention, the E3 ligase-binding moiety (CRBN-binding moiety) in the present invention may be that referred to in Non Patent Literature 9.

[0107]

In one embodiment of the present invention, the VHL-binding moiety includes VH032 (J. D. Sander and J. K. Joung, Nat. Biotechnol., 2014, 32, 347-355), VH101 (M. Toure and C. M. Crews, Angew. Chem., Int. Ed., 2016, 55, 1966-1973), VH298 (S. L. Schreiber, Cell, 2021, 184, 3-9), and derivatives of these.

[0108]

In one embodiment of the present invention, the cIAP-

binding moiety includes MeBS (J. A. Doudna and E. Charpentier, Science, 2014, 346, 1258096), MV1 (Y. Fedorov, et al., RNA, 2006, 12, 1188-1196), LCL161 (A. L. Jackson, et al., J. Burchard, M. Mao, B. Li, G. Cavet and P. S. Linsley, Nat. Biotechnol., 2003, 21, 635-637), and derivatives of these.
[0109]

In one embodiment of the present invention, the DCAF11-binding moiety includes the ligands disclosed in S. Khan, X. et al., Nat. Med., 2019, 25, 1938-1947, and derivatives thereof.
[0110]

In one embodiment of the present invention, the DCAF15-binding moiety includes E7820 (L. Snyder, American Association for Cancer Research Annual Meeting, April 2021) and a derivative thereof.
[0111]

In one embodiment of the present invention, the DCAF16-binding moiety includes KB02 (G. Weng, et al., Nucleic Acids Res., 2021, 49, D1381-D1387) and a derivative thereof.
[0112]

In one embodiment of the present invention, the MDM2-binding moiety includes Nutlin-3a (J. S. Lazo and E. R. Sharlow, Annu. Rev. Pharmacol. Toxicol., 2016, 56, 23-40), Idasanutlin (L. Jin, W. Wang and G. Fang, Annu. Rev. Pharmacol. Toxicol., 2014, 54, 435-456), and derivatives of these.
[0113]

In one embodiment of the present invention, the KEAP1-binding moiety includes CDDO (R. G. Guenette, et al., Chem. Soc. Rev., 2022, 51, 5740-5756), the ligands disclosed in L. Snyder, American Association for Cancer Research Annual Meeting, April 2021, and derivatives of these.
[0114]

In one embodiment of the present invention, the RNF4-binding moiety includes CCW-16 (I. Susic, et al., Chem. Soc. Rev., 2022, 51, 3487-3534) and a derivative thereof.
[0115]

In one embodiment of the present invention, the RNF114-binding moiety includes Nimbolide (M. Bekes, et al., Nat. Rev. Drug Discovery, 2022, 21, 181-200), EN219 (M. He, et al., Signal Transduction Targeted Ther., 2022, 7, 181), and

5 derivatives of these.

[0116]

In one embodiment of the present invention, the AhR-binding moiety includes beta-NF (K. Li and C. M. Crews, Chem. Soc. Rev., 2022, 51, 5214-5236), and a derivative thereof.

10 [0117]

In one embodiment of the present invention, the FEM1B-binding moiety includes EN106 (M. He, et al., Front. Cell Dev. Biol., 2021, 9, 685106), and a derivative thereof.

[0118]

15 As the E3 ligase-binding moiety in the present invention, any of the structures defined as "R⁶" in a formula represented by the below-mentioned formula (2) may be adopted.

[0119]

<5. Linker>

20 In the polyfunctional molecule of the present invention, the moiety corresponding to a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof may be directly linked to other functional moiety as long as the desired function (e.g., SF-1 inhibitory activity or SF-1
25 degradation activity) is exhibited, but is preferably linked via a linker. Therefore, in one embodiment of the present invention, a polyfunctional molecule in which the moiety corresponding to a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof and other functional
30 moiety (e.g., E3 ligase-binding moiety) are directly linked or linked via a linker, preferably linked via a linker, is provided. The linker used in the polyfunctional molecule of the present invention is not particularly limited as long as it does not impair the desired function (e.g., SF-1 inhibitory
35 activity or SF-1 degradation activity). Therefore, any linker

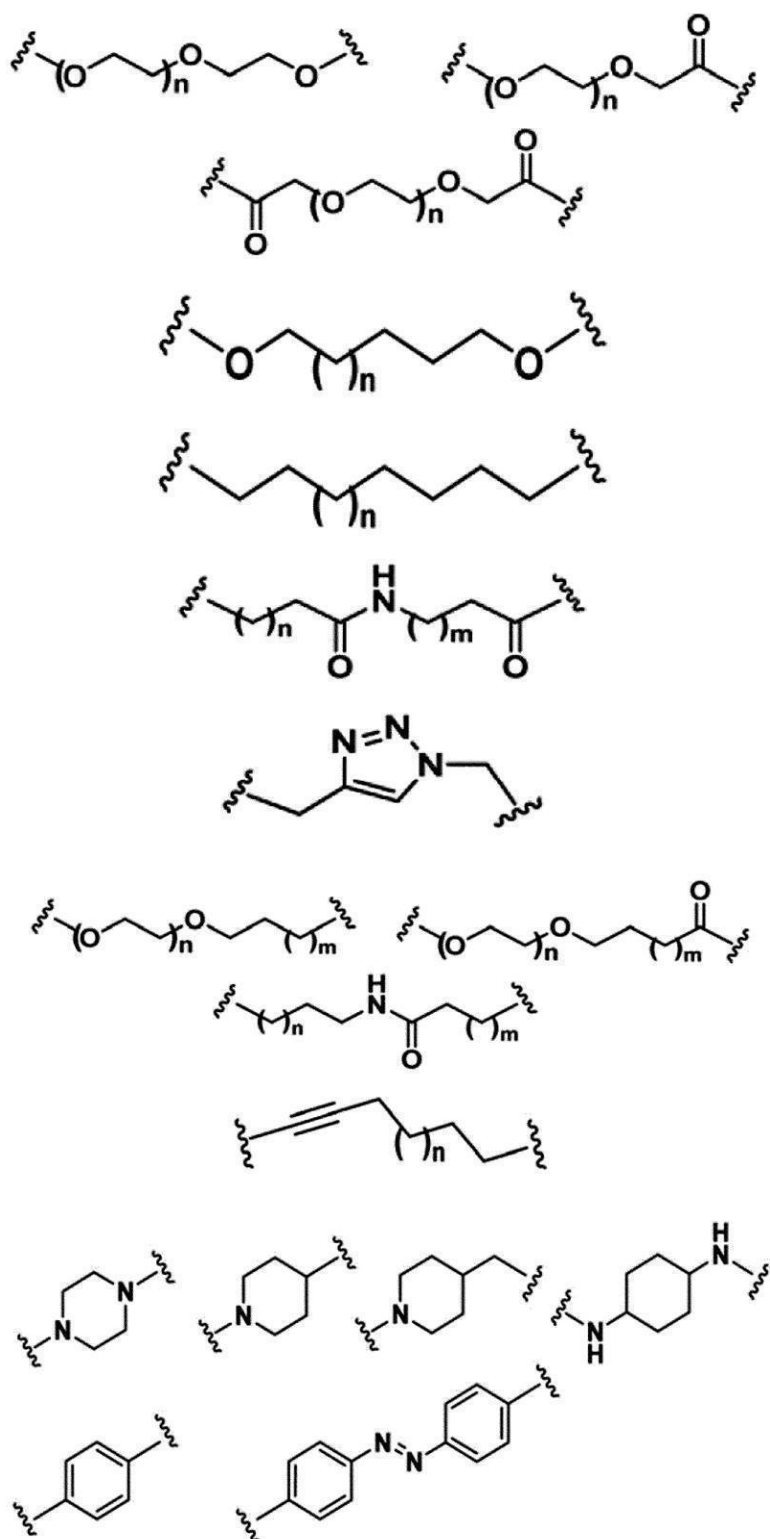
having a structure that is reasonably expected not to impair the desired function (e.g., SF-1 inhibitory activity or SF-1 degradation activity) can be used.

[0120]

5 As described above, in the TPD platform, it is known that the composition and length of the linker can affect the formation of a ternary complex of POI/heterobifunctional molecule/E3 ligase, the degradation induction activity of POI, and the target selectivity. There have been many reports on
10 linker structures used in targeted protein degraders and technical theories for designing and optimizing them (e.g., Patent Literatures 1-8, Non Patent Literatures 7-9). As described above, the present invention presents a novel POI-binding moiety that can be used in such TPD platform.
15 Therefore, when a linker whose effectiveness has already been proven is adopted, there is a high probability that the desired effect will be obtained. Therefore, in one embodiment of the present invention, as the linker portion in the polyfunctional molecule of the present invention, any of the linker portions
20 of targeted protein degraders that have been confirmed to be useful, for example, the linker portions disclosed in Patent Literatures 1-8, Non Patent Literatures 7-9 or the linker portions of ARV-471, ARV-110, CFT8634, ARV-766, AR-LDD, GT20029, NX-2127, HSK29116, BGB-16673, DT-2216, FHD-609,
25 LNK01002, KT-474, KT-413, NX-5948, KT-333, CG001419, CFT7455, CFT1946, or CFT8919 that have been reported to have been subjected to clinical trials or preclinical trials can be applied. In one embodiment of the present invention, for example, the linker may be selected from the linker structures
30 shown in Non Patent Literature 8, Table 2, specifically, those having any structural motif represented by the following formula:

[0121]

[Chem. 17]



[0122]

wherein n and m indicate each independently an integer of 1 to 10. Generally, it is known that use of a too short linker
 5 tends to decrease the efficiency of formation of a ternary complex (POI/heterobifunctional molecule/E3 ligase), and instead, increase the directivity of formation of a binary

complex (POI/heterobifunctional molecule or heterobifunctional molecule/E3 ligase). On the other hand, it is known that use of a too long linker tends to increase the spatial degree of freedom, decrease the efficiency of formation of a ternary
5 complex, and also decrease the stability of the entire molecule. Therefore, it is preferable to adopt a linker of an appropriate length in the present invention. From the above-mentioned aspects, in one embodiment of the present invention, n and m in the above-mentioned formula are each independently
10 an integer of 1 to 5; in another embodiment of the present invention, n and m in the above-mentioned formula are each independently an integer of 1 to 4; in yet another embodiment of the present invention, n and m in the above-mentioned formula are each independently an integer of 1 to 3; in yet
15 another embodiment of the present invention, n and m in the above-mentioned formula are each independently an integer of 1 or 2.

[0123]

In the TPD platform, it is known that the binding
20 position between the linker and the POI, or the linker and the E3 ligase can also affect the formation of a ternary complex of POI/heterobifunctional molecule/E3 ligase, the degradation induction activity of the POI, and the target selectivity. Regarding the binding position of the linker, it is generally
25 considered to be essential that the linker is not linked to the main active site in the POI-binding moiety and E3 ligase-binding moiety, and that the linker is linked to a solvent-exposed site in the POI-binding moiety and E3 ligase-binding moiety. From such aspects, in the polyfunctional molecule of
30 the present invention, the moiety corresponding to a compound represented by the formula (1) or a pharmaceutically acceptable salt thereof is preferably linked to the linker at any position in R⁵, and is particularly preferably linked to the linker at the carboxy or amine moiety in R⁵. Furthermore, the binding
35 moiety of the linker and the E3 ligase-binding moiety is

preferably selected as appropriate from the above-mentioned aspects, with reference to known reports.

[0124]

In one embodiment of the present invention, the linker of
5 the present invention may be "-L²-L³-L⁴-" defined in the below-mentioned formula (2).

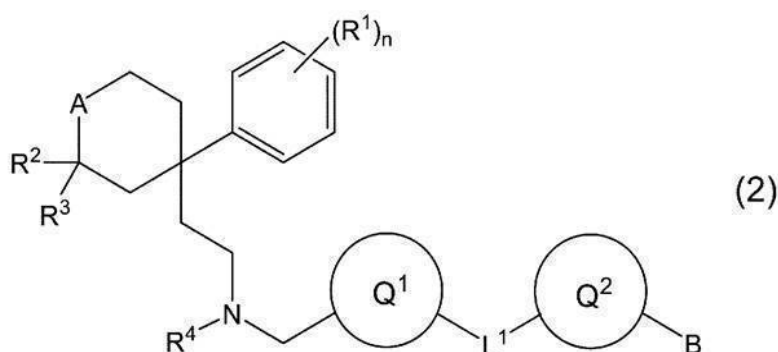
[0125]

<6. SF-1 degrader>

In one embodiment of the present invention, a compound
10 represented by the following formula (2):

[0126]

[Chem. 18]



[0127]

15 wherein

A is -O-, -S-, -NR^a- or -CR^bR^c-,

wherein

R^a is hydrogen or C₁₋₃ alkyl,

R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and
20

the aforementioned alkyl is unsubstituted or substituted by 1 to 3 halogens,

each R¹ in the number of n is independently halogen, hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered
25 heterocycloalkyl,

wherein

the aforementioned alkyl and alkenyl are each

independently unsubstituted or substituted by 1 to 3 halogens,
the aforementioned cycloalkyl and heterocycloalkyl are
each independently unsubstituted or substituted by 1 to 3
groups selected from the group consisting of halogen,
5 unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
the aforementioned heterocycloalkyl has 1 or 2 hetero
atoms selected from oxygen, nitrogen, and sulfur as ring member
atoms,
R² and R³ are each independently hydrogen, halogen, C₁₋₆
10 alkyl, or C₂₋₆ alkenyl,
wherein
the aforementioned alkyl and alkenyl are each
independently unsubstituted or substituted by 1 to 3 halogens,
R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅
15 alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl),
C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,
wherein
the aforementioned C₁₋₆ alkyl is unsubstituted or
substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-
20 membered heterocycloalkyl,
the aforementioned aryl, heteroaryl, cycloalkyl, and
heterocycloalkyl are each independently unsubstituted or
substituted by 1 to 3 groups selected from the group consisting
of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
25 the aforementioned heteroaryl and heterocycloalkyl have 1
or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as
ring member atoms,
ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
30 aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a
3- to 7-membered heterocycloalkene ring,
wherein
the aforementioned aromatic hydrocarbocycle, aromatic
35 heterocycle, cycloalkane ring, heterocycloalkane ring,

cycloalkene ring, and heterocycloalkene ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

5 the aforementioned aromatic heterocycle, heterocycloalkane ring and heterocycloalkene ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

L¹ is a single bond, -O-, -S-, -NH-, C₁₋₃ alkylene, C₂₋₃
10 alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -OC(=O)-,

wherein

the aforementioned alkylene and alkenylene are each independently unsubstituted or substituted by 1 to 3 halogens,

15 ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3- to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane
20 ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aforementioned aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, heterocycloalkene ring, spirocycloalkane
25 ring, and spiroheterocycloalkane ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aforementioned aromatic heterocycle,
30 heterocycloalkane ring, heterocycloalkene ring, and spiroheterocycloalkane ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

B is -L²-L³-L⁴-R⁶,

L² is a single bond, C₁₋₆ alkylene, -C(=O)-, -C(=O)NH-, -
35 (CH₂)_k-C(=O)NH- (k indicates an integer of 1 to 3), or -

NHC(=O)-,

L³ is a single bond, C₁₋₆ alkylene, C₃₋₆ cycloalkylene, piperazinediyl, piperazin-2-onediyl, piperidinediyl, pyrrolidinediyl, azetidinediyl, or 3-oxa-9-

5 azabicyclo[3.3.1]nonanediyl,

L⁴ is a single bond, -NH-, -N(-R⁷)- (R⁷ indicates C₁₋₆ alkyl), -CH₂-, or -C(=O)-,

R⁶ is an E3 ligase-binding moiety, an autophagy-recruiting moiety, a lysosome-recruiting moiety, a kinase-
10 recruiting moiety, a phosphatase-recruiting moiety, a glycosyltransferase-recruiting moiety, an acetyltransferase-recruiting moiety, or ADC, and

n is an integer of 0 to 3,

or a pharmaceutically acceptable salt thereof is provided.

15 [0128]

In one embodiment of the present invention, A in the above-mentioned formula (2) is -O-, -S-, or -CR^bR^c-, preferably -O- or -CR^bR^c-, more preferably -O- or -CF₂-, particularly preferably -O-.

20 [0129]

In one embodiment of the present invention, R^a in the above-mentioned formula (2) is hydrogen or C₁₋₂ alkyl, preferably hydrogen or methyl, more preferably hydrogen.

[0130]

25 In one embodiment of the present invention, R^b and R^c in the above-mentioned formula (2) are each independently hydrogen or halogen, preferably halogen, more preferably F.

[0131]

In one embodiment of the present invention, each R¹ in
30 the number of n in the above-mentioned formula (2) is independently halogen, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, or 3- to 7-membered heterocycloalkyl (the aforementioned heterocycloalkyl has 1 or 2 nitrogen atoms as ring member atoms). In another embodiment of the present
35 invention, each R¹ in the number of n in the above-mentioned

formula (1) is independently halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom, preferably -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom, more preferably -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, further preferably -O-C₁₋₃ alkyl, most preferably methoxy.

10 [0132]

In one embodiment of the present invention, R² in the above-mentioned formula (2) is hydrogen or C₁₋₆ alkyl, preferably C₁₋₃ alkyl, more preferably methyl or ethyl, further preferably methyl.

15 [0133]

In one embodiment of the present invention, R³ in the above-mentioned formula (2) is hydrogen or C₁₋₆ alkyl, preferably C₁₋₃ alkyl, more preferably methyl or ethyl, further preferably methyl.

20 [0134]

In one embodiment of the present invention, each R⁴ in the above-mentioned formula (2) is C₁₋₆ alkyl, -C(=O)-C₁₋₆ alkyl, or 6- to 12-membered heteroaryl (the aforementioned heteroaryl has 1 or 2 nitrogen atoms as ring member atoms), each of which is unsubstituted or substituted by C₃₋₇ cycloalkyl. In another embodiment of the present invention, R⁴ in the above-mentioned formula (2) is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen), preferably C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is

optionally substituted by one halogen), more preferably 3,3,3-trifluoro-2,2-dimethylpropyl or $-C(=O)-C_{1-6}$ alkyl optionally substituted by 1 to 3 halogens, most preferably 3,3,3-trifluoro-2,2-dimethylpropyl.

5 [0135]

In one embodiment of the present invention, ring Q^1 in the above-mentioned formula (2) is C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle (the aromatic heterocycle has 1
10 or 2 nitrogen atoms as ring member atoms), a C_{3-7} cycloalkane ring, or a C_{3-7} cycloalkene ring. In another embodiment of the present invention, ring Q^1 in the above-mentioned formula (1) is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C_{1-3} alkyl, a 6- to 12-
15 membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C_{4-7} cycloalkane ring, or a C_{4-7} cycloalkene ring, preferably a benzene ring optionally having one substituent selected from the group consisting of halogen and C_{1-3} alkyl, or a pyridine ring, more
20 preferably a benzene ring optionally having one substituent selected from the group consisting of halogen and C_{1-3} alkyl, particularly preferably a benzene ring.

[0136]

In one embodiment of the present invention, L^1 in the
25 above-mentioned formula (2) is preferably a single bond, $-O-$, C_{1-3} alkylene, or $-C(=O)-$, more preferably a single bond, $-O-$, $-CH_2-$, or $-C(=O)-$, further preferably a single bond, $-O-$, or $-C(=O)-$, particularly preferably a single bond.

[0137]

30 In one embodiment of the present invention, ring Q^2 in the above-mentioned formula (2) is a C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a C_{3-7} cycloalkane ring, a 3- to 7-membered heterocycloalkane ring (the aforementioned heterocycloalkane ring has 1 or 2 nitrogen atoms as ring member
35 atoms), a C_{3-7} cycloalkene ring, or a 5- to 12-membered

spiroheterocycloalkane ring (the aforementioned spiroheterocycloalkane ring has 1 or 2 nitrogen atoms as ring member atoms). In another embodiment of the present invention, ring Q² in the above-mentioned formula (1) is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring optionally substituted by one halogen, a piperidine ring, or a 7-azaspiro[3.5]nonane ring, preferably a benzene ring, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring, further preferably a C₄₋₇ cycloalkene ring.

10 [0138]

In one embodiment of the present invention, L² in the above-mentioned formula (2) is preferably C₁₋₆ alkylene, -C(=O)-, or -C(=O)NH-, more preferably C₁₋₆ alkylene or -C(=O)-, further preferably C₁₋₆ alkylene.

15 [0139]

In one embodiment of the present invention, L³ in the above-mentioned formula (2) is preferably piperazinediyl, piperazin-2-onediyl, piperidinediyl, pyrrolidinediyl, azetidinediyl, or 3-oxa-9-azabicyclo[3.3.1]nonanediyl, more preferably piperazinediyl, piperazin-2-onediyl, piperidinediyl, or 3-oxa-9-azabicyclo[3.3.1]nonanediyl, further preferably piperazinediyl or piperidinediyl, particularly preferably piperazinediyl.

[0140]

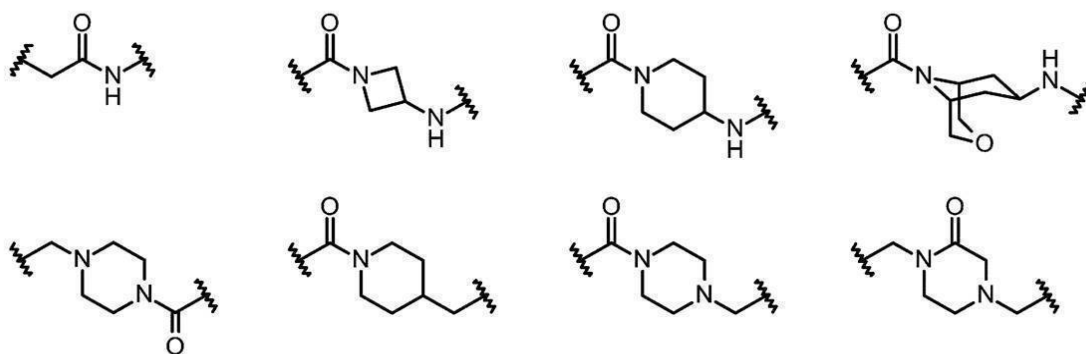
25 In one embodiment of the present invention, L⁴ in the above-mentioned formula (2) is preferably -NH-, -CH₂-, or -C(=O)-, more preferably -NH- or -C(=O)-, further preferably -C(=O)-.

[0141]

30 In one embodiment of the present invention, "-L²-L³-L⁴-" in the above-mentioned formula (2) indicates any structure selected from the groups represented by the following formulas:

[0142]

[Chem. 19]



[0143]

wherein a wavy line indicates the bonding position with Q^2 and R^6 .

5 [0144]

In one embodiment of the present invention, a compound of the above-mentioned formula (2), wherein

A is -O-,

R^2 is methyl,

10 R^3 is methyl,

R^4 is C_{1-6} alkyl optionally substituted by 1 to 3 halogens, $-C(=O)-C_{1-6}$ alkyl optionally substituted by 1 to 3 halogens, or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted
15 by one halogen),

ring Q^1 is a benzene ring optionally having one substituent selected from the group consisting of halogen and C_{1-3} alkyl, or a pyridine ring,

L^1 is a single bond, -O-, or $-C(=O)-$, and

20 ring Q^2 is a benzene ring, a C_{4-7} cycloalkane ring, or a C_{4-7} cycloalkene ring,
or a pharmaceutically acceptable salt thereof is provided.

[0145]

In another embodiment of the present invention, a
25 compound of the above-mentioned formula (2), wherein

each R^1 in the number of n is methoxy, and

R^4 is 3,3,3-trifluoro-2,2-dimethylpropyl,

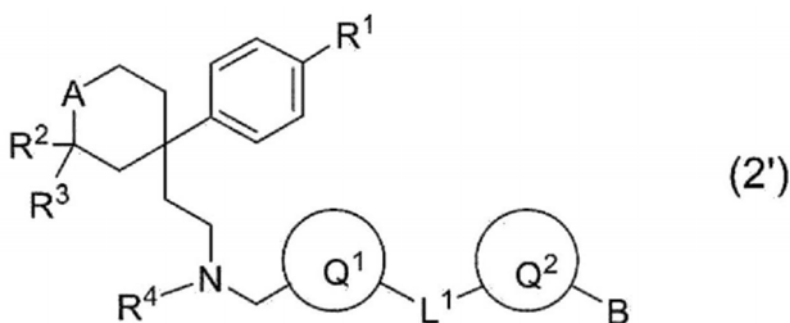
or a pharmaceutically acceptable salt thereof is provided.

[0146]

In another embodiment of the present invention, a compound represented by the formula (2) or a pharmaceutically acceptable salt thereof is a compound represented by the following formula (2') or a pharmaceutically acceptable salt thereof. Therefore, in one embodiment of the present invention, a compound represented by the following formula (2'):

[0147]

[Chem. 20]



10

[0148]

wherein

A is -O- or -CF₂-,

R¹ is halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom,

R² and R³ are each independently hydrogen or C₁₋₆ alkyl,

R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl, or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen),

ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring,

L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,
ring Q² is a benzene ring optionally substituted by one
halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring
optionally substituted by one halogen, a piperidine ring, or a
5 7-azaspiro[3.5]nonane ring,

B is -L²-L³-L⁴-R⁶,

L² is a single bond, C₁₋₆ alkylene, -C(=O)-, -C(=O)NH-, -
(CH₂)_k-C(=O)NH- (k indicates an integer of 1 to 3), or -
NHC(=O)-,

10 L³ is a single bond, C₁₋₆ alkylene, C₃₋₆ cycloalkylene,
piperazinediyl, piperazin-2-onediyl, piperidinediyl,
pyrrolidinediyl, azetidinediyl, or 3-oxa-9-
azabicyclo[3.3.1]nonanediyl,

L⁴ is a single bond, -NH-, -N(-R⁷)- (R⁷ indicates C₁₋₆
15 alkyl), -CH₂-, or -C(=O)-, and

R⁶ is an E3 ligase-binding moiety, an autophagy-
recruiting moiety, a lysosome-recruiting moiety, a kinase-
recruiting moiety, a phosphatase-recruiting moiety, a
glycosyltransferase-recruiting moiety, an acetyltransferase-
20 recruiting moiety, or ADC,
or a pharmaceutically acceptable salt thereof is provided.
[0149]

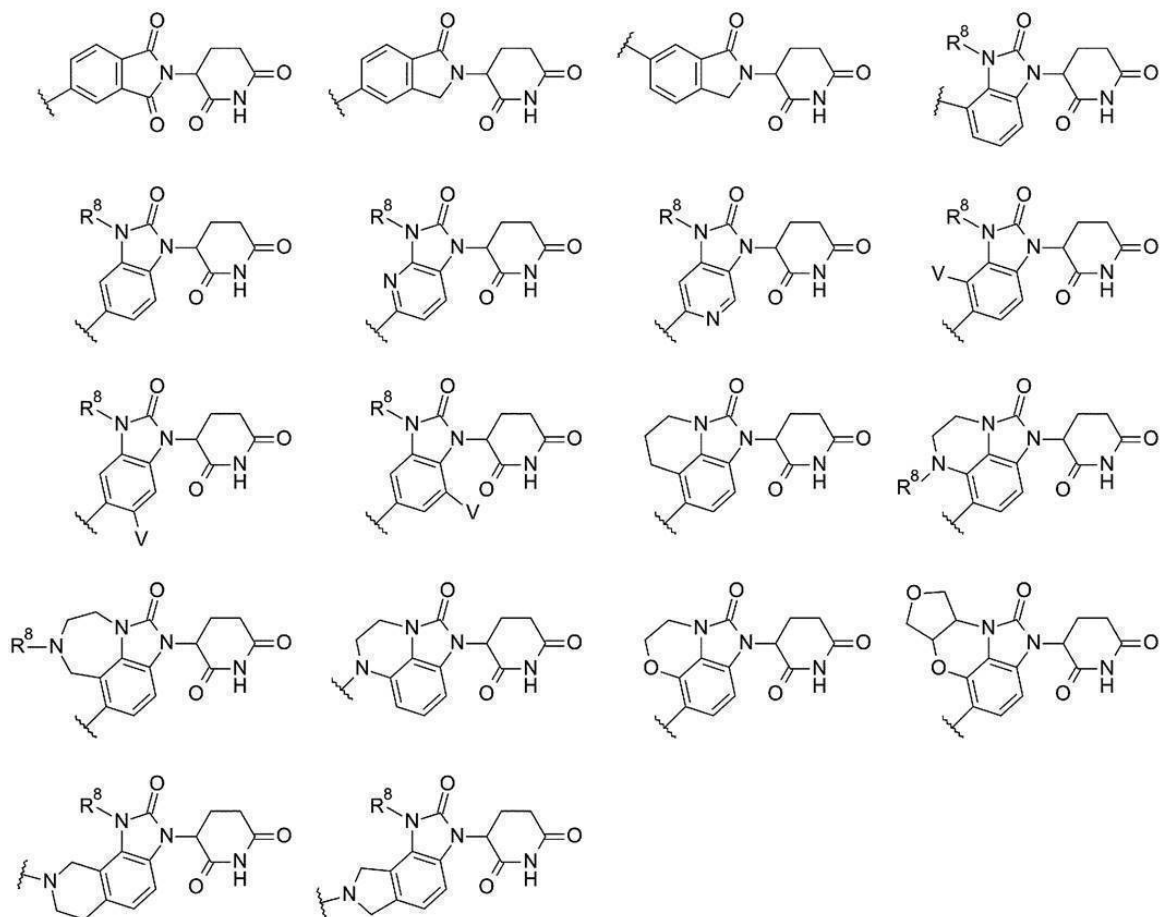
Since the formula (2') corresponds to a lower concept of
the formula (2), the definitions, explanations, preferred
25 embodiments, and the like of each group in the formula (2) in
the above all apply to each group in the formula (2'). Also,
in the present specification, when "a compound represented by
the formula (2)" is mentioned without any particular
reservation, this means a concept also including "a compound
30 represented by the formula (2')", in other words, "compounds
represented by the formula (2) and the formula (2')".
[0150]

In one embodiment of the present invention, R⁶ in the
above-mentioned formula (2) and the formula (2') is an E3
35 ligase-binding moiety. In another embodiment of the present

In yet another embodiment of the present invention, R^6 in the above-mentioned formula (2) and the formula (2') is any group selected from the following formulas:

[0155]

5 [Chem. 22]



[0156]

wherein

R^8 is hydrogen or C_{1-6} alkyl,

10 V is halogen, and

a wavy line indicates the bonding position with L^4 .

[0157]

In one embodiment of the present invention, a compound of the above-mentioned formula (2) or the formula (2'), wherein

15 R^1 is $-O-C_{1-6}$ alkyl optionally substituted by 1 to 3 halogens,

R^4 is C_{1-6} alkyl optionally substituted by 1 to 3 halogens, or C_{3-6} cycloalkylmethyl optionally substituted by one

trifluoromethyl,

ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₆ alkyl, a 9- to 10-membered bicyclic aromatic heterocycle having 1 or 2
5 nitrogen atoms as ring member atoms, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring, and

L¹ is a single bond or -O-,
or a pharmaceutically acceptable salt thereof is provided.

[0158]

10 In one embodiment of the present invention, a compound of the above-mentioned formula (2) or the formula (2'), wherein

A is -O-,

R² is methyl, and

R³ is methyl,

15 or a pharmaceutically acceptable salt thereof is provided.

[0159]

In one embodiment of the present invention, a compound of the above-mentioned formula (2) or the formula (2'), wherein

R¹ is methoxy, and

20 R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl,

or a pharmaceutically acceptable salt thereof is provided.

[0160]

In one embodiment of the present invention, a compound of the above-mentioned formula (2) or the formula (2'), wherein

25 ring Q¹ is a benzene ring optionally having one halogen,

L¹ is a single bond, and

ring Q² is a cyclohexene ring,

or a pharmaceutically acceptable salt thereof is provided.

[0161]

30 In another embodiment of the present invention, any one compound selected from the following group:

3-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
35 yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-

1H-benzimidazol-1-yl}piperidine-2,6-dione,
 (3R)-3-{5-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-
 2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 5 4-yl]methyl}piperazin-1-yl) carbonyl]-3-methyl-2-oxo-2,3-
 dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione,
 (3S)-3-{5-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-
 2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 10 4-yl]methyl}piperazin-1-yl) carbonyl]-3-methyl-2-oxo-2,3-
 dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione,
 3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-
 dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
 15 yl]methyl}piperazin-1-yl) carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 (3R)-3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-
 2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 20 4-yl]methyl}piperazin-1-yl) carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 (3S)-3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-
 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-
 2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
 25 4-yl]methyl}piperazin-1-yl) carbonyl]-2-oxo-5,6-dihydro-4H-
 imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,
 3-{7-[(1-{ [(4R)-2'-fluoro-4'-{ [{2-[(4R)-4-(4-
 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
 yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
 30 2,3,4,5-tetrahydro[biphenyl]-4-yl] carbonyl}piperidin-4-
 yl) amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-
 yl}piperidine-2,6-dione,
 (3R)- 3-{7-[(1-{ [(4R)-2'-fluoro-4'-{ [{2-[(4R)-4-(4-
 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
 35 yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-

2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,

(3S)-3-{7-[(1-{[(4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione,

10 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione,

15 (3R)-3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione, and

20 (3S)-3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione

25 or a pharmaceutically acceptable salt thereof is provided. All of these compounds correspond to a compound represented by the aforementioned formula (2) or a pharmaceutically acceptable salt thereof.

[0162]

30 In another embodiment of the present invention, a compound represented by the formula (2) or a pharmaceutically acceptable salt thereof may be a crystal thereof. Therefore, in one embodiment of the present invention, a crystal of a compound represented by the formula (2) or a pharmaceutically acceptable salt thereof is provided. The crystal can be

produced by a method known per se, or the method described in the below-mentioned Example, or a method analogous thereto.
[0163]

The powder X-ray diffraction measurement of crystals may
5 be performed by a method generally used in the pertinent field, for example, by the method described in the below-mentioned Examples. Generally, the diffraction angle (2θ) in powder X-ray diffraction may vary within a range of about $\pm 0.2^\circ 2\theta$. For example, the lattice constant of a hydrate or dehydrate may
10 change due to the attachment and detachment of water of crystallization, which may cause a change in the diffraction angle (2θ) in powder X-ray diffraction. The intensity of the diffraction peak may vary depending on the difference in the crystal growth plane (crystal habit), and the like. Therefore,
15 when the crystal of the present invention is expressed based on the data of powder X-ray diffraction, crystals having the same diffraction angles of peaks and X-ray diffraction patterns in powder X-ray diffraction, as well as hydrates and dehydrates obtained therefrom are included in the scope of the present
20 invention.

[0164]

In one embodiment of the present invention, the crystal is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
25 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate, the crystal having peaks at diffraction angles (2θ) of 2.15 ± 0.2 , 8.30 ± 0.2 , 10.29 ± 0.2 , 14.75 ± 0.2 ,
30 17.19 ± 0.2 , 20.00 ± 0.2 , 21.34 ± 0.2 , 22.68 ± 0.2 , 23.77 ± 0.2 , and 25.23 ± 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray ($\lambda = 1.54$ angstroms).

[0165]

In one embodiment of the present invention, the crystal
35 is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-

methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
ethanesulfonate, the crystal having peaks at diffraction angles
(2 θ) of 2.21 $\pm$ 0.2, 12.04 $\pm$ 0.2, 14.87 $\pm$ 0.2, 17.69 $\pm$ 0.2, 18.93 $\pm$ 0.2, 20.41 $\pm$ 0.2, 22.42 $\pm$ 0.2, 23.19 $\pm$ 0.2, 24.13 $\pm$ 0.2, and 27.98 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray (λ =1.54 angstroms).

[0166]

In one embodiment of the present invention, the crystal is a crystal of (3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
camphorsulfonate, the crystal having peaks at diffraction angles (2 θ) of 3.89 $\pm$ 0.2, 6.81 $\pm$ 0.2, 7.68 $\pm$ 0.2, 8.20 $\pm$ 0.2, 10.28 $\pm$ 0.2, 13.15 $\pm$ 0.2, 15.97 $\pm$ 0.2, 16.81 $\pm$ 0.2, 18.58 $\pm$ 0.2, and 23.56 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray (λ =1.54 angstroms).

[0167]

In one embodiment of the present invention, the crystal is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl)methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
ethanesulfonate ethanesulfonate, the crystal having peaks at
diffraction angles (2 θ) of 2.27 $\pm$ 0.2, 8.18 $\pm$ 0.2, 9.88 $\pm$ 0.2, 13.09 $\pm$ 0.2, 14.57 $\pm$ 0.2, 15.80 $\pm$ 0.2, 16.91 $\pm$ 0.2, 17.77 $\pm$ 0.2, 18.87 $\pm$ 0.2, and 20.14 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper K α ray (λ =1.54 angstroms).

[0168]

In one embodiment of the present invention, the crystal

is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-
5 4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione salicylate, the crystal having peaks at diffraction angles (2θ) of 2.20±0.2, 4.34±0.2, 9.45±0.2, 10.97±0.2, 13.23±0.2, 16.98±0.2, 18.09±0.2, 20.20±0.2, 21.32±0.2, and 25.19±0.2 in a powder X-ray diffraction pattern obtained by irradiation with
10 copper Kα ray (λ=1.54 angstroms).
[0169]

In one embodiment of the present invention, the crystal is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
15 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate, the crystal having peaks at diffraction angles (2θ) of 2.19±0.2, 8.87±0.2, 10.86±0.2, 12.55±0.2,
20 13.05±0.2, 14.99±0.2, 17.84±0.2, 20.62±0.2, 21.43±0.2, and 25.27±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms).
[0170]

In one embodiment of the present invention, the crystal
25 is a crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
30 10-camphorsulfonate, the crystal having peaks at diffraction angles (2θ) of 2.20±0.2, 7.82±0.2, 11.05±0.2, 12.42±0.2, 13.34±0.2, 15.23±0.2, 16.49±0.2, 17.86±0.2, 20.15±0.2, and 24.36±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms).
35 [0171]

<7. Salt, isomer, prodrug and the like>

The "pharmaceutically acceptable salt" in the present invention means a salt that can be used as a medicament. When the compound or polyfunctional molecule of the present invention has an acidic group, it can be reacted with a base to form a basic salt (also referred to as a "base addition salt"), and when it has a basic group, it can be reacted with an acid to form an acidic salt (also referred to as an "acid addition salt"). Therefore, in one embodiment of the present invention, a pharmaceutically acceptable salt of a compound represented by the formula (1) or a compound represented by the formula (2) is a basic salt, and in another embodiment of the present invention, a pharmaceutically acceptable salt of a compound represented by the formula (1) or a compound represented by the formula (2) is an acidic salt.

[0172]

Preferred examples of the "basic salt" in the present invention include alkali metal salts such as sodium salt, potassium salt, and lithium salt; alkaline earth metal salts such as magnesium salt and calcium salt; organic base salts such as N-methylmorpholine salt, triethylamine salt, tributylamine salt, diisopropylethylamine salt, dicyclohexylamine salt, N-methylpiperidine salt, pyridine salt, 4-pyrrolidinopyridine salt, and picoline salt; and amino acid salts such as glycine salt, lysine salt, arginine salt, ornithine salt, glutamic acid salt, and aspartic acid salt.

[0173]

Preferred examples of the "acidic salt" in the present invention include inorganic acid salts such as hydrohalide (e.g., hydrofluoride, hydrochloride, hydrobromide, hydroiodide), nitrate, perchlorate, sulfate, and phosphate; lower alkanesulfonate (e.g., methanesulfonate, trifluoromethanesulfonate, ethanesulfonate), arylsulfonate (e.g., benzenesulfonate, p-toluenesulfonate), organic acid salts such as acetate, malate, fumarate, succinate, citrate,

ascorbate, tartrate, oxalate, and maleate; and amino acid salts such as glycinate, lysinate, argininate, ornithinate, glutamate, and aspartate.

[0174]

5 The compound or a pharmaceutically acceptable salt thereof of the present invention may become a hydrate by incorporating water molecules when left in the air or when recrystallized, and such hydrates are also included in the present invention. The compound or a pharmaceutically
10 acceptable salt thereof of the present invention may absorb a certain type of solvent when left in a solvent or recrystallized, and become a solvate, and such solvates are also included in the present invention. Furthermore, the compound of the present invention or a pharmaceutically
15 acceptable salt thereof can also exist in amorphous or crystalline form.

[0175]

 The compound or a pharmaceutically acceptable salt thereof of the present invention may be labeled with
20 pharmaceutically acceptable one or more radioactive or non-radioactive isotopes. Examples of the isotopes that can be incorporated into the compound of the present invention or a pharmaceutically acceptable salt thereof include, but are not limited to, isotopes of hydrogen, carbon, nitrogen, oxygen, and
25 fluorine, for example, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , and ^{18}F , respectively. The radioactive or non-radioactive labeled compound can be useful to help determine or measure the effectiveness of the compound of the present invention, for example, by characterizing the site of action or mode of
30 action, or binding affinity to a pharmacologically important site of action. Such isotopically labeled compounds can generally be prepared by conventional techniques known to those skilled in the art.

[0176]

35 In the compound, pharmaceutically acceptable salt thereof

or solvate thereof of the present invention, various isomers such as geometric isomers such as cis-forms and trans-forms, tautomers, rotamers, optical isomers such as d-form and l-form (including enantiomers and diastereomers) and the like can be present depending on the type and combination of substituents. The compound of the present invention includes all of these isomers and stereoisomers, and mixtures of these isomers and stereoisomers in any ratio, unless otherwise specified.

[0177]

10 The present invention also includes prodrugs of the compounds represented by the formula (1) or the formula (2). A prodrug is a compound having a group that can be converted to an amino group, a hydroxy group, a carboxy group, or the like of a compound by hydrolysis or under physiological conditions. 15 Examples of groups that form such prodrugs include the groups described in Prog. Med., Vol. 5, pp. 2157-2161, 1985, and the like. More specifically, examples of the prodrug include:

(1) compounds in which, when an amino group is present in the compound, the amino group is acylated, alkylated, or 20 phosphorylated (e.g., compounds in which the amino group is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, or tert-butylated, etc.),

25 (2) compounds in which, when a hydroxy group is present in the compound, the hydroxy group is acylated, alkylated, phosphorylated, or borated (e.g., compounds in which the hydroxy group is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, or 30 dimethylaminomethylcarbonylated, etc.),

(3) compounds in which, when a carboxy group is present in the compound, the carboxy group is esterified or amidated (e.g., compounds in which the carboxy group is ethyl esterified, phenyl esterified, carboxymethyl esterified, 35 dimethylaminomethyl esterified, pivaloyloxymethyl esterified,

ethoxycarbonyloxyethyl esterified, amidated, or methylamidated, etc.), and the like.

[0178]

<8. Composition and pharmaceutical use>

5 In one embodiment of the present invention, a composition for inhibiting SF-1, a composition for inducing degradation of SF-1, or a pharmaceutical composition containing a compound represented by the aforementioned formula (1) or a pharmaceutically acceptable salt thereof, a polyfunctional
10 molecule containing the moiety corresponding to the compound or a pharmaceutically acceptable salt thereof, or a compound represented by the aforementioned formula (2) or a pharmaceutically acceptable salt thereof, or a crystal thereof is provided. In another embodiment of the present invention, a
15 method for treating a disease, including administering an effective amount of a compound represented by the aforementioned formula (1) or a pharmaceutically acceptable salt thereof, a polyfunctional molecule containing the moiety corresponding to the compound or a pharmaceutically acceptable
20 salt thereof, or a compound represented by the aforementioned formula (2) or a pharmaceutically acceptable salt thereof, or a crystal thereof to a subject in need of a treatment of the disease is provided. In a yet another embodiment of the present invention, a compound represented by the aforementioned
25 formula (1) or a pharmaceutically acceptable salt thereof, a polyfunctional molecule containing the moiety corresponding to the compound or a pharmaceutically acceptable salt thereof, or a compound represented by the aforementioned formula (2) or a pharmaceutically acceptable salt thereof, or a crystal thereof
30 for use in the treatment of a disease is provided. In addition, in yet another embodiment of the present invention, a compound represented by the aforementioned formula (1) or a pharmaceutically acceptable salt thereof, a polyfunctional molecule containing the moiety corresponding to the compound or
35 a pharmaceutically acceptable salt thereof, or a compound

represented by the aforementioned formula (2) or a pharmaceutically acceptable salt thereof, or a crystal thereof for use in the production of a medicament for the treatment of a disease is provided.

5 [0179]

In the present invention, the "composition for inhibiting SF-1" refers to a composition intended to inhibit SF-1. Inhibition of SF-1 typically means inhibiting the physiological activity of SF-1, particularly blocking or attenuating the
10 expression of a gene transcriptionally controlled by SF-1. The embodiment of inhibiting SF-1 includes an embodiment in which the transcription induction activity of downstream genes by SF-1 is blocked or attenuated by binding directly to SF-1, but also includes an embodiment in which the physiological activity
15 of SF-1 is consequently blocked or attenuated by acting on a protein upstream of SF-1 without directly binding to SF-1. The "composition for inhibiting SF-1" includes not only a composition intended solely for the inhibition of SF-1, but also one having the inhibition of SF-1 as one of its purposes.
20 The "composition for inhibiting SF-1" typically includes a composition indicating inhibition of SF-1 as one of its intended uses in the package insert, package, promotional materials, etc., but also includes a composition that substantially includes inhibition of SF-1 as one of its
25 intended uses even if there is no such explicit indication.
[0180]

In the present invention, "composition for inducing degradation of SF-1" means a composition intended to induce degradation of SF-1. The "composition for inducing degradation
30 of SF-1" includes not only a composition intended solely for inducing the degradation of SF-1, but also one having induction of the degradation of SF-1 as one of its purposes. The "composition for inducing degradation of SF-1" typically includes a composition indicating induction of the degradation
35 of SF-1 as one of its intended uses in the package insert,

package, promotional materials, etc., but also includes a composition that substantially includes induction of the degradation of SF-1 as one of its intended uses even if there is no such explicit indication.

5 [0181]

In the present invention, the "pharmaceutical composition" means a composition used for the treatment/prevention of any disease. Since the compound or polyfunctional molecule of the present invention has SF-1
10 antagonist activity, it can be used as a composition for the treatment and/or prevention of a disease in which SF-1 is involved in the development or progression. Such diseases include, but are not limited to, cancer such as castration-resistant prostate cancer, adrenocortical carcinoma, Leydig
15 cell tumor, hormone-sensitive prostate cancer, breast cancer and the like, Cushing's syndrome, and primary aldosteronism. Thus, in one embodiment of the present invention, the pharmaceutical composition of the present invention is for treating cancer such as castration-resistant prostate cancer,
20 adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer and the like, Cushing's syndrome or primary aldosteronism. In a further embodiment of the present invention, the pharmaceutical composition of the present invention is for treating castration-resistant prostate
25 cancer or adrenocortical carcinoma, in another embodiment of the present invention, the pharmaceutical composition of the present invention is for treating castration-resistant prostate cancer, and in yet another embodiment of the present invention, the pharmaceutical composition of the present invention is for
30 treating adrenocortical carcinoma.

[0182]

The route of administration of such compositions to humans or other animals may be oral administration using tablet, pill, capsule, granule, powder, liquid, and the like,
35 or parenteral administration using intra-articular,

intravenous, or intramuscular injection, etc., suppository, eye drop, eye ointment, transdermal liquid, ointment, transdermal adhesive preparation, transmucosal liquid, transmucosal adhesive preparation, inhalant, and the like. Considering that
5 the molecular weight of the compound or polyfunctional molecule of the present invention is not extremely large, oral administration is preferred from the viewpoint of reducing the burden of taking drugs.

[0183]

10 Solid composition for oral administration includes tablet, powder, granule, and the like. Such solid composition contains at least one inactive excipient, such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium
15 aluminometasilicate, etc., in addition to the compound or polyfunctional molecule of the present invention. Such solid composition may contain inactive additives, such as lubricants such as magnesium stearate, disintegrants such as sodium carboxymethyl starch, stabilizer, solubilizing agent, and the
20 like, according to conventional methods. Tablets or pills may be coated with sugar coatings or films of gastric or enteric soluble substances, as necessary.

[0184]

Liquid compositions for oral administration include
25 pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, and the like. To such liquid compositions, it is possible to add generally used inert diluents, such as purified water or ethanol. In addition to the inert diluents, such liquid compositions may contain auxiliary agents such as
30 solubilizer and wetting agent, sweetener, flavoring, fragrance, preservative, and the like.

[0185]

Examples of the injections for parenteral administration includes sterile aqueous or non-aqueous solution, suspension,
35 emulsion, and the like. Aqueous solvents include, for example,

distilled water for injection, physiological saline, and the like. Non-aqueous solvents include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, polysorbate 80, and the like. Such
5 injection compositions may further contain isotonic agent, preservative, wetting agent, emulsifier, dispersant, stabilizer, solubilizing agent, and the like. These injection compositions may be sterilized, for example, by filtration through a bacteria-retaining filter, by blending with a
10 bactericide, or by irradiation. In addition, these injection compositions may be prepared as sterile solid compositions, which may be dissolved or suspended in sterile water or a sterile solvent for injection before use.

[0186]

15 Examples of the external preparation include ointment, plaster, cream, jelly, cataplasm, spray, lotion, eye drop, eye ointment and the like. These external preparations may contain generally used ointment base, lotion base, aqueous or non-aqueous liquid, suspension, emulsion and the like. For
20 example, ointment or lotion base includes polyethylene glycol, propylene glycol, white petrolatum, white beeswax, polyoxyethylene hydrogenated castor oil, glycerin monostearate, stearyl alcohol, cetyl alcohol, lauromacrogol, sorbitan sesquiolate, and the like.

25 [0187]

Transmucosal agents such as inhalants and nasal agents may be solid, liquid, or semisolid, and can be produced according to a conventional known method. For example, known excipients and further pH adjusters, preservatives,
30 surfactants, lubricants, stabilizers, thickeners, and the like may be appropriately added. For these transmucosal agents, a suitable device for inhalation or insufflation may be used as a method of administration. For example, the compound or polyfunctional molecule can be administered as a powder, either
35 alone or in a formulated mixture powder, or in a solution or

suspension in combination with a pharmaceutically acceptable carrier, using known devices and nebulizers, such as metered dose inhalation device and the like. Dry powder inhalers and the like may be for single or multiple dose administration, and
5 dry powder or powder-containing capsule can be used.

Alternatively, a suitable propellant can also be used. The compositions may be in the form of a pressurized aerosol spray using, for example, a suitable gas such as chlorofluoroalkane, hydrofluoroalkane, carbon dioxide, or the like.

10 [0188]

The composition of the present invention may contain other active ingredients, or may be used in combination with another composition containing other active ingredients. The combined use may be simultaneous administration, or separate
15 consecutive administration or administration at a desired time interval. The simultaneous administration preparation may be a combination drug or separate formulations.

[0189]

The amount of the compound or polyfunctional molecule of
20 the present invention loaded into a composition or the amount administered to a subject is not particularly limited as long as it is an amount effective for achieving the purpose, and can be appropriately selected depending on the purpose of use, and the age, weight, symptoms, health condition, disease
25 progression and the like of the subject. The frequency of administration is not particularly limited, and it can be appropriately selected depending on the purpose. For example, the daily dosage may be administered once a day or may be administered in multiple doses.

30 [0190]

In the present invention, the "effective amount" or "therapeutically effective amount" means an amount effective for treating, preventing the progression of, or alleviating existing symptoms in the subject being treated. The effective
35 amount can be appropriately determined according to

conventional methods, taking into account the desired therapeutic effect and side effects.

[0191]

<9. Combined use>

5 The compound or pharmacologically acceptable salt thereof, polyfunctional molecule, composition for inhibiting SF-1, composition for inducing degradation of SF-1, or pharmaceutical composition of the present invention can be used in combination with other antitumor agents. Examples of other
10 antitumor agents include alkylating agents, antimetabolites, antitumor antibiotics, microtubule inhibitors, topoisomerase inhibitors, BRMs (biological response modifiers), hormonal agents, vitamins, antitumor antibodies, molecular target drugs, other antitumor agents and the like.

15 [0192]

More specifically, examples of the alkylating agents include alkylating agents such as nitrogen mustard, nitrogen mustard-N-oxide, chlorambucil and the like; aziridine-based alkylating agents such as carboquone, thiotepa and the like;
20 epoxide-based alkylating agents such as dibromomannitol, dibromodulcitol and the like; nitrosourea-based alkylating agents such as carmustine, lomustine, semustine, nimustine hydrochloride, streptozocin, chlorozotocin, ranimustine and the like; busulfan; improsulfan tosylate; dacarbazine and the like.

25 [0193]

Examples of various antimetabolites include purine antimetabolites such as 6-mercaptopurine, 6-thioguanine, thioinosine, and the like; pyrimidine antimetabolites such as fluorouracil, tegafur, tegafur-uracil, carmofur, doxifluridine,
30 broxuridine, cytarabine, enocitabine, capecitabine and the like; folic acid antimetabolites such as methotrexate, trimetrexate, pemetrexed and the like; activated folic acid agents such as levofolinate; and the like.

[0194]

35 Examples of the antitumor antibiotics include

anthracycline antibiotic antitumor agents such as daunorubicin, aclarbicin, doxorubicin, pirarubicin, THP-adriamycin, 4'-epidoxorubicin, epirubicin, amrubicin and the like; mitomycin C; bleomycin; peplomycin; chromomycin A3, actinomycin D and the
5 like.

[0195]

Examples of the microtubule inhibitors include vinca alkaloids such as vindesine, vincristine, vinblastine, vinorelbine, and the like; taxanes such as paclitaxel,
10 docetaxel, cabazitaxel, and the like; eribulin, and the like.

[0196]

Examples of the topoisomerase inhibitors include epipodophyllotoxins such as etoposide, teniposide and the like; camptothecin derivatives such as irinotecan and the like, and
15 the like.

[0197]

Examples of the BRMs include tumor necrosis factor, indomethacin and the like.

[0198]

20 Examples of the hormonal agents include hydrocortisone, cortisone acetate, fludrocortisone, fludrocortisone acetate, dexamethasone, methylprednisolone, prednisolone, prasterone, betamethasone, triamcinolone, oxymetholone, nandrolone, methenolone, fosfestrol, ethinylestradiol, chlormadinone,
25 glucocorticoids, medroxyprogesterone, bicalutamide, enzalutamide, apalutamide, grolutamide, flutamide, anastrozole, exemestane, letrozole, abiraterone, goserelin, leuprorelin, toremifene, degarelix, mitotane, tamoxifen, and the like.

[0199]

30 Examples of the vitamin include vitamin C, vitamin A and the like.

[0200]

Examples of the antitumor antibodies, molecular target drugs include antitumor antibodies such as trastuzumab,
35 rituximab, cetuximab, pertuzumab, nimotuzumab, pembrolizumab,

camrelizumab, denosumab, bevacizumab, infliximab, ramucirumab and the like (including their modified forms); kinase inhibitors such as imatinib, gefitinib, erlotinib, sunitinib, lapatinib, eganelisib, sorafenib, dasatinib, nilotinib, vemurafenib, osimertinib, apatinib, cabozantinib and the like; PARP inhibitors such as olaparib, rucaparib, velparib, niraparib and the like; and molecular target drugs such as OR-449 and the like.

[0201]

10 Examples of other antitumor agents include platinum compounds such as cisplatin, carboplatin, oxaliplatin and the like, ifosfamide, cyclophosphamide, melphalan, L-asparaginase, aceglatone, sizofiran, picibanil, procarbazine, pipobroman, neocarzinostatin, hydroxyurea, ubenimex, krestin, and the like.

15 [0202]

 The compound of or a pharmaceutically acceptable salt thereof, polyfunctional molecule, composition for inhibiting SF-1, composition for inducing degradation of SF-1, or pharmaceutical composition of the present invention may be used
20 in combination with an antibody-drug conjugate (ADC) containing the above-mentioned other antitumor agent as a payload, or a targeted protein degrader having the above-mentioned other antitumor agent as a POI ligand.

[0203]

25 The compound of or a pharmaceutically acceptable salt thereof, polyfunctional molecule, composition for inhibiting SF-1, composition for inducing degradation of SF-1, or pharmaceutical composition of the present invention may be administered simultaneously or separately at the same time or
30 at different times with the above-mentioned drugs to be used in combination, and may be prepared as a combination drug or a kit formulation.

[0204]

 In the treatment of adrenocortical carcinoma, antitumor
35 agents that are preferably used in combination with the

compound of or a pharmaceutically acceptable salt thereof,
polyfunctional molecule, composition for inhibiting SF-1,
composition for inducing degradation of SF-1, or pharmaceutical
composition of the present invention include, for example, one
5 or more selected from anthracycline compounds such as
doxorubicin; platinum compounds such as cisplatin and
carboplatin; antitumor antibodies such as nivolumab,
pembrolizumab, and camrelizumab; molecular target drugs such as
eganelisib, apatinib, cabozantinib, and OR-449; mitotane; and
10 etoposide.

[0205]

In the treatment of castration-resistant prostate cancer,
antitumor agents that are preferably used in combination with
the compound of or a pharmaceutically acceptable salt thereof,
15 polyfunctional molecule, composition for inhibiting SF-1,
composition for inducing degradation of SF-1, or pharmaceutical
composition of the present invention include, for example, one
or more selected from hormonal agents such as abiraterone,
enzalutamide, grolutamide, apalutamide, and the like;
20 microtubule inhibitors such as docetaxel, cabazitaxel, and the
like; PARP inhibitors such as olaparib, rucaparib, and the
like; androgen receptor degraders such as ARV-110, ARV-766, CC-
94676, and the like; CYP11A1 enzyme inhibitors such as ODM-208,
and the like; and anti-tumor antibodies such as nivolumab,
25 pembrolizumab, camrelizumab, and the like.

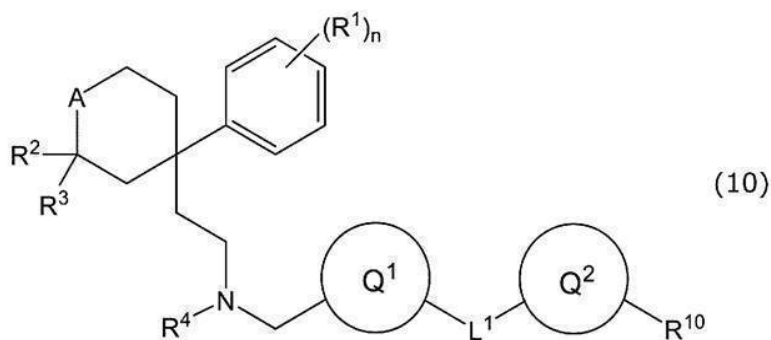
[0206]

<10. Novel intermediate>

In one embodiment of the present invention, a compound
represented by the following formula (10):

30 [0207]

[Chem. 23]



[0208]

wherein

A is $-O-$, $-S-$, $-NR^a-$, or $-CR^bR^c-$,

5 wherein

R^a is hydrogen or C_{1-3} alkyl,

R^b and R^c are each independently hydrogen, halogen, or C_{1-3} alkyl, and

the aforementioned alkyl is unsubstituted or substituted
10 by 1 to 3 halogens,

each R^1 in the number of n is independently halogen, hydroxy, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, $-O-C_{1-6}$ alkyl, $-N(H)-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl,

15 wherein

the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,

the aforementioned cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3
20 groups selected from the group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

the aforementioned heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

25 R^2 and R^3 are each independently hydrogen, halogen, C_{1-6} alkyl, or C_{2-6} alkenyl,

wherein

the aforementioned alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,

R^4 is C_{1-6} alkyl, $-C(=O)-R^d$ (R^d indicates C_{1-6} alkyl, C_{2-5} alkenyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl), C_{6-12} aryl, or 6- to 12-membered heteroaryl,

wherein

5 the aforementioned C_{1-6} alkyl is unsubstituted or substituted by 1 to 3 halogens, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl,

the aforementioned aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are each independently unsubstituted or
10 substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

the aforementioned heteroaryl and heterocycloalkyl have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

15 ring Q^1 is a C_{6-12} monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C_{3-7} cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C_{3-7} cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

20 wherein

the aforementioned aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, and heterocycloalkene ring are each independently unsubstituted or substituted by 1 to 3 groups
25 selected from the group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

the aforementioned aromatic heterocycle, heterocycloalkane ring and heterocycloalkene ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring
30 member atoms,

L^1 is a single bond, $-O-$, $-S-$, $-NH-$, C_{1-3} alkylene, C_{2-3} alkenylene, $-C(=O)-$, $-C(=O)NH-$, $-NHC(=O)-$, $-C(=O)O-$, or $-OC(=O)-$,

wherein

35 the aforementioned alkylene and alkenylene are each

independently unsubstituted or substituted by 1 to 3 halogens,
ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-
5 membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3-
to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane
ring, or a 5- to 12-membered spiroheterocycloalkane ring,
wherein
the aforementioned aromatic hydrocarbocycle, aromatic
10 heterocycle, cycloalkane ring, heterocycloalkane ring,
cycloalkene ring, heterocycloalkene ring, spirocycloalkane
ring, and spiroheterocycloalkane ring are each independently
unsubstituted or substituted by 1 to 3 groups selected from the
group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃
15 haloalkyl, and
the aforementioned aromatic heterocycle,
heterocycloalkane ring, heterocycloalkene ring, and
spiroheterocycloalkane ring has 1 or 2 hetero atoms selected
from oxygen, nitrogen, and sulfur as ring member atoms,
20 R¹⁰ is C₁₋₆ alkyl,
wherein
the aforementioned C₁₋₆ alkyl is substituted by one or two
3- to 7-membered heterocycloalkyls,
the aforementioned heterocycloalkyl has 1 or 2 hetero
25 atoms selected from oxygen, nitrogen, and sulfur as ring member
atoms, and
the aforementioned heterocycloalkyl is unsubstituted, or
substituted by an amino-protecting group, and
n is an integer of 0 to 3,
30 or a pharmaceutically acceptable salt thereof is provided.

[0209]

The compound of the formula (10) of the present invention
can be used as a production intermediate for the compound of
the formula (2) or the formula (2') of the present invention,
35 or is useful as a production intermediate, as described in

detail in the following general production method and examples.
The compound of the formula (10) of the present invention is
the same as the compound of the formula (1), except that the
definition of R^{10} is different from that of the compound of the
5 formula (1). Therefore, the definitions, explanations,
preferred embodiments, and the like of each group in the above-
mentioned formula (1), except for those relating to R^5 , also
apply to each group in the formula (10).

[0210]

10 In one embodiment of the present invention, R^{10} in the
above-mentioned formula (10) is C_{1-6} alkyl substituted by one 3-
to 7-membered heterocycloalkyl (the aforementioned
heterocycloalkyl is unsubstituted or substituted by an amino-
protecting group), preferably C_{1-6} alkyl substituted by one 4-
15 to 6-membered heterocycloalkyl (the aforementioned
heterocycloalkyl is unsubstituted or substituted by an amino-
protecting group), further preferably C_{1-6} alkyl substituted by
one 6-membered heterocycloalkyl (the aforementioned
heterocycloalkyl is unsubstituted or substituted by an amino-
20 protecting group), particularly preferably C_{1-6} alkyl
substituted by piperazine (the aforementioned heterocycloalkyl
is unsubstituted or substituted by an amino-protecting group).

[0211]

In one embodiment of the present invention, the "amino-
25 protecting group" means a protecting group used as a protecting
group for an amino group in the synthesis of an organic
compound, and examples thereof include alkoxycarbonyl groups
such as tert-butoxycarbonyl group, methoxycarbonyl group,
ethoxycarbonyl group, 2,2,2-trichloroethoxycarbonyl group, 2-
30 trimethylsilylethoxycarbonyl group and the like;
allyloxycarbonyl group; arylmethoxycarbonyl groups such as
benzyloxycarbonyl group, 4-methoxybenzyloxycarbonyl group, 4-
nitrobenzyloxycarbonyl group, 2-nitrobenzyloxycarbonyl group
and the like; 9-fluorenylmethyloxycarbonyl group; arylmethyl
35 groups such as benzyl group, 4-methoxybenzyl group, 2,3-

dimethoxybenzyl group, 3,4-dimethoxybenzyl group,
diphenylmethyl group, triphenylmethyl group and the like;
alkanoyl groups such as formyl group, acetyl group,
trimethylacetyl group, trichloroacetyl group, trifluoroacetyl
5 group and the like; aroyl groups such as benzoyl group and the
like; arylsulfonyl groups such as benzenesulfonyl group, p-
toluenesulfonyl group, 2-nitrobenzenesulfonyl group, 4-
nitrobenzenesulfonyl group, 2,4-di-nitrobenzenesulfonyl group
and the like, and the like. These amino-protecting groups can
10 be selected depending on the properties of the compound that
protects the amino group, and the removal of the protecting
groups can be performed by selecting reagents and conditions
according to the protecting group.

[0212]

15 <11. General production method>

Representative methods for producing the compound of the
present invention or a pharmaceutically acceptable salt thereof
are described below.

The compound of the present invention can be produced by
20 various production methods, and the production methods shown
below and Reference Examples and Examples described below are
only examples, and the present invention should not be
interpreted as being limited to these.

Each raw material compound may form a salt as long as it
25 does not inhibit the reaction, and examples of such salts
include the same as the pharmaceutically acceptable salts of
the compound described above.

When no specific production method is described, the raw
material compounds can be easily obtained from commercial
30 sources and used, or can be produced according to a method
known per se or a method equivalent thereto. In addition, the
production intermediates generated in the following production
methods may be isolated and purified by a method such as column
chromatography (including normal phase and reverse phase) using
35 silica gel or alumina, recrystallization, reprecipitation,

distillation, and the like, or may be used directly in the next reaction without isolation and purification.

In the present specification, all patent literatures, non-patent literatures, or references expressly cited herein
5 may all be cited herein as a part of the present specification.

The compound, a pharmaceutically acceptable salt thereof, and a production intermediate therefor can be produced by utilizing the characteristics based on the kind of the basic skeleton or substituent, and applying various known production
10 methods. Examples of the known methods include the methods described in "ORGANIC FUNCTIONAL GROUP PREPARATIONS", 2nd edition, ACADEMIC PRESS, INC., 1989, "Comprehensive Organic Transformations", 2nd edition, VCH Publishers Inc., 1999, and the like.

15 In such cases, depending on the type of functional group present in the compound, it may be effective in terms of manufacturing technology to protect the functional group with an appropriate protecting group at the starting material or intermediate stage, or to replace the functional group with a
20 group that can be easily converted to the functional group concerned.

Examples of the functional group include amino group, hydroxy group, formyl group, carbonyl group, carboxy group, and the like, and examples of the protecting group thereof include
25 the protecting groups described in P. G. Wuts, "Protective Groups in Organic Synthesis", 5th edition, Wiley, 2014.

The protecting group or the group that can be easily converted into the functional group may be appropriately selected depending on the reaction conditions of the production
30 method for producing the compound.

According to such a method, a desired compound can be obtained by introducing the group and performing a reaction, and then removing the protecting group as necessary or converting same into a desired group.

35 A prodrug of the compound can be produced by, similar to

the above-mentioned protecting groups, introducing a particular group in the stage of a starting material or intermediate, or by a reaction using the obtained compound. The reaction for producing a prodrug can be performed by those of ordinary skill
5 in the art, by applying a known method such as general esterification, amidation, dehydration, hydrogenation and the like.

Furthermore, functional group conversion and use of protecting groups in the production intermediates used in each
10 step of the following methods can be performed by known methods or methods analogous thereto, or the methods described in the below-mentioned examples or methods analogous thereto.

In the following description of the general production methods, symbols used in the formulas without a definition have
15 the same meaning as defined above.

[0213]

A general production method of the compound of the formula (1) of the present invention is described below. In the following description, the abbreviations shown here may be
20 used.

THF: tetrahydrofuran

DMF: N,N-dimethylformamide

DMA: N,N-dimethylacetamide

HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-
25 triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

DIPEA: N,N-diisopropylethylamine

RuPhos Pd G3: (2-dicyclohexylphosphino-2',6'-
diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-
biphenyl)]palladium(II) methanesulfonate (CAS Registry Number:
30 1445085-77-7)

BrettPhos Pd G3: [(2-dicyclohexylphosphino-3,6-dimethoxy-
2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-
biphenyl)]palladium(II) methanesulfonate methanesulfonate (CAS
Registry Number: 1470372-59-8)

35 Tf: trifluoromethanesulfonyl group

SEM: 2-(trimethylsilyl)ethoxymethyl group

XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
(CAS Registry Number: 161265-03-8)

tBuXPhos: 2-di-tert-butylphosphino-2',4',6'-

5 triisopropylbiphenyl (CAS Registry Number: 564483-19-8)

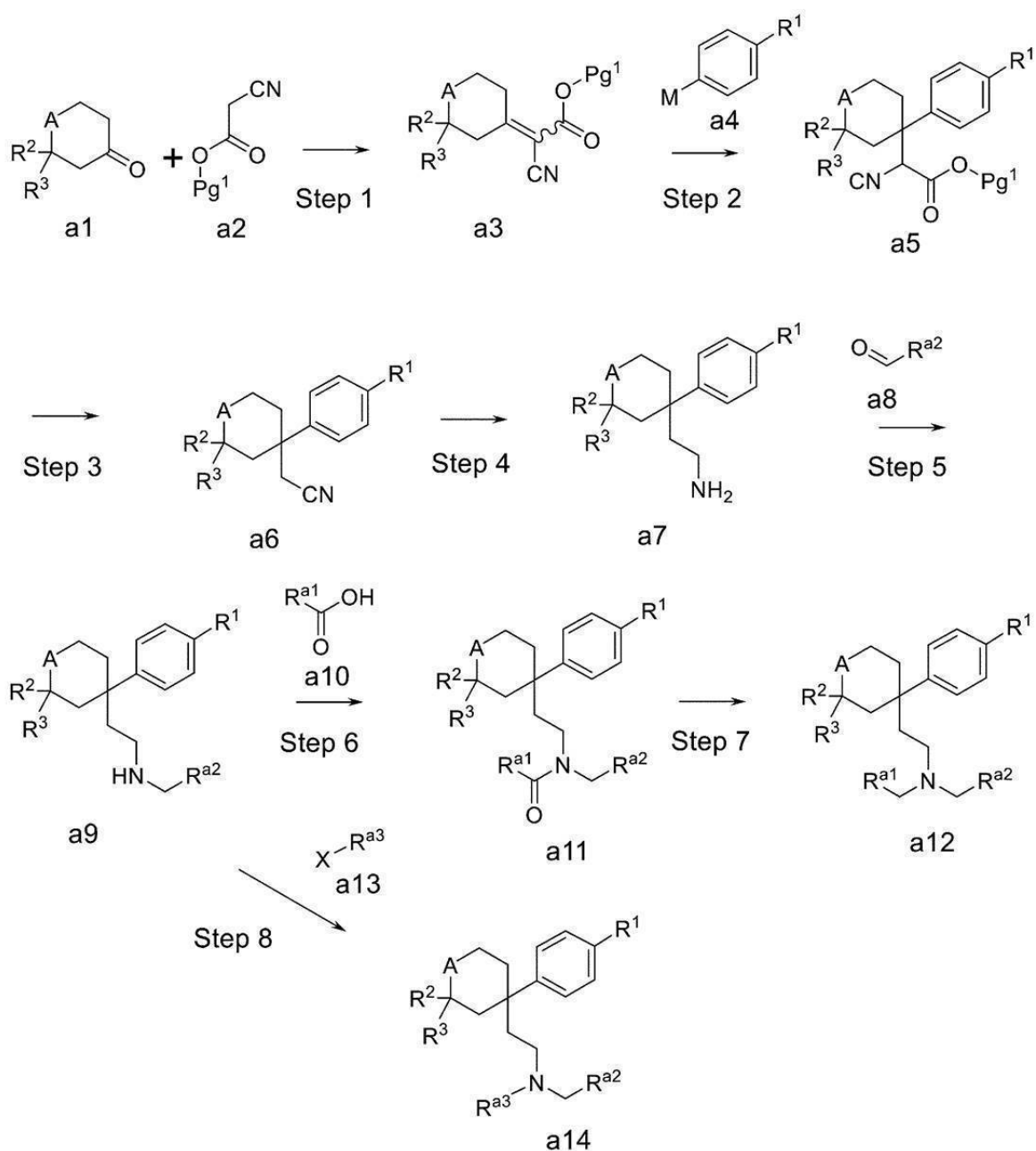
[0214]

(Method A)

Among the compounds represented by the formula (1),
compound a12 wherein R⁴ is a C₁₋₆ alkyl group optionally
10 substituted by 1 to 3 halogen atoms, or a C₃₋₆ cycloalkylmethyl
group optionally substituted by one trifluoromethyl group,
compound a11 wherein R⁴ is a C₁₋₆ alkylcarbonyl group optionally
substituted by 1 to 3 halogen atoms, and compound a14 wherein
R⁴ is 6-membered heteroaryl having 1 or 2 nitrogen atoms as
15 ring member atoms (the heteroaryl group is optionally
substituted by one halogen atom) can be produced according to
the following method. A general production method for each
reaction site is shown in order, but it is not necessary to
perform each step in the order shown below as long as it does
20 not affect the reaction substrate and reaction product.

[0215]

[Chem. 24]



[0216]

wherein Pg^1 is a carboxy-protecting group (e.g., methyl group, ethyl group, benzyl group, or tert-butyl group, etc.),

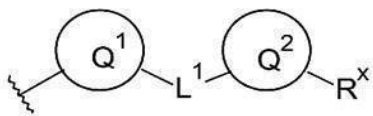
5 M is metal or halogenated metal (e.g., magnesium halide, lithium or zinc halide, etc.),

R^{a1} is a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, or C_{3-6} cycloalkyl group optionally substituted by one trifluoromethyl group,

10 R^{a2} is a substituent represented by the following formula:

[0217]

[Chem. 25]



[0218]

5 R^x is R⁵ or a group that can be converted to R⁵,

 R^{a3} is a 6-membered heteroaryl group having 1 or 2
nitrogen atoms as ring member atoms (the heteroaryl group is
optionally substituted by one halogen atom.

[0219]

10 In the first step, compound a3 is obtained by aldol
condensation reaction of compound a1 and compound a2. The
aldol condensation reaction in this step can be performed by
reacting compound a1 with compound a2 using, for example,
acetic acid and piperidine as catalysts.

15 [0220]

 In the second step, compound a5 is obtained by 1,4-
nucleophilic addition of compound a4 to the α,β -unsaturated
ester of compound a3. The 1,4-nucleophilic addition reaction
in this step can be performed, for example, by reacting
20 compound a3 with compound a4 in a solvent such as THF and the
like in the presence of a copper reagent such as copper(II)
bromide and the like. The reaction temperature is preferably
from -78°C to room temperature.

[0221]

25 In the third step, compound a6 is obtained by hydrolysis
of the ester of compound a5 and decarboxylation of the
resulting carboxy group. The hydrolysis and decarboxylation
reaction in this step can be performed, for example, by
reacting compound a5 with a base such as sodium hydroxide and
30 the like under heating in a solvent such as ethylene glycol and
the like.

[0222]

 In the fourth step, compound a7 is obtained by reducing

the cyano group of compound a6. The reduction reaction in this step can be performed, for example, by reacting compound a6 with a reducing agent such as lithium aluminum hydride and the like under heating in a solvent such as THF and the like.

5 [0223]

In the fifth step, compound a9 is obtained from compound a7 and compound a8 by reductive amination reaction. The reductive amination reaction in this step can be performed, for example, by reacting compound a7 and compound a8 with a
10 reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride and the like in a solvent such as dichloromethane, methanol and the like. In this reaction, it may be preferable to add an acid such as acetic acid and the like. The reductive amination reaction in this step can also
15 be performed, for example, by reacting a reducing agent such as sodium borohydride in a solvent such as methanol with the imine obtained by reacting compound a7 with compound a8 in a solvent such as toluene and then heating same, using a Dean-Stark apparatus.

20 [0224]

In the sixth step, compound a11 is obtained by condensing compound a9 and compound a10. The condensation reaction in this step can be performed, for example, by reacting compound a9 and compound a10 with a condensing agent such as HATU and
25 the like in a solvent such as DMF and the like. The condensation reaction in this step can also be performed, for example, by reacting acid chloride obtained by reacting oxalyl chloride and the like with compound a10 in a solvent such as dichloromethane and the like, with compound a9 in a solvent
30 such as dichloromethane and the like, in the presence of a base such as DIPEA and the like.

[0225]

In the seventh step, compound a12 is obtained by reducing carbonyl group of compound a11. The reduction reaction in this
35 step can be performed, for example, by reacting compound a11

with a reducing agent such as borane-THF complex and the like under heating in a solvent such as THF and the like.

[0226]

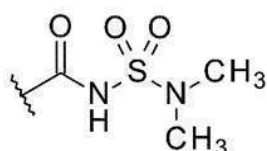
In the eighth step, compound a14 is obtained from
5 compound a9 and compound a13 by Buchwald amination reaction or aromatic nucleophilic substitution reaction. The Buchwald amination reaction in this step can be performed, for example, by reacting compound a9 with compound a13 under heating in a solvent such as 1,4-dioxane and the like, in the presence of a
10 base such as cesium carbonate and the like and a metal catalyst such as RuPhos Pd G3 or BrettPhos Pd G3 and the like. The aromatic nucleophilic substitution reaction in this step can be performed, for example, by reacting compound a9 with compound a13 under heating in a solvent such as 2-butanol, N,N-
15 dimethylacetamide and the like, in the presence of a base such as 1,8-diazabicyclo[5.4.0]-7-undecene, potassium carbonate and the like.

[0227]

When R⁵ is a group represented by the following formula:

20 [0228]

[Chem. 26]



[0229]

R⁵ moiety can be introduced according to a known method.

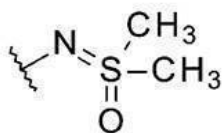
25 Examples of literature on the known method include, but are not limited to, WO 2013088315 A1, WO 2020192588 A1 and the like.

[0230]

When R⁵ is a group represented by the following formula:

[0231]

30 [Chem. 27]



[0232]

R⁵ moiety can be introduced according to a known method.

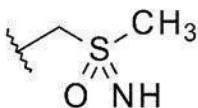
Examples of literature on the known method include, but are not
 5 limited to, J. Org. Chem., 2000, 65, 1, 169-175, Tetrahedron
 Lett., 1998, 39, 5731-5734 and the like.

[0233]

When R⁵ is a group represented by the following formula:

[0234]

10 [Chem. 28]



[0235]

R⁵ moiety can be introduced according to a known method.

Examples of literature on the known method include, but are not
 15 limited to, J. Org. Chem., 2015, 80, 6391-6399, WO 2019148132
 A1 and the like.

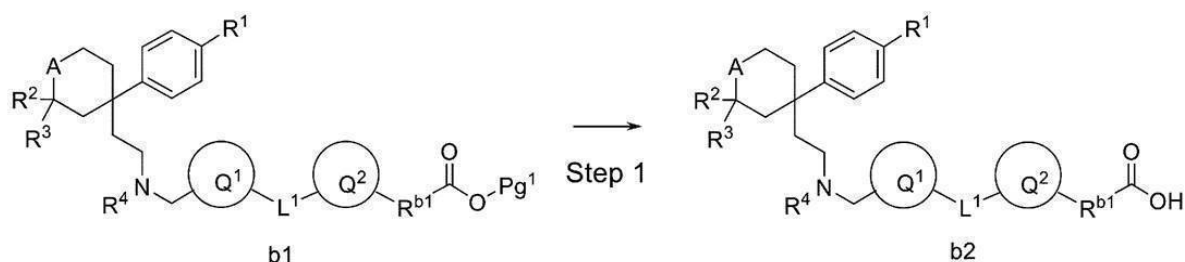
[0236]

(Method B)

Among the compounds represented by the formula (1), a
 20 compound represented by the following formula b2 can be
 produced according to the following method.

[0237]

[Chem. 29]



25 [0238]

wherein R^{b1} is a single bond or a C₁₋₆ alkylene group optionally having a group selected from the group consisting of a hydroxy group, a C₁₋₆ alkoxy group, a piperazinyl group and a 1-tert-butoxy carbonylpiperazinyl group, and Pg¹ is a carboxy-
5 protecting group.

[0239]

In the first step, compound b₂ is obtained from compound b₁ by a deprotection reaction of the carboxy-protecting group Pg¹. The deprotection reaction in this reaction can be
10 performed by a method generally used for deprotecting a carboxy-protecting group. For example, when Pg¹ is a methyl group or an ethyl group, the deprotection reaction can be performed by reacting compound b¹ with a base such as an aqueous sodium hydroxide solution in a solvent such as
15 methanol.

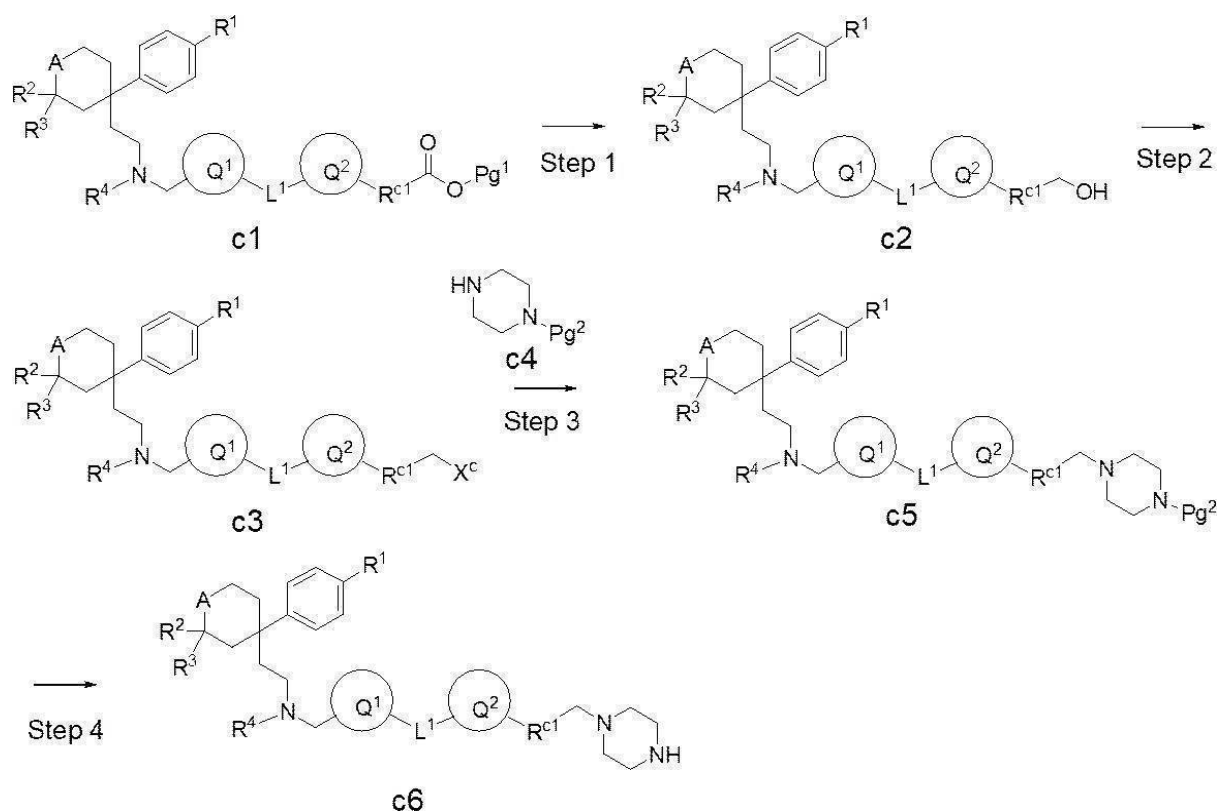
[0240]

(Method C)

Among the compounds represented by the formula (1), compounds represented by the following formulas c₂ and c₅ can
20 be produced according to the following methods.

[0241]

[Chem. 30]



[0242]

wherein R^{c1} is a single bond or a C_{1-6} alkylene group optionally having substituent(s) selected from the group consisting of a carboxy group, a hydroxy group and a C_{1-6} alkoxy group, Pg^1 is a carboxy-protecting group, Pg^2 is an amino-protecting group, and X^c is a leaving group.

[0243]

In the first step, compound **c2** is obtained by reducing the ester of compound **c1**. The reduction reaction in this step can be performed, for example, by reacting compound **c1** with a reducing agent such as lithium aluminum hydride, diisobutylaluminum hydride and the like in a solvent such as THF and the like.

[0244]

In the second step, compound **c3** is obtained by converting the hydroxy group of compound **c2** into a leaving group. Examples of the leaving group in this step include a methanesulfonyloxy group, a para-toluenesulfonyloxy group, and the like and the group can be converted by a generally used method (reagent, solvent, reaction conditions, etc.).

[0245]

In the third step, compound c5 is obtained from compound c3 and compound c4 by nucleophilic substitution reaction. The nucleophilic substitution reaction in this step can be performed by reacting compound c3 with compound c4 under heating in a solvent such as DMF, acetonitrile and the like, and/or can also be performed in the presence of a base such as N,N-diisopropylethylamine and the like.

[0246]

10 In the fourth step, compound c6 is obtained by deprotecting the amino-protecting group Pg² of compound c5. The deprotection reaction in this step can be performed by a method generally used for deprotecting an amino-protecting group. For example, when Pg² is a tert-butoxy carbonyl group, 15 the deprotection reaction can be performed by reacting compound c5 with an acid such as hydrogen chloride, trifluoroacetic acid and the like in a solvent such as dichloromethane.

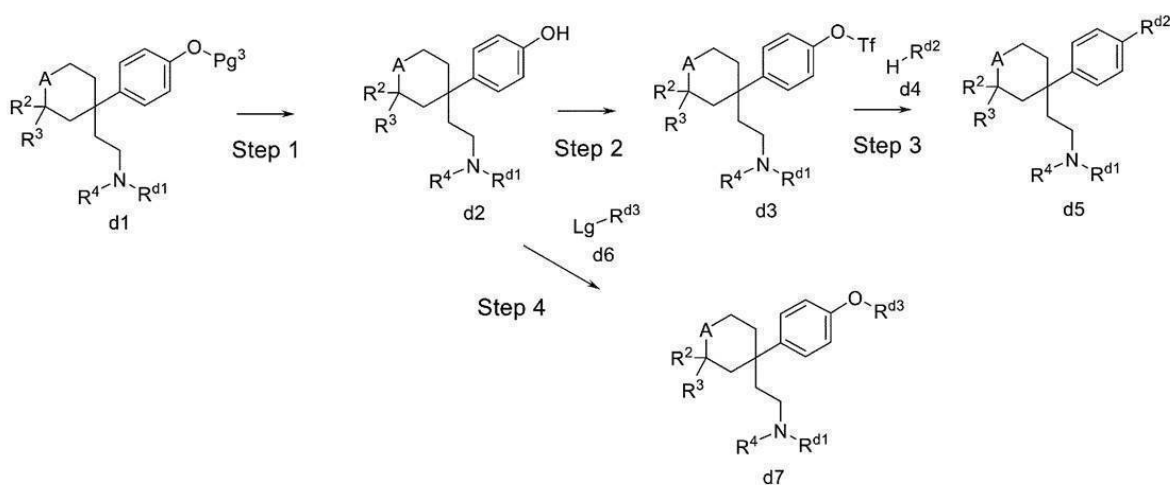
[0247]

(Method D)

20 Among the compounds represented by the formula (1), a compound represented by the following formula d5 or d7 can be produced according to the following production method.

[0248]

[Chem. 31]



25

[0249]

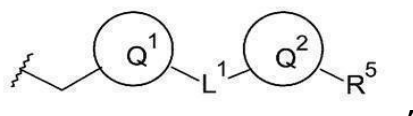
wherein Pg^3 is a hydroxy-protecting group (e.g., methyl group, benzyl group, methoxymethyl group, etc.),

Lg is a leaving group,

R^{d1} is a group represented by the following formula:

5 [0250]

[Chem. 32]



[0251]

or a group that can be converted to the group,

10 R^{d2} is a C_{1-3} alkylamino group, a di- C_{1-3} alkylamino group, or a 4- to 6-membered saturated heterocyclic group having one nitrogen atom as a ring member atom, and

R^{d3} is a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms.

15 [0252]

In the first step, compound d2 is obtained from compound d1 by a deprotection reaction of a hydroxy-protecting group Pg^3 . The deprotection reaction in this step can be performed by a method generally used for deprotection of a hydroxy-protecting group. For example, when Pg^3 is a methyl group, the deprotection reaction can be performed by reacting compound d1 with sodium thiomethoxide under heating in a solvent such as DMF and the like. This reaction can also be performed under microwave irradiation. The reaction temperature is preferably 20 80°C to 160°C.

[0253]

In the second step, compound d3 is obtained from compound d2 by triflation of a hydroxy group. The triflation reaction in this step can be performed, for example, by reacting a triflation agent such as trifluoromethanesulfonic anhydride and 30 the like and compound d2 in a solvent such as dichloromethane and the like, in the presence of a base such as pyridine and the like.

[0254]

In the third step, compound d5 is obtained from compound d3 and amine d4 by Buchwald amination reaction. The Buchwald amination reaction in this step can be performed by reacting
5 compound d3 and amine d4 under heating in a solvent such as 1,4-dioxane and the like, in the presence of a ligand such as 2-(di-tert-butylphosphino)biphenyl and the like, and a metal catalyst such as tris(dibenzylideneacetone)dipalladium(0) and the like.

10 [0255]

In the fourth step, compound d7 is obtained by alkylation reaction of compound d2 with an alkylating agent d6. The alkylation reaction in this step can be performed, for example, by reacting alkylating agent d6 and compound d2 under heating
15 in a solvent such as DMF and the like, in the presence of a base such as potassium carbonate and the like. The reaction temperature is preferably from room temperature to 150°C.

[0256]

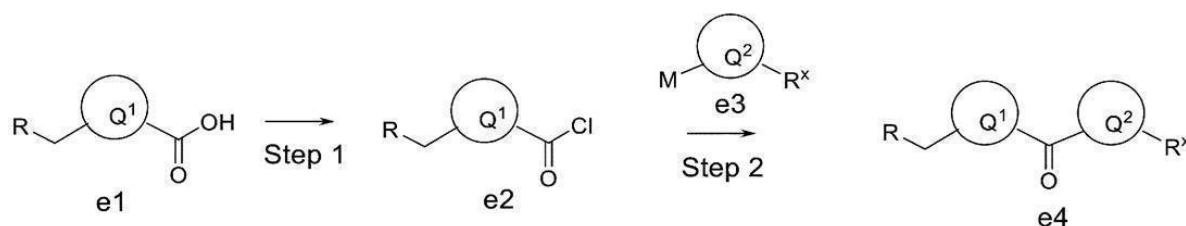
(Method E)

20 Compound e4, which is a compound represented by the formula (1) wherein L¹ is -C(=O)-, can be produced according to the following method.

[0257]

[Chem. 33]

25

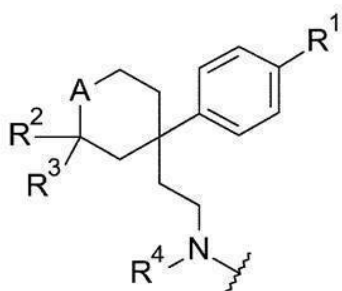


[0258]

wherein R is a group represented by the following formula:

[0259]

[Chem. 34]



[0260]

M is a dihydroxyboryl group, a pinacolatoboryl group and the like,

5 R^x is R^5 or a group that can be converted to R^5 .

[0261]

In the first step, carboxylic acid e1 is converted to acid chloride e2. Chlorination reaction in this step can be performed, for example, by reacting compound e1 and a
 10 chlorinating agent such as oxalyl chloride, thionyl chloride and the like in a solvent such as dichloromethane and the like, in the presence of a catalytic amount of DMF.

[0262]

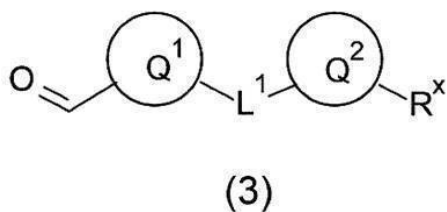
In the second step, compound e4 is obtained by coupling
 15 reaction of compound e2 and compound e3. The coupling reaction in this step can be performed, for example, by reacting compound e2 and compound e3 under heating in a solvent such as toluene and the like in the presence of a base such as cesium carbonate and the like and a metal catalyst such as
 20 tetrakis(triphenylphosphine)palladium(0) and the like. Examples of literature on the coupling reaction of this step include Catalysts, 2019, 9(1), 53.

[0263]

A production method of a starting compound represented by
 25 the formula (3):

[0264]

[Chem. 35]



[0265]

wherein R^x is R^5 or a group that can be converted to R^5 is shown below.

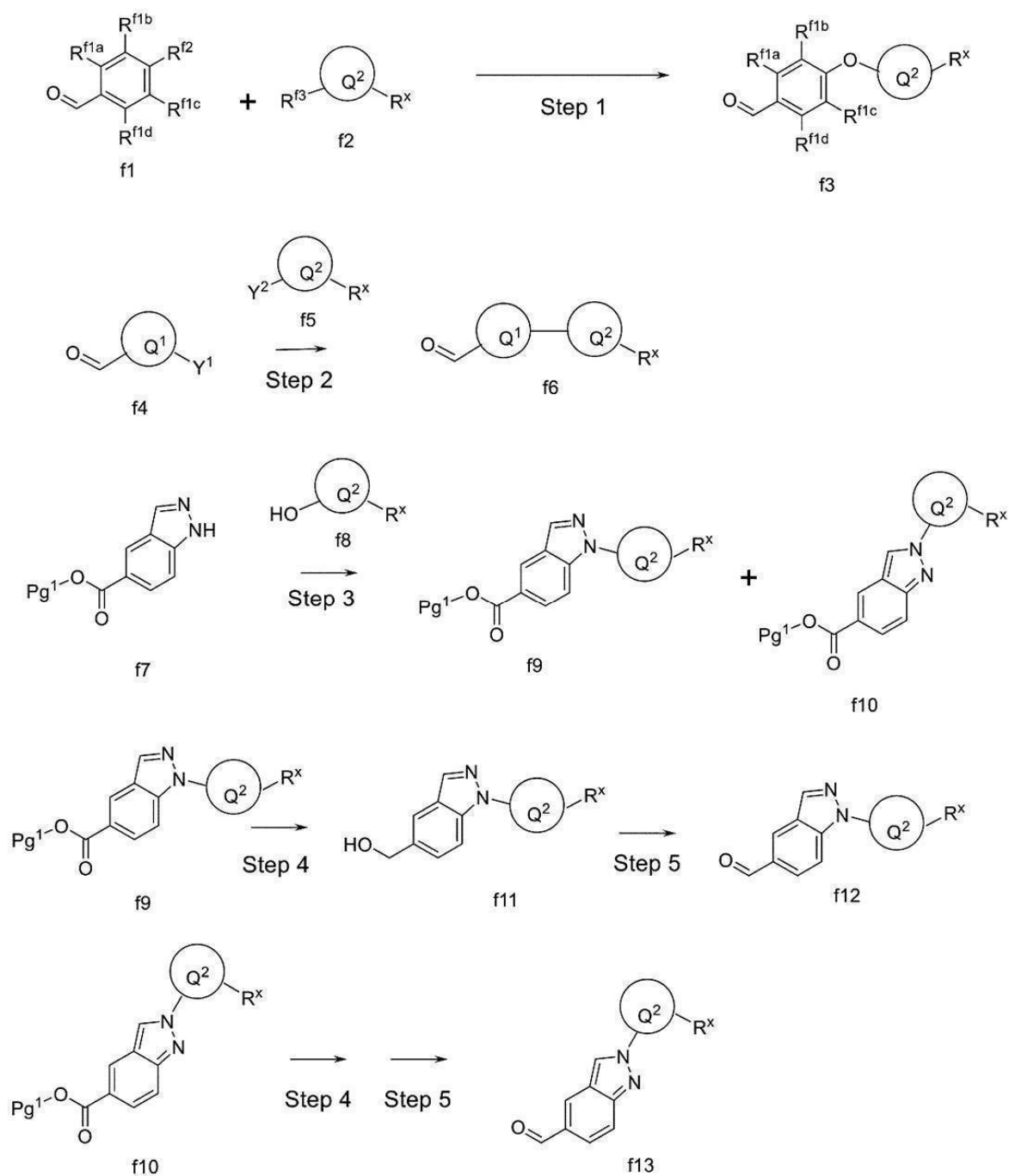
5 [0266]

(Method F)

Among starting compounds (3), compound f3 wherein L^1 is oxygen atom, compound f6 wherein L^1 is a single bond, and compounds f12 and f13 wherein Q^1 is a 7-azaspiro[3.5]nonane
 10 ring can be produced according to the following methods.

[0267]

[Chem. 36]



[0268]

wherein R^{f1a}, R^{f1b}, R^{f1c}, and R^{f1d} are each independently a hydrogen atom, a halogen atom, or a C₁₋₆ alkyl group,

5 R^{f2} is OH or a leaving group, wherein when R^{f2} is OH, then R^{f3} is OH or a leaving group and when R^{f2} is a leaving group, then R^{f3} is OH,

Y¹ is a halogen atom, a trifluoromethanesulfonyloxy group, a pinacolatoboryl group, or a dihydroxyboryl group,
 10 wherein when Y¹ is a halogen atom or a

trifluoromethanesulfonyloxy group, then Y^2 is a pinacolatoboryl group or a dihydroxyboryl group or when Y^1 is a pinacolatoboryl group or a dihydroxyboryl group, then Y^2 is a halogen atom or a trifluoromethanesulfonyloxy group,

5 Pg^1 is a carboxy-protecting group, and

R^X is R^5 or a group that can be converted to R^5 .

[0269]

In the first step, compound f3 is obtained from compound f1 and and compound f2. When R^{f2} is OH and R^{f3} is OH, this
10 reaction can be performed by Mitsunobu reaction. The Mitsunobu reaction in this step can be performed, for example, by reacting compound f1 and compound f2 with phosphine such as triphenylphosphine and the like and azodicarboxylic acid ester such as diisopropyl azodicarboxylate and the like in a solvent
15 such as THF and the like. When R^{f2} or R^{f3} is a leaving group, this reaction can be performed by a nucleophilic substitution reaction. The nucleophilic substitution reaction in this step can be performed, for example, by reacting compound f1 and compound f2 with a base such as potassium carbonate, cesium
20 carbonate and the like under heating in a solvent such as DMF, N,N-dimethylacetamide and the like.

[0270]

In the second step, compound f6 is obtained by coupling reaction of compound f4 and compound f5. The coupling reaction
25 in this step can be performed, for example, by heating compound f4 and compound f5 in a solvent such as aqueous 1,4-dioxane and the like, in the presence of a base such as potassium carbonate and the like and a metal catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride
30 dichloromethane adduct and the like.

[0271]

In the third step, compound f9 and compound f10 are obtained by Mitsunobu reaction of compound f7 and compound f8. The Mitsunobu reaction in this step can be performed, for
35 example, by reacting compound f7 and compound f8 with a

phosphorane reagent such as cyanomethylenetributylphosphorane and the like under heating in a solvent such as toluene and the like.

[0272]

5 In the fourth step, compound f11 is obtained by reduction reaction of compound f9. The reduction reaction in this step can be performed under the same conditions as in the first step of Method C.

[0273]

10 In the fifth step, compound f12 is obtained from compound f11 by oxidation reaction. The oxidation reaction in this step can be performed, for example, by reacting compound f11 with an oxidizing agent such as 1,1,1-triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3-(1H)-one, manganese(IV) oxide and the like in a
15 solvent such as dichloromethane and the like.

[0274]

Compound f13 can be obtained by subjecting compound f10 to the same steps as the fourth step and the fifth step of this method.

20 [0275]

In the following, a general production method of a compound of the formula (2) of the present invention is described.

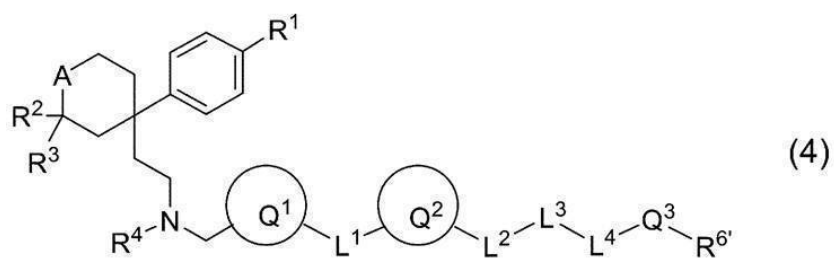
[0276]

25 (Method G)

Method G is a production method of a compound represented by the formula (2).

[0277]

[Chem. 37]

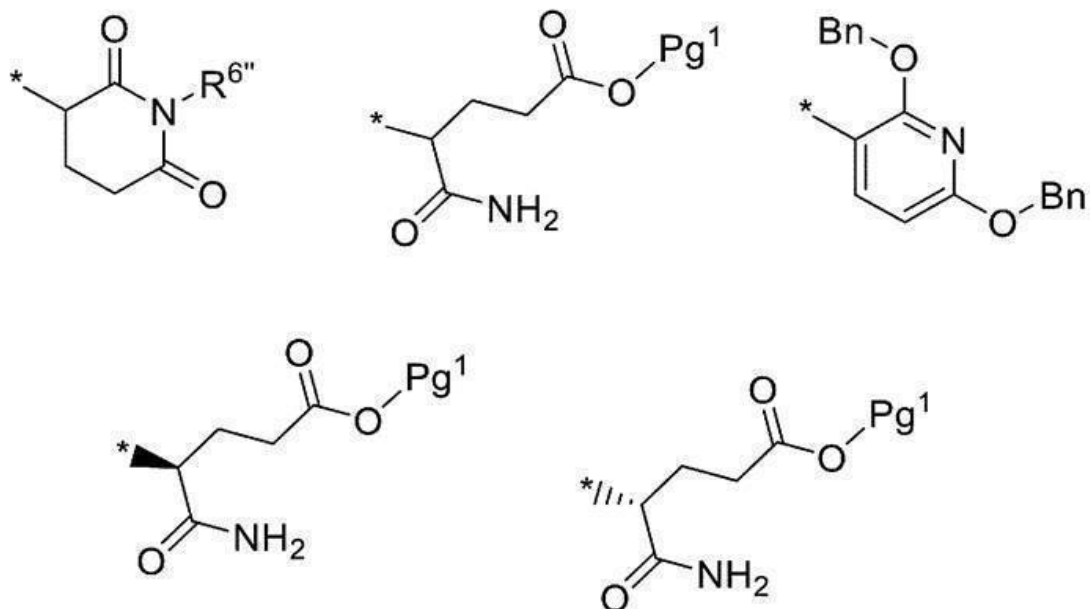


[0278]

wherein R^{6'} is any group selected from the groups represented by the following formulas:

5 [0279]

[Chem. 38]



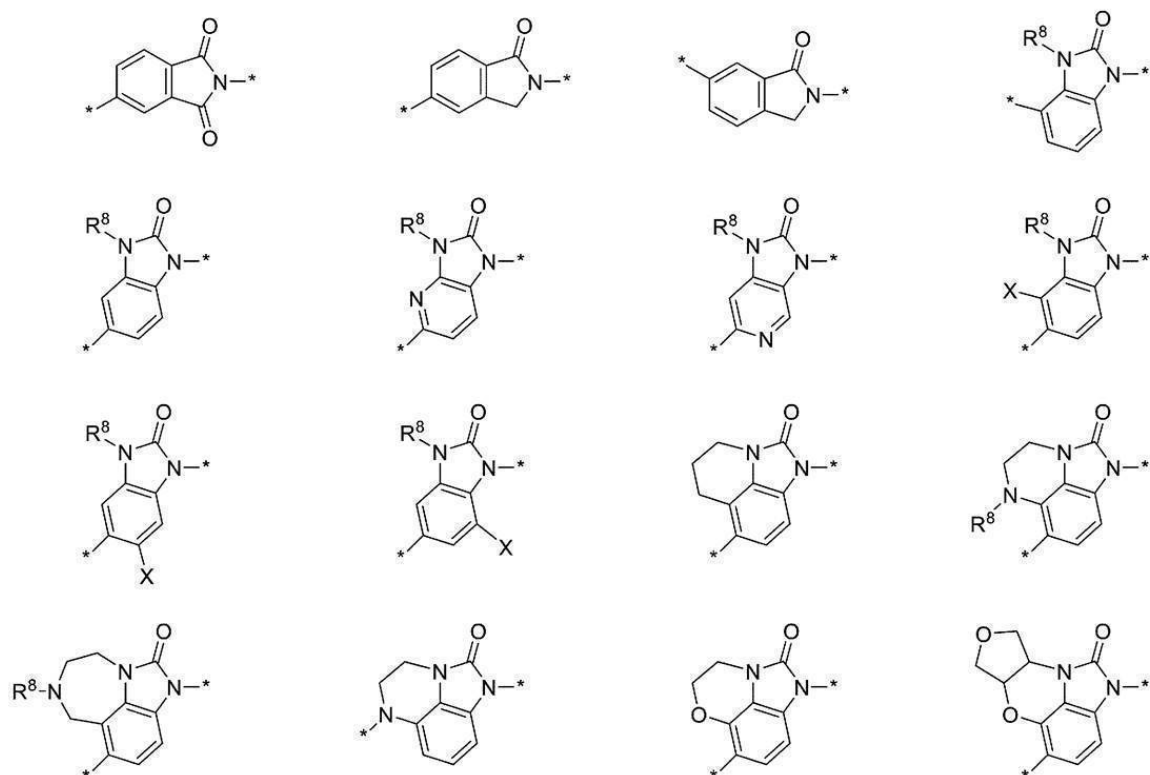
[0280]

R^{6''} is an imide-protecting group (e.g., (2-
 10 trimethylsilylethoxy)methyl group, tert-butoxycarbonyl group,
 benzyloxymethyl group, etc.),

Q³ is any group selected from the following formulas:

[0281]

[Chem. 39]



5 , and

[0282]

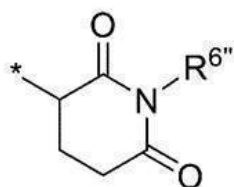
Pg¹ is a carboxy-protecting group (e.g., methyl group, ethyl group, tert-butyl group, etc.).

[0283]

10 When R^{6'} is a group represented by the following formula:

[0284]

[Chem. 40]



[0285]

15 this step can be performed by deprotecting the protecting group of compound (4).

[0286]

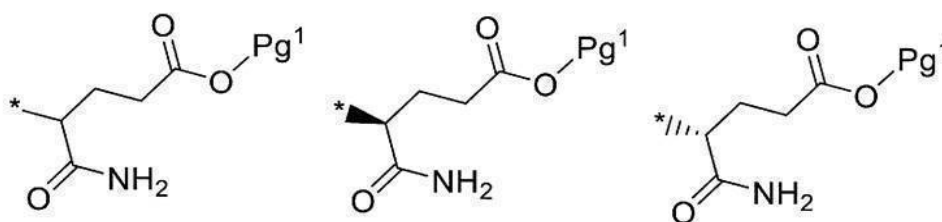
The deprotection reaction in this step can be performed by a method generally used for deprotecting a protecting group for the nitrogen atom of imide. For example, when the protecting group is an SEM group, the deprotection reaction in this step can be performed by reacting compound (4) with an acid such as trifluoroacetic acid and the like in a dichloromethane solvent to remove trimethylsilyl ethyl group, followed by reaction with a base such as N,N'-dimethylethylenediamine and the like in a solvent such as ethyl acetate and the like.

[0287]

When R^{6'} is any group selected from the following formulas:

[0288]

[Chem. 41]



[0289]

this step can be performed by a cyclization reaction.

[0290]

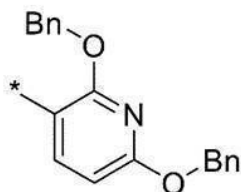
When Pg¹ is a tert-butyl group, the cyclization reaction in this step can be performed, for example, by reacting compound (4) and an acid such as benzenesulfonic acid and the like under heating in a solvent such as acetonitrile and the like. When Pg¹ is a methyl group or an ethyl group, the cyclization reaction in this step can be performed, for example, by reacting compound (4) with a base such as potassium tert-butoxide and the like in a solvent such as THF and the like.

[0291]

When R^{6'} is a group represented by the following formula:

[0292]

[Chem. 42]



[0293]

5 this step can be performed by a catalytic hydrogenation reaction.

[0294]

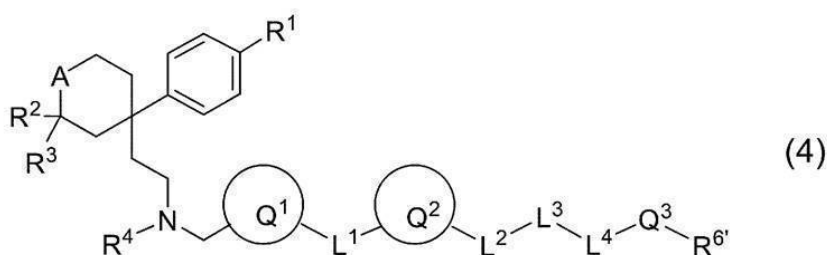
The catalytic hydrogenation reaction in this step can be performed, for example, by reacting compound (4) with a metal
10 catalyst such as palladium carbon and the like under a hydrogen atmosphere in a solvent such as ethyl acetate, ethanol and the like.

[0295]

A production method of a starting compound represented by
15 the formula (4):

[0296]

[Chem. 43]



[0297]

20 is shown below.

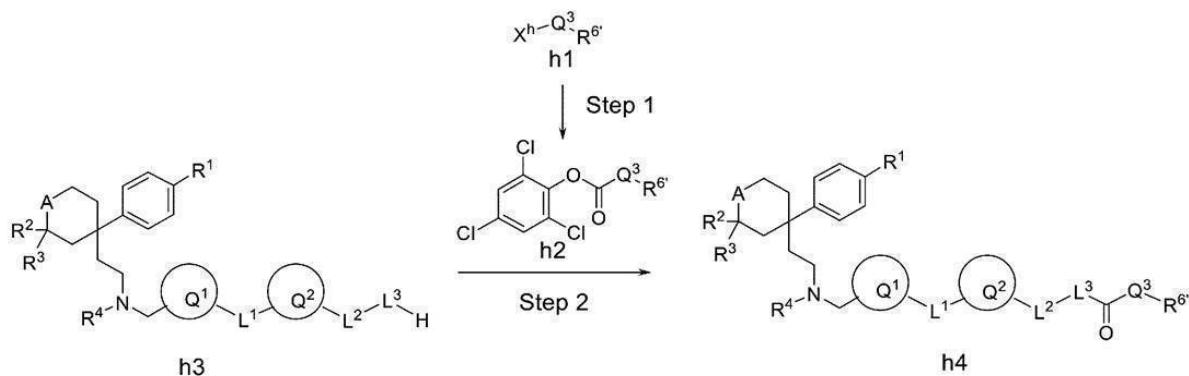
[0298]

(Method H)

Compound h4, which is a starting compound (4) wherein L⁴ is -C(=O)- can be produced according to the following method.

25 [0299]

[Chem. 44]



[0300]

wherein R^1 , R^2 , R^3 , R^4 , $\text{R}^{6'}$, ring Q^1 , ring Q^2 , ring Q^3 , L^1 , and L^2 are as defined above, L^3 is a piperazinediyl group, a piperazin-2-onediyl group, a piperidinediyl group, a pyrrolidinediyl group, an azetidinediyl group, or a 3-oxa-9-azabicyclo[3.3.1]nonanedyl group, and X^{h} is a halogen atom.

[0301]

In the first step, compound h1 is converted to compound h2 by a carbonylation reaction. The carbonylation reaction in this step can be performed, for example, by reacting compound h1 and 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) under heating in a solvent such as toluene and the like, in the presence of a base such as triethylamine and the like, a ligand such as XantPhos and the like, and a metal catalyst such as palladium(II) acetate and the like in a carbon monoxide atmosphere.

[0302]

In the second step, compound h4 is obtained from compound h2 and compound h3 by an amidation reaction. The amidation reaction in this step can be performed, for example, by reacting compound h2 and compound h3 under heating in a solvent such as acetonitrile and the like, in the presence of a base such as DIPEA and the like, and a catalyst such as 4-dimethylaminopyridine and the like.

[0303]

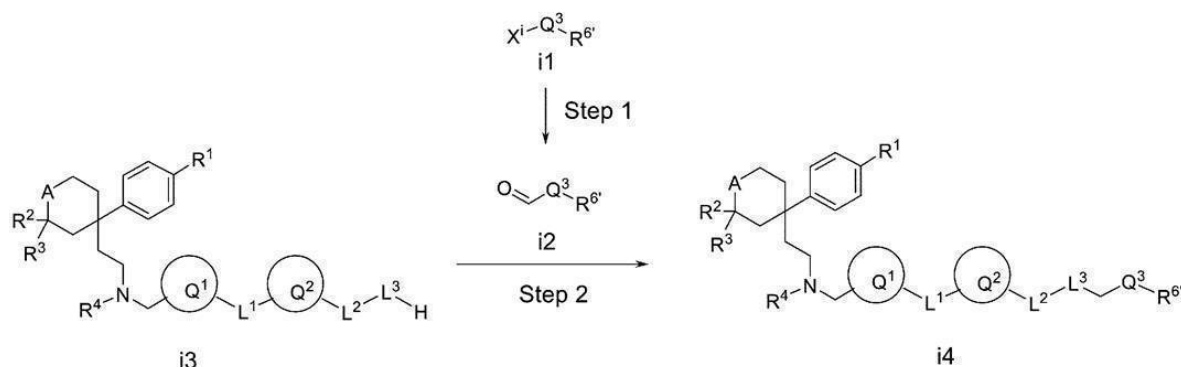
(Method I)

Compound i4, which is a starting compound (4) wherein L^4

is $-\text{CH}_2-$, can be produced according to the following method.

[0304]

[Chem. 45]



5 [0305]

wherein R^1 , R^2 , R^3 , R^4 , $\text{R}^{6'}$, ring Q^1 , ring Q^2 , ring Q^3 , L^1 , and L^2 are as defined above, L^3 is a piperazinediyl group, a piperazin-2-onediyl group, a piperidinediyl group, a pyrrolidinediyl group, an azetidinediyl group, or a 3-oxa-9-azabicyclo[3.3.1]nonanediyl group, and X^i is a halogen atom.

10 [0306]

In the first step, compound **i1** is converted to compound **i2** by a formylation reaction. The formylation reaction in this step can be performed, for example, by reacting compound **i1** with a reducing agent such as triethylsilane and the like under heating in a solvent such as toluene and the like, in the presence of a base such as triethylamine and the like, a ligand such as XantPhos and the like, and a metal catalyst such as palladium(II) acetate and the like in a carbon monoxide atmosphere. In this reaction, it may be preferable to add saccharin.

20 [0307]

In the second step, compound **i4** is obtained from compound **i2** and compound **i3** by a reductive amination reaction. The reductive amination reaction in this step can be performed, for example, by reacting compound **i2** and compound **i3** with a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride and the like in a solvent such as

dichloromethane, methanol and the like. In this reaction, it may be preferable to add an acid such as acetic acid and the like. The reductive amination reaction in this step can also be performed, for example, by reacting a reducing agent such as sodium borohydride in a solvent such as methanol with the imine obtained by reacting compound i3 with compound i2 under heating in a solvent such as toluene, using a Dean-Stark apparatus.

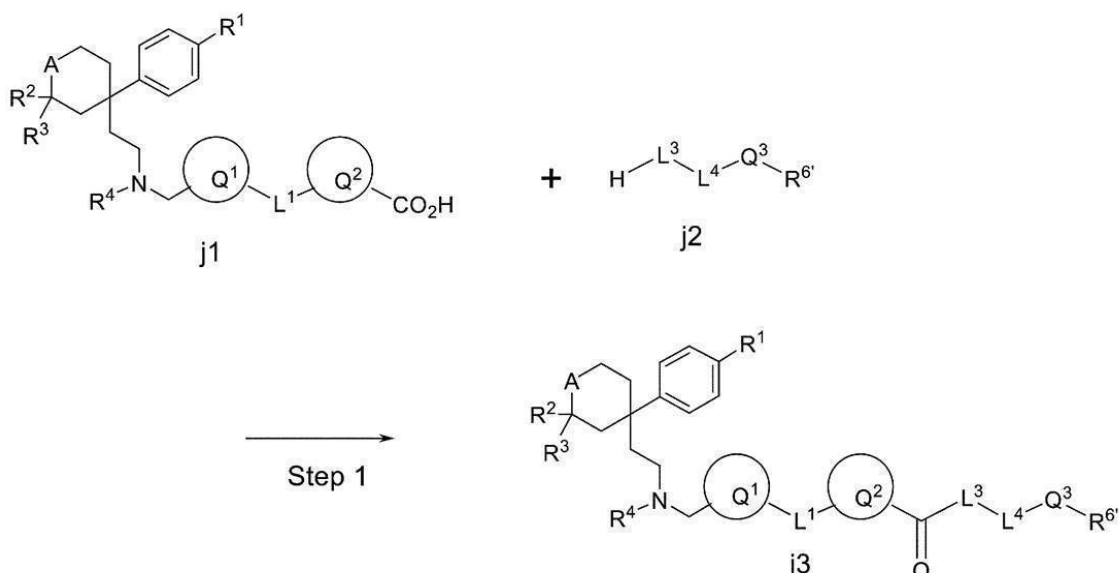
[0308]

(Method J)

10 Compound j3, which is a starting compound (4) wherein L^2 is $C=O$, can be produced according to the following method.

[0309]

[Chem. 46]



15 [0310]

wherein R^1 , R^2 , R^3 , R^4 , $R^{6'}$, ring Q^1 , ring Q^2 , ring Q^3 , L^1 , and L^4 are as defined above, L^3 is a piperazinediyl group, a piperazin-2-onediyl group, a piperidinediyl group, a pyrrolidinediyl group, an azetidinediyl group, or a 3-oxa-9-azabicyclo[3.3.1]nonanediy group.

20

[0311]

In the first step, compound j3 is obtained by condensing compound j1 and compound j2. The condensation reaction in this step can be performed, for example, by reacting compound j1 and

compound j2 with a condensing agent such as HATU and the like in a solvent such as DMF and the like. The condensation reaction in this step can also be performed, for example, by reacting acid chloride obtained by reacting a chlorinating agent such as oxalyl chloride and the like with compound j1 in a solvent such as dichloromethane and the like, in the presence of a catalytic amount of DMF, with compound j1 in a solvent such as dichloromethane and the like, in the presence of a base such as DIPEA and the like.

10 [0312]

A compound wherein L^2 is CONH or $(CH_2)_nCONH$ (n indicates an integer of 1 to 3) can be obtained under similar conditions by changing compound j1 and compound j2 to the corresponding carboxylic acid and amine, respectively.

15 [0313]

A compound wherein L^2 is NHCO can be obtained under similar conditions by changing compound j1 and compound j2 to the corresponding amine and carboxylic acid, respectively.

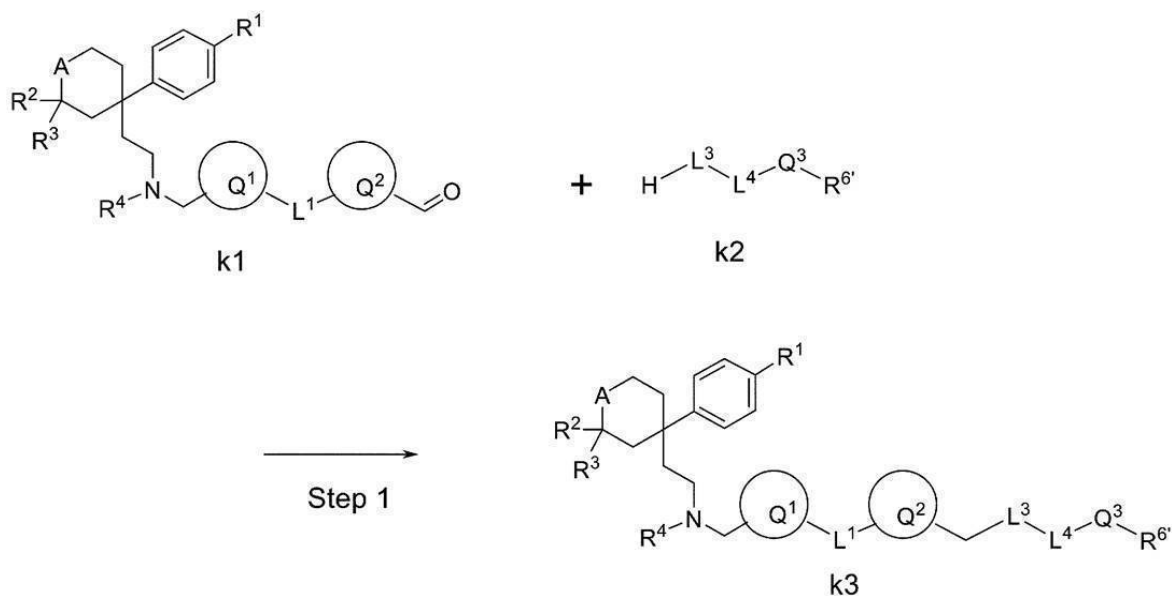
[0314]

20 (Method K)

Compound k3, which is a starting compound (4) wherein L^2 is $-CH_2-$, can be produced according to the following method.

[0315]

[Chem. 47]



[0316]

wherein R^1 , R^2 , R^3 , R^4 , $R^{6'}$, ring Q^1 , ring Q^2 , ring Q^3 , L^1 , and L^4 are as defined above, L^3 is a piperazinediyl group, a
 5 piperazin-2-onediyl group, a piperidinediyl group, a pyrrolidinediyl group, an azetidinediyl group, or a 3-oxa-9-azabicyclo[3.3.1]nonanedyl group.

[0317]

In the first step, compound k3 is obtained from compound
 10 k1 and compound k2 by a reductive amination reaction. The reductive amination reaction in this step can be performed as in the second step of Method I.

[0318]

A compound wherein L^2 is a C_{2-6} alkylene group can also be
 15 obtained under the same conditions by changing compound k1 to the corresponding aldehyde.

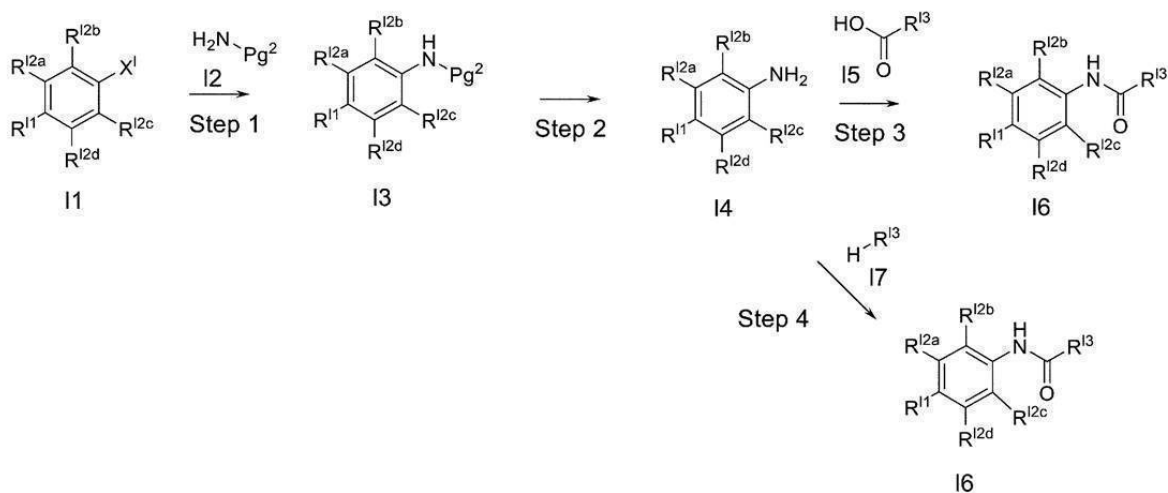
[0319]

(Method L)

Compound 16, which is a starting compound (4) wherein Q^2
 20 is a benzene ring optionally substituted by one halogen atom and L^2 is $-NHCO-$ can be produced according to the following method.

[0320]

[Chem. 48]



[0321]

wherein X¹ is a halogen atom,

Pg² is an amino-protecting group,

5 R¹¹ is a group represented by the following formula:

[0322]

[Chem. 49]



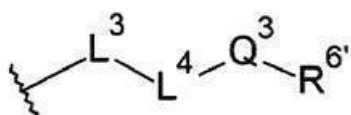
[0323]

10 R^{12a}, R^{12b}, R^{12c}, and R^{12d} are each independently a hydrogen atom or a halogen atom, and

R¹³ is a group represented by the following formula:

[0324]

[Chem. 50]



15

[0325]

or a group that can be converted to the group.

[0326]

In the first step, compound 13 is obtained from compound

11 and compound 12 by a Buchwald amination reaction. The amination reaction in this step can be performed, for example, by reacting compound 11 and compound 12 under heating in a solvent such as tert-butyl alcohol, DMSO and the like, in the presence of a ligand such as 1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene, tBuXPhos and the like; a metal catalyst such as tris(dibenzylideneacetone)dipalladium(0) and the like; and a base such as cesium carbonate, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene and the like.

10 [0327]

In the second step, compound 13 is converted to compound 14 by a deprotection reaction of an amino-protecting group Pg². The deprotection reaction in this step can be performed by a method generally used for the deprotection of an amino-protecting group. For example, when Pg² is a tert-butoxy carbonyl group, it can be performed by reacting compound 13 with an acid such as hydrochloric acid and the like in a solvent such as dichloromethane and the like.

[0328]

20 In the third step, compound 16 is obtained by a condensation reaction of compound 14 and compound 15. The condensation reaction in this step can be performed under the same conditions as in the first step of Method J.

[0329]

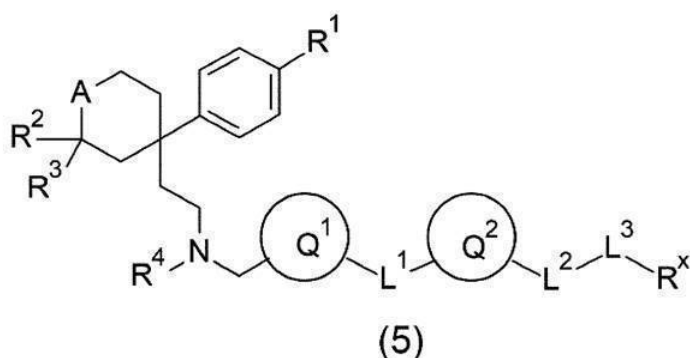
25 In the fourth step, compound 16 is obtained from compound 14 and compound 17 by a ureation reaction. The ureation reaction in this step can be performed by reacting carbamoyl chloride obtained by reacting compound 14 with triphosgene in a solvent such as dichloromethane and the like, in the presence of a base such as triethylamine, pyridine and the like, with compound 17 in a solvent such as dichloromethane and the like, in the presence of a base such as triethylamine and the like.

[0330]

A production method of the starting compound represented by the formula (5):

[0331]

[Chem. 51]

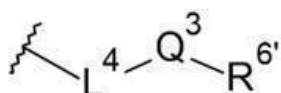


[0332]

5 wherein R^x is a group that can be converted to a group represented by the following formula:

[0333]

[Chem. 52]



10 [0334]

is shown.

[0335]

Among the starting compounds (5), a compound wherein L^2 is $C=O$, $CONH$, $(CH_2)_nCONH$ (n indicates an integer of 1 to 3), or
15 $NHCO$ can be produced according to a method similar to that of Method J. Among the starting compounds (5), a compound wherein L^2 is a C_{1-6} alkylene group can be produced according to a method similar to that of Method K.

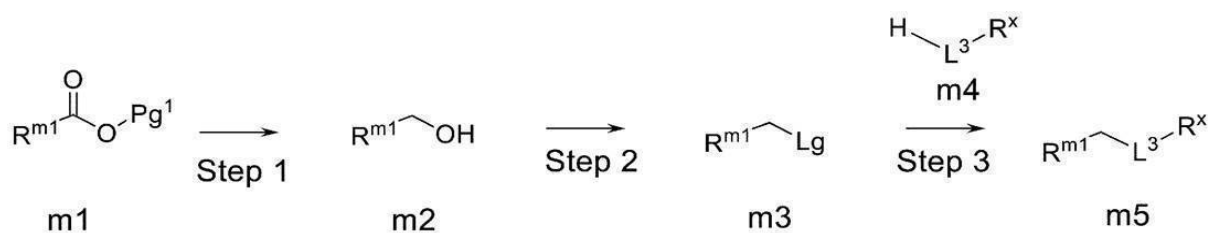
[0336]

20 (Method M)

Compound m5, which is a starting compound (5) wherein L^2 is a C_{1-6} alkylene group, can be produced according to the following method.

[0337]

25 [Chem. 53]



[0338]

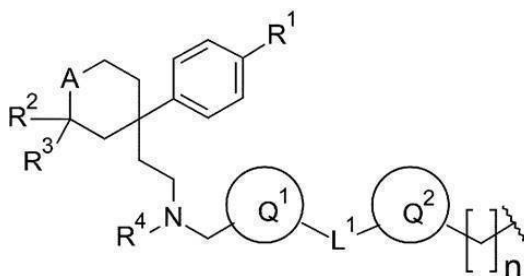
wherein L³ is a piperazinediyl group, a piperazin-2-onediyl group, a piperidinediyl group, a pyrrolidinediyl group, an
 5 azetidinediyl group, or a 3-oxa-9-azabicyclo[3.3.1]nonanediy group,

Lg is a leaving group (e.g., bromine atom, iodine atom, chlorine atom, methanesulfonyloxy group, para-
 10 toluenesulfonyloxy group, trifluoromethanesulfonyloxy group, etc.),

R^{m1} is a group represented by the following formula:

[0339]

[Chem. 54]



15 [0340]

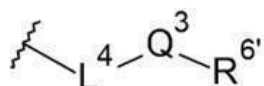
wherein n is an integer of 0 to 5,

Pg¹ is a carboxy-protecting group,

R^x is a group that can be converted to a group represented by the following formula:

20 [0341]

[Chem. 55]



[0342]

[0343]

In the first step, compound m2 is obtained by reducing the ester group of compound m1. The reduction reaction in this step can be performed, for example, by reacting compound m1 with a reducing agent such as lithium aluminum hydride,
5 diisobutylaluminum hydride and the like in a solvent such as tetrahydrofuran and the like.

[0344]

In the second step, compound m3 is obtained by converting the hydroxy group of compound m2 to a leaving group. Examples
10 of the leaving group in this step include bromine atom, iodine atom, chlorine atom, methanesulfonyloxy group, para-toluenesulfonyloxy group, trifluoromethanesulfonyloxy group and the like, and conversion to a leaving group can be performed by a method used generally (reagent, solvent, reaction conditions,
15 etc.).

[0345]

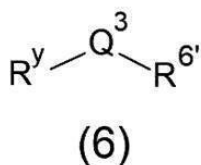
In the third step, compound m5 is obtained from compound m3 and compound m4 by a nucleophilic substitution reaction. The nucleophilic substitution reaction in this step can be
20 performed by reacting compound m3 and compound m4 under heating, in a solvent such as DMF, acetonitrile and the like. In this reaction, it may be preferable to add a base such as N,N-diisopropylethylamine and the like.

[0346]

25 A production method of a starting compound represented by the formula (6):

[0347]

[Chem. 56]

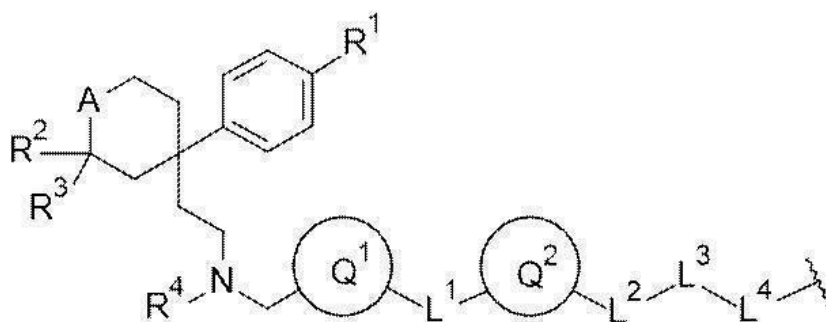


30 [0348]

wherein R^y is a group that can be converted to a group represented by the following formula:

[0349]

[Chem. 57]



[0350]

5 is shown below.

[0351]

The starting compound (6) is either known or is produced according to a known or similar method using a known compound as a starting material. Known compounds can be purchased from commercial suppliers or can be readily synthesized by methods described in literatures or similar methods thereto. Examples of the known literatures include, but are not limited to, WO2022081928 A1, WO2022081927 A1, WO2019060693 A1, WO2019038717 A1, ACS Med. Chem. Lett., 2021, 12, 1733, WO2021170109 A1 and the like.

[0352]

As examples of the production methods of the starting compound (6), Method N to Method P are described below, but the synthetic method of the starting compound (6) is not limited to these.

[0353]

(Method N)

Compound n8, which is a starting compound (6) wherein Q^3 is a group selected from the following formulas:

25 [0354]

[Chem. 58]

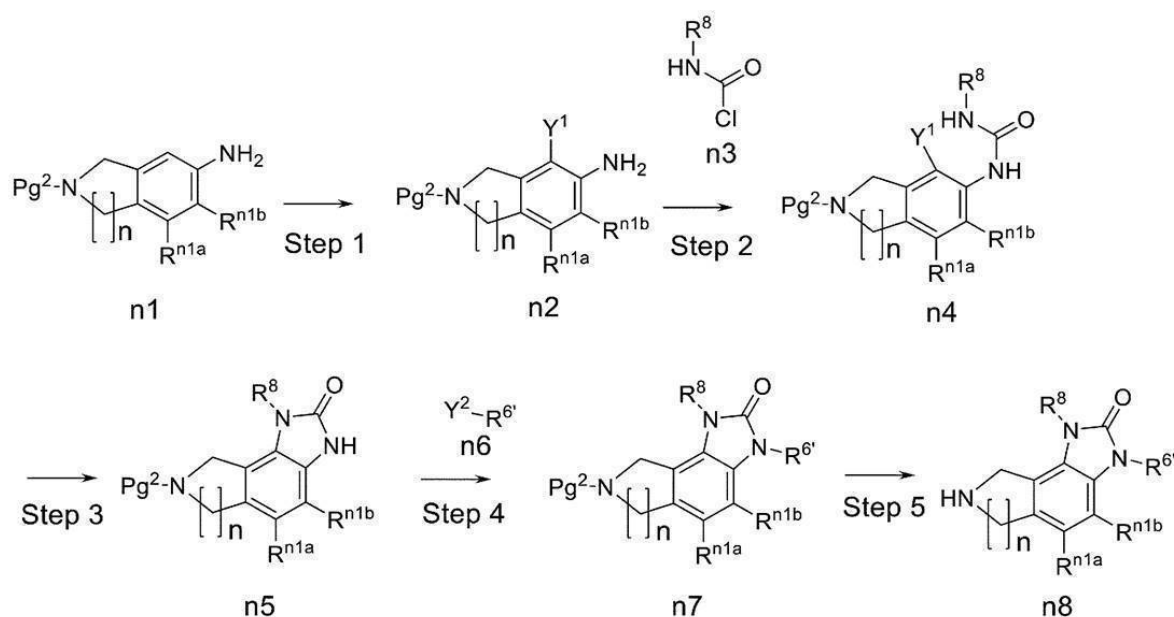


[0355]

can be produced according to the following method.

[0356]

5 [Chem. 59]



[0357]

wherein Y¹ is a halogen atom,

Y² is a halogen atom, a dihydroxyboryl group or a
10 pinacolatoboryl group and the like,

R^{n1a} and R^{n1b} are each independently a hydrogen atom or a
halogen atom,

Pg² is an amino-protecting group, and

n is an integer of 1 or 2.

15 [0358]

In the first step, compound n1 is converted to compound
n2 by a halogenation reaction. The halogenation in this step
can be performed, for example, in a solvent such as DMF and the
like, by reacting compound n1 with a halogenating agent such as
20 N-bromosuccinimide, benzyltrimethylammonium tribromide, N-

iodosuccinimide and the like.

[0359]

In the second step, compound n4 is obtained by ureation of compound n2 using compound n3. The ureation reaction in
5 this step can be performed, for example, by reacting compound n2 with compound n3 in a solvent such as dichloromethane and the like, in the presence of a base such as DIPEA and the like.
[0360]

In the third step, compound n5 is obtained by a
10 cyclization reaction of compound n4. The cyclization reaction in this step can be performed, for example, by reacting compound n4 with a copper catalyst such as copper(I) iodide and the like under heating in a solvent such as DMSO and the like, in the presence of a copper ligand such as trans-4-hydroxy-L-
15 proline and the like and a base such as tripotassium phosphate and the like. The reaction temperature is preferably 80°C to 160°C.
[0361]

In the fourth step, compound n7 is obtained from compound
20 n5 and compound n6. When Y² is a halogen atom, this step can be performed by an alkylation reaction. The alkylation reaction in this step can be performed, for example, by reacting compound n5 with compound n6 in a solvent such as DMF and the like, in the presence of a base such as potassium
25 carbonate, cesium carbonate and the like. When Y² is a pinacolatoboryl group, this step can be performed by Chan-Lam-Evans coupling reaction. The Chan-Lam-Evans coupling reaction in this step can be performed, for example, by reacting compound n5 with compound n6 under heating in an organic
30 solvent such as acetonitrile and the like, in the presence of a base such as triethylamine and the like and a metal catalyst such as copper(II) acetate and the like.
[0362]

In the fifth step, compound n7 is converted to compound
35 n8 by a deprotection reaction of an amino-protecting group Pg².

The deprotection reaction in this step can be performed by a method generally used for the deprotection of an amino-protecting group.

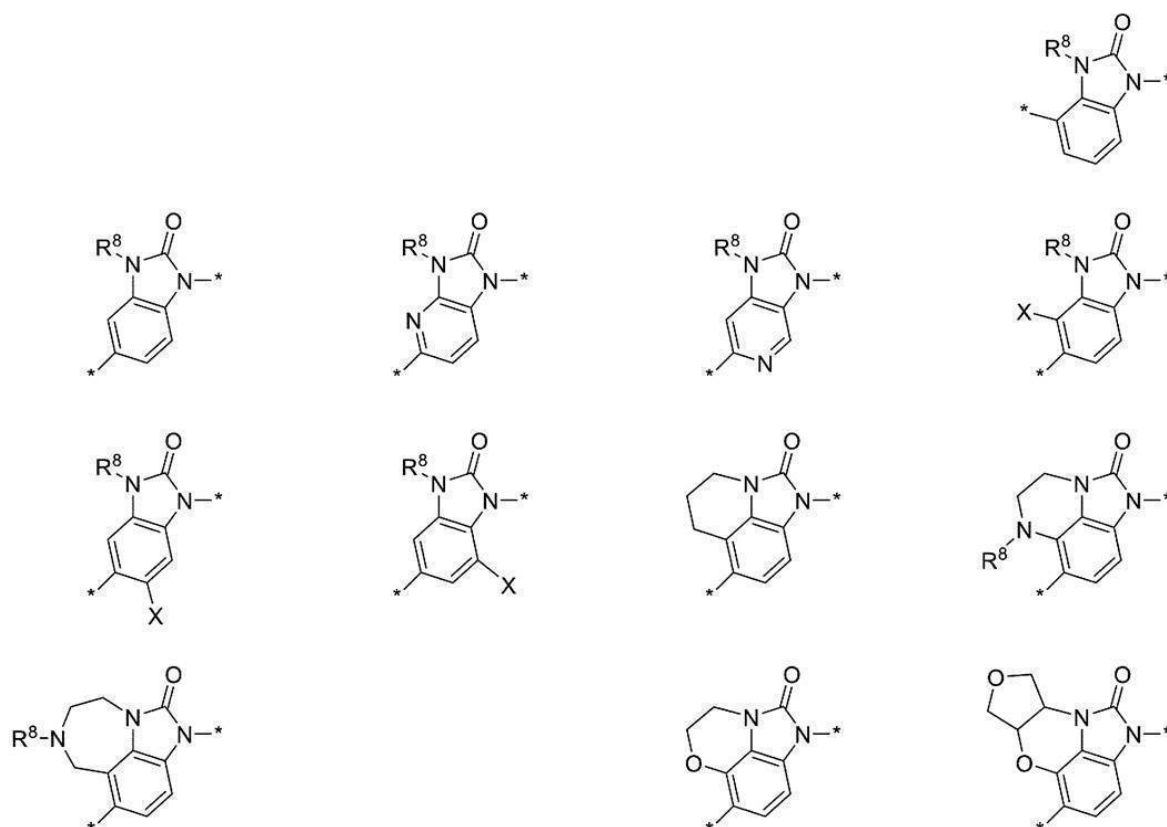
[0363]

5 (Method O)

Compound o4, which is a starting compound (6) wherein Q³ is any group selected from the following formulas:

[0364]

[Chem. 60]



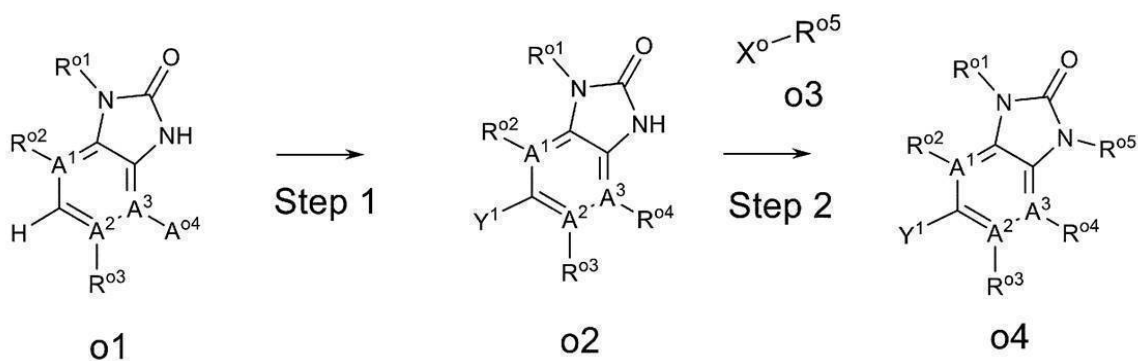
10

[0365]

can be produced according to the following method.

[0366]

[Chem. 61]



[0367]

wherein A^1 , A^2 , and A^3 are each independently a carbon atom or a nitrogen atom,

5 X^o is a halogen atom or a pinacolatoboryl group and the like,

Y^1 is a nitro group or a halogen atom,

R^{o1} is R^8 or $R^{6'}$,

R^{o4} is R^8 or $R^{6'}$,

10 when A^1 is a nitrogen atom, R^{o2} is absent,

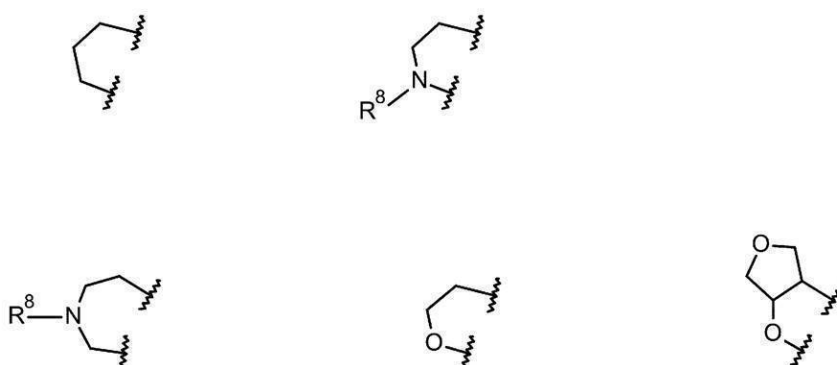
when A^1 is a carbon atom, R^{o2} is a hydrogen atom or a halogen atom, or

R^{o1} and R^{o2} are bonded to each other to optionally form any partial structure selected from the group represented by the

15 following formulas:

[0368]

[Chem. 62]



[0369]

20 wherein the lower end of the partial structure is a bond of R^{o2} , and the upper end of the partial structure is a bond of

R^{o1},

when A² is a nitrogen atom, R^{o3} is absent,

when A² is a carbon atom, R^{o3} is a hydrogen atom or a halogen atom,

5 when A³ is a nitrogen atom, R^{o4} is absent, and

when A³ is a carbon atom, R^{o4} is a hydrogen atom or a halogen atom.

[0370]

Compound o1 and compound o2 are either known or can be
10 produced according to a known method or by appropriately combining similar methods using a known compound as a starting material. Examples of literatures on the above-mentioned known method include, but are not limited to, Bioorg. Med. Chem., 2013, 21, 125, J. Med. Chem., 1995, 38, 5, 771-793,
15 WO2011163355 A1, WO2005044793 A2, WO2007015877 A2, WO2021213929 A1, WO2018039384 A1, WO2016097749 A1 and the like.

[0371]

In the first step, compound o2 is obtained by nitration or halogenation of compound o1. The nitration reaction in this
20 step can be performed, for example, by reacting compound o1 with a nitrating agent such as potassium nitrite and the like in an acid solvent such as trifluoroacetic acid and the like. The halogenation in this step can be performed under the same conditions as in the first step of Method N.

25 [0372]

In the second step, compound o4 is obtained from compound o2 and compound o3 by an alkylation reaction or Chan-Lam-Evans coupling reaction. The alkylation or Chan-Lam-Evans coupling reaction in this step can be performed under the same
30 conditions as in the fourth step of Method N.

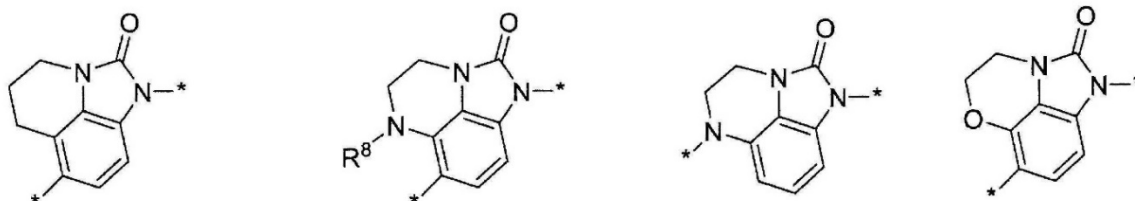
[0373]

(Method P)

Compound p5, which is a starting compound (6) wherein Q³ is any group selected from the following formulas:

35 [0374]

[Chem. 63]

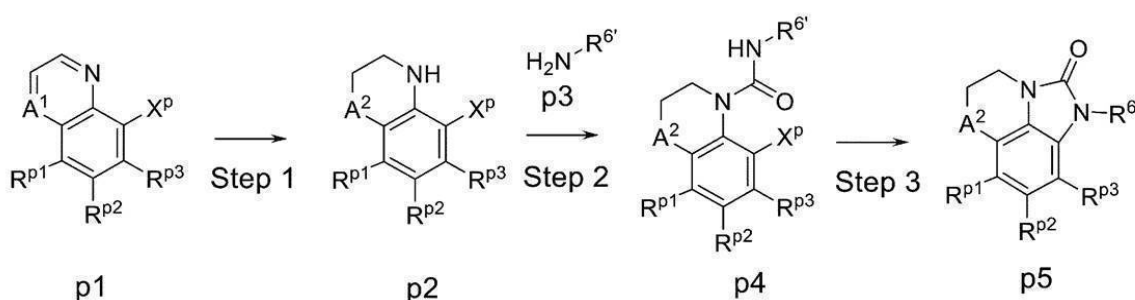


[0375]

can be produced according to the following method.

5 [0376]

[Chem. 64]



[0377]

wherein A¹ is CH or a nitrogen atom,

10 A² is CH₂ or NH,

X^p is a halogen atom,

R^{p1}, R^{p2}, and R^{p3} are each independently a hydrogen atom or a halogen atom.

[0378]

15 In the first step, compound p2 is obtained by a nuclear hydrogenation of compound p1. The nuclear hydrogenation reaction in this step can be performed, for example, by reacting compound p1 with a reducing agent such as diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate and the like
20 under heating in a solvent such as dichloroethane and the like, in the presence of an acid such as boronic acid, para-toluenesulfonic acid and the like.

[0379]

In the second step, compound p4 is obtained from compound
25 p2 and compound p3 by ureation. The ureation reaction in this step can be performed under the same conditions as in the

fourth step of Method L.

[0380]

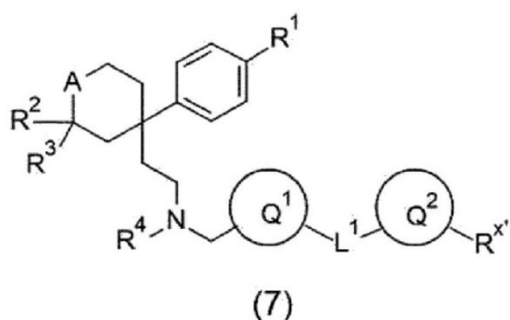
In the third step, compound p5 is obtained by cyclization reaction of compound p4. The cyclization reaction in this step
5 can be performed under the same conditions as in the third step of Method N. The reaction temperature is preferably from room temperature to 100°C.

[0381]

A production method of a starting compound represented by
10 the formula (7):

[0382]

[Chem. 65]

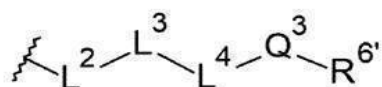


[0383]

15 wherein R^{x'} is a group that can be converted to a group represented by the following formula:

[0384]

[Chem. 66]



20 [0385]

is shown below.

[0386]

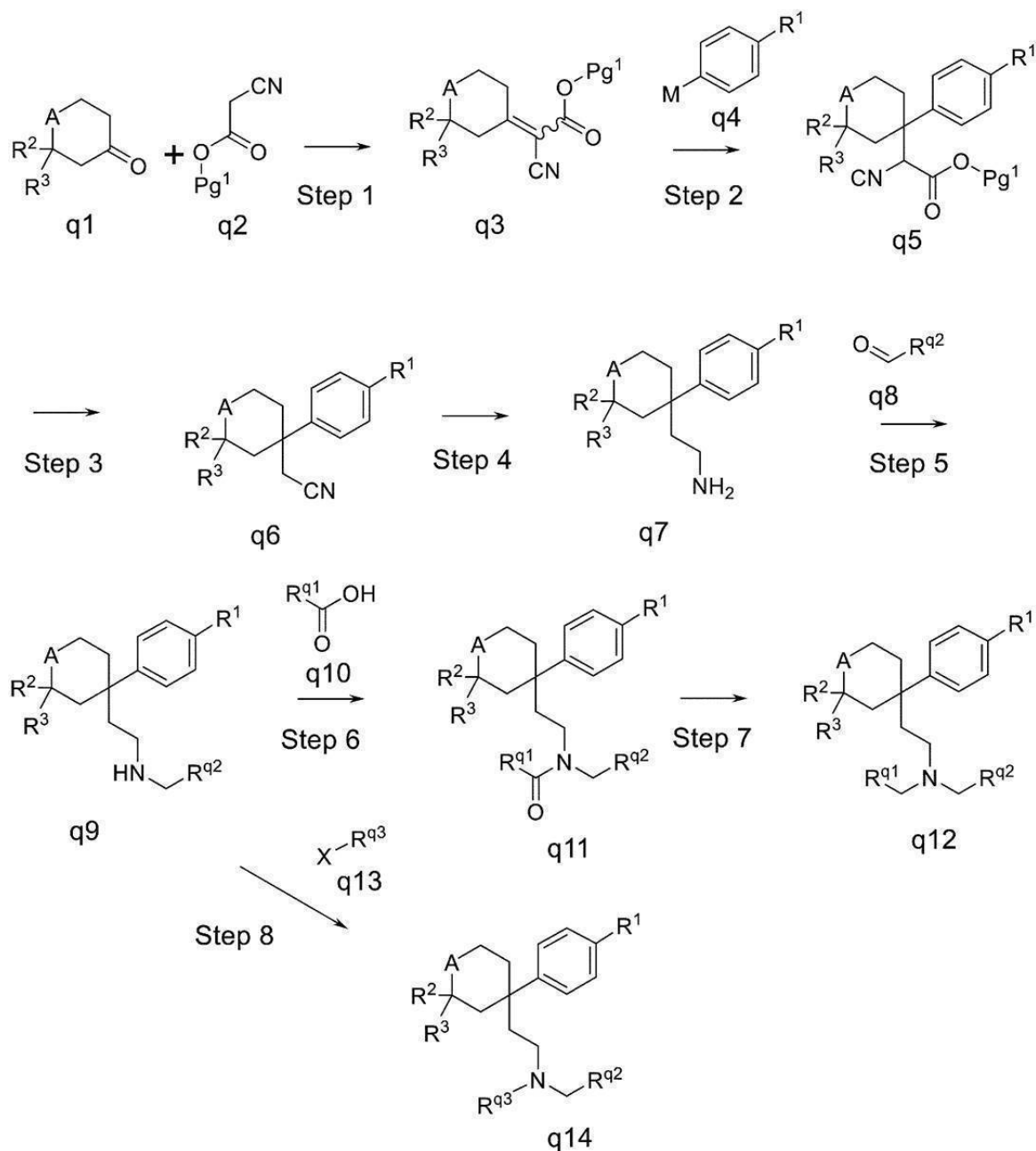
(Method Q)

Among the starting compounds (7), compound q12 wherein R⁴
25 is a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms or a C₃₋₆ cycloalkylmethyl group optionally substituted by one trifluoromethyl group, compound q11 wherein R⁴ is a C₁₋₆

alkylcarbonyl group optionally substituted by 1 to 3 halogen atoms, and compound q14 wherein R⁴ is a 6-membered heteroaryl group having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl group is optionally substituted by one halogen atom)
5 can be produced according to the following method. A general production method for each reaction site is shown in order, but it is not necessary to perform each step in the order shown below as long as it does not affect the reaction substrate and reaction product.

10 [0387]

[Chem. 67]



[0388]

wherein Pg¹ is a carboxy-protecting group,

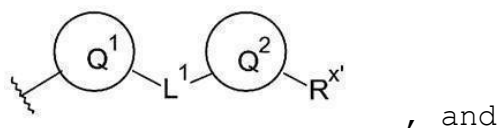
M is a metal or a metal halide (e.g., magnesium halide,
 5 lithium, zinc halide, etc.),

R^{q1} is a hydrogen atom, a C₁₋₅ alkyl group optionally
 substituted by 1 to 3 halogen atoms, or a C₃₋₆ cycloalkyl group
 optionally substituted by one trifluoromethyl group,

R^{q2} is a group represented by the following formula:

10 [0389]

[Chem. 68]



[0390]

R^{q3} is a 6-membered heteroaryl group having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl group is optionally substituted by one halogen atom.

[0391]

In the first step, compound q3 is obtained by aldol condensation reaction of compound q1 and compound q2. The aldol condensation reaction in this step can be performed by reacting compound q1 with compound q2 using, for example, acetic acid and piperidine as catalysts.

[0392]

In the second step, compound q5 is obtained by 1,4-nucleophilic addition of compound q4 to the α,β -unsaturated ester of compound q3. The 1,4-nucleophilic addition reaction in this step can be performed, for example, by reacting compound q3 with compound q4 in a solvent such as THF and the like in the presence of a copper reagent such as copper(II) bromide and the like. The reaction temperature is preferably from -78°C to room temperature.

[0393]

In the third step, compound q6 is obtained by hydrolysis of the ester group of compound q5 and decarboxylation of the resulting carboxy group. The hydrolysis and decarboxylation reaction in this step can be performed, for example, by reacting compound q5 with a base such as sodium hydroxide and the like under heating in a solvent such as ethylene glycol and the like.

[0394]

In the fourth step, compound q7 is obtained by reducing the cyano group of compound q6. The reduction reaction in this step can be performed, for example, by reacting compound q7 with a reducing agent such as lithium aluminum hydride and the

like under heating in a solvent such as THF and the like.

[0395]

In the fifth step, compound q9 is obtained from compound q7 and compound q8 by reductive amination reaction. The
5 reductive amination reaction in this step can be performed under the same conditions as in the second step of Method I.

[0396]

In the sixth step, compound q11 is obtained by condensing compound q9 and compound q10. The condensation reaction in
10 this step can be performed under the same conditions as in the first step of Method J.

[0397]

In the seventh step, compound q12 is obtained by reducing carbonyl group of compound q11. The reduction reaction in this
15 step can be performed, for example, by reacting compound q11 with a reducing agent such as borane-THF complex and the like under heating in a solvent such as THF and the like.

[0398]

In the eighth step, compound q14 is obtained from
20 compound q9 and compound q13 by Buchwald amination reaction or aromatic nucleophilic substitution reaction. The Buchwald amination reaction in this step can be performed, for example, by reacting compound q9 with compound q13 under heating in a solvent such as 1,4-dioxane and the like, in the presence of a
25 base such as cesium carbonate and the like and a metal catalyst such as RuPhos Pd G3, BrettPhos Pd G3 and the like. The aromatic nucleophilic substitution reaction in this step can be performed, for example, by reacting compound q9 with compound q13 under heating in a solvent such as 2-butanol, N,N-
30 dimethylacetamide and the like, in the presence of a base such as 1,8-diazabicyclo[5.4.0]-7-undecene, potassium carbonate and the like.

[0399]

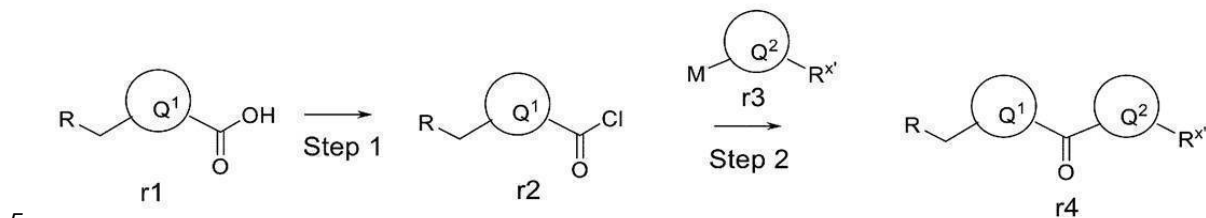
(Method R)

35 Compound r4, which is a compound represented by the

formula (7) wherein L¹ is -C(=O)-, can be produced according to the following method.

[0400]

[Chem. 69]

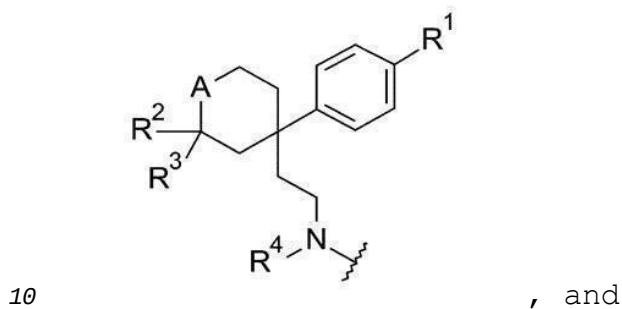


[0401]

wherein R is a group represented by the following formula:

[0402]

[Chem. 70]



[0403]

M is a dihydroxyboryl group, a pinacolatoboryl group, or the like.

[0404]

15 In the first step, carboxylic acid r1 is converted to acid chloride r2. The chlorination reaction in this step can be performed, for example, by reacting compound r1 with a chlorinating agent such as oxalyl chloride, thionyl chloride and the like in a solvent such as dichloromethane and the like,
20 in the presence of DMF.

[0405]

In the second step, compound r4 is obtained by coupling reaction of compound r2 and compound r3. the coupling reaction in this step can be performed, for example, by reacting
25 compound r2 with compound r3 under heating in a solvent such as toluene and the like, in the presence of a base such as cesium

carbonate and the like and a metal catalyst such as tetrakis(triphenylphosphine)palladium(0) and the like. Examples of literature on this step include Catalysts 2019, 9(1), 53.

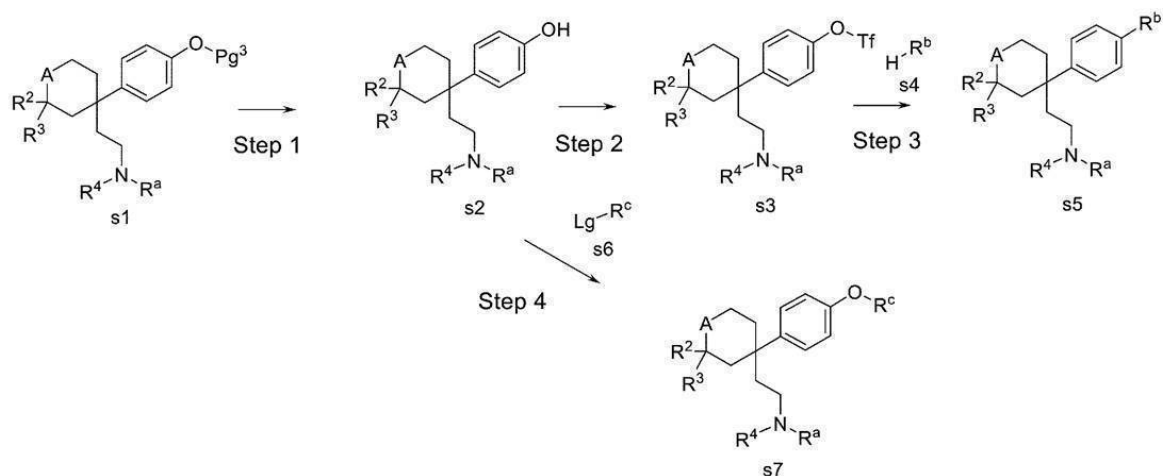
5 [0406]

(Method S)

The R^1 moiety in a compound represented by the formula (7) can be produced according to the following production method.

10 [0407]

[Chem. 71]



[0408]

wherein Pg^3 is a hydroxy-protecting group (e.g., methyl group, benzyl group, methoxymethyl group, etc.),

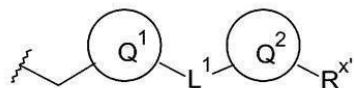
Lg is a leaving group,

R^a is a group represented by the following formula:

[0409]

[Chem. 72]

20



[0410]

or a group that can be converted to a group represented by the formula,

R^b is a C_{1-3} alkylamino group, a di- C_{1-3} alkylamino group,

or a 4- to 6-membered saturated heterocyclic group having one nitrogen atom as a ring member atom, and

R^c is a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms.

5 [0411]

In the first step, compound s2 is obtained from compound s1 by a deprotection reaction of a hydroxy-protecting group Pg³. The deprotection reaction in this step can be performed by a method generally used for deprotection of a hydroxy-
10 protecting group. For example, when Pg³ is a methyl group, the deprotection can be performed by reacting compound s1 with sodium thiomethoxide under heating in a solvent such as DMF and the like. This reaction can also be performed under microwave irradiation. The reaction temperature is preferably 80°C to
15 160°C.

[0412]

In the second step, compound s3 is obtained by triflation of a hydroxy group of compound s2. The triflation reaction in this step can be performed, for example, by reacting compound
20 s2 with a triflation agent such as trifluoromethanesulfonic anhydride and the like in a solvent such as dichloromethane and the like, in the presence of a base such as pyridine and the like.

[0413]

25 In the third step, compound s5 is obtained from compound s3 and amine s4 by Buchwald amination reaction. The Buchwald amination reaction in this step can be performed by reacting compound s3 and amine s4 under heating in a solvent such as 1,4-dioxane and the like, in the presence of a ligand such as
30 2-(di-tert-butylphosphino)biphenyl and the like and a metal catalyst such as tris(dibenzylideneacetone)dipalladium(0) and the like.

[0414]

In the fourth step, compound s7 is obtained from compound
35 s2 by alkylation reaction using an alkylating agent s6. The

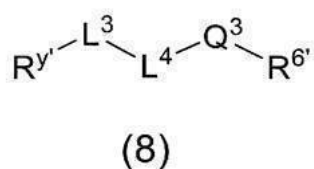
alkylation reaction in this step can be performed, for example, by reacting compound s2 with an alkylating agent s6 such as alkyl halide and the like under heating in a solvent such as DMF and the like, in the presence of a base such as potassium carbonate and the like. The reaction temperature is preferably from room temperature to 150°C.

[0415]

A production method of a starting compound represented by the formula (8):

10 [0416]

[Chem. 73]

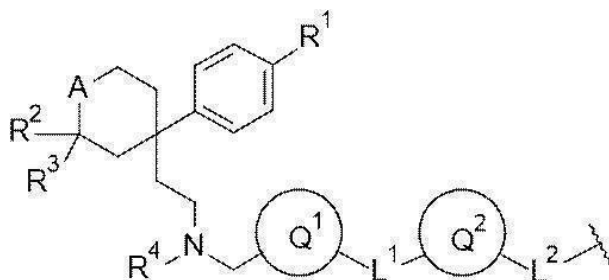


[0417]

wherein $R^{y'}$ is a group that can be converted to a group represented by the following formula:

[0418]

[Chem. 74]



[0419]

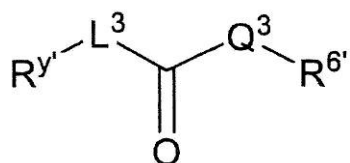
20 is shown below.

[0420]

Among the starting compounds (8), a compound wherein L^4 is $-C(=O)-$ as shown in the following formula:

[0421]

25 [Chem. 75]



[0422]

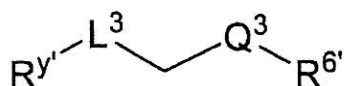
can be produced according to a method similar to that of Method H.

5 [0423]

Among the starting compounds (8), a compound wherein L^4 is CH_2 as shown in the following formula:

[0424]

[Chem. 76]



10

[0425]

can be produced according to a method similar to that of Method I.

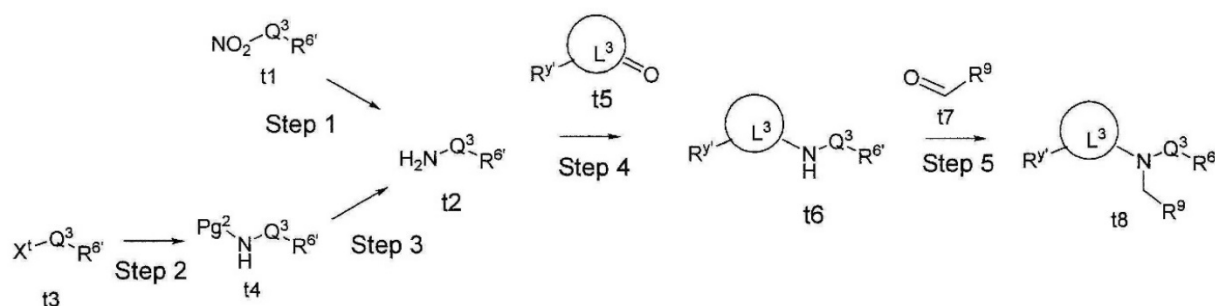
[0426]

15 (Method T)

Among the starting compounds (8), compound t6 wherein L^4 is NH , and compound t8 wherein L^4 is $\text{N}-\text{R}^9$ (R^9 indicates a C_{1-6} alkyl group) can be produced according to the following method.

[0427]

20 [Chem. 77]



[0428]

wherein X^t is a halogen atom and Pg^2 is an amino-protecting group.

[0429]

In the first step, compound t2 is obtained from compound t1 by reduction reaction of nitro group. the reduction reaction in this step can be performed by reacting compound t1
5 with a metal catalyst such as palladium carbon and the like in a solvent such as ethanol, THF and the like under a hydrogen atmosphere.

[0430]

In the second step, compound t4 is obtained from compound
10 t3 by Buchwald amination reaction. The amination reaction in this step can be performed under the same conditions as in the first step of Method L.

[0431]

In the third step, compound t2 is obtained by
15 deprotection reaction of the amino-protecting group Pg² of compound t4. The deprotection reaction in this step can be performed by a method generally used for deprotecting an amino-protecting group. For example, when Pg² is a tert-butoxycarbonyl group, the deprotection reaction can be
20 performed by reacting compound t4 with an acid such as hydrochloric acid and the like in a solvent such as dichloromethane and the like.

[0432]

In the fourth step in this step, compound t6 is obtained
25 from compound t2 and compound t5 by reductive amination reaction. The reductive amination reaction in this step can be performed under the same conditions as in the second step of Method I. The reductive amination reaction in this step can also be performed by reacting compound t2 and compound t5 with
30 a reducing agent such as borane-THF complex and the like in a solvent such as THF and the like.

[0433]

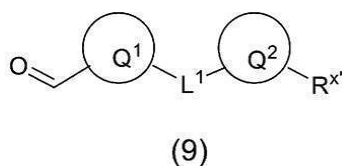
In the fifth step, compound t8 is obtained from compound t6 and compound t7 by reductive amination reaction. The
35 reductive amination reaction in this step can be performed

under the same conditions as in the fourth step of this method.
[0434]

A production method of a starting compound represented by
the formula (9):

5 [0435]

[Chem. 78]



[0436]

is shown below.

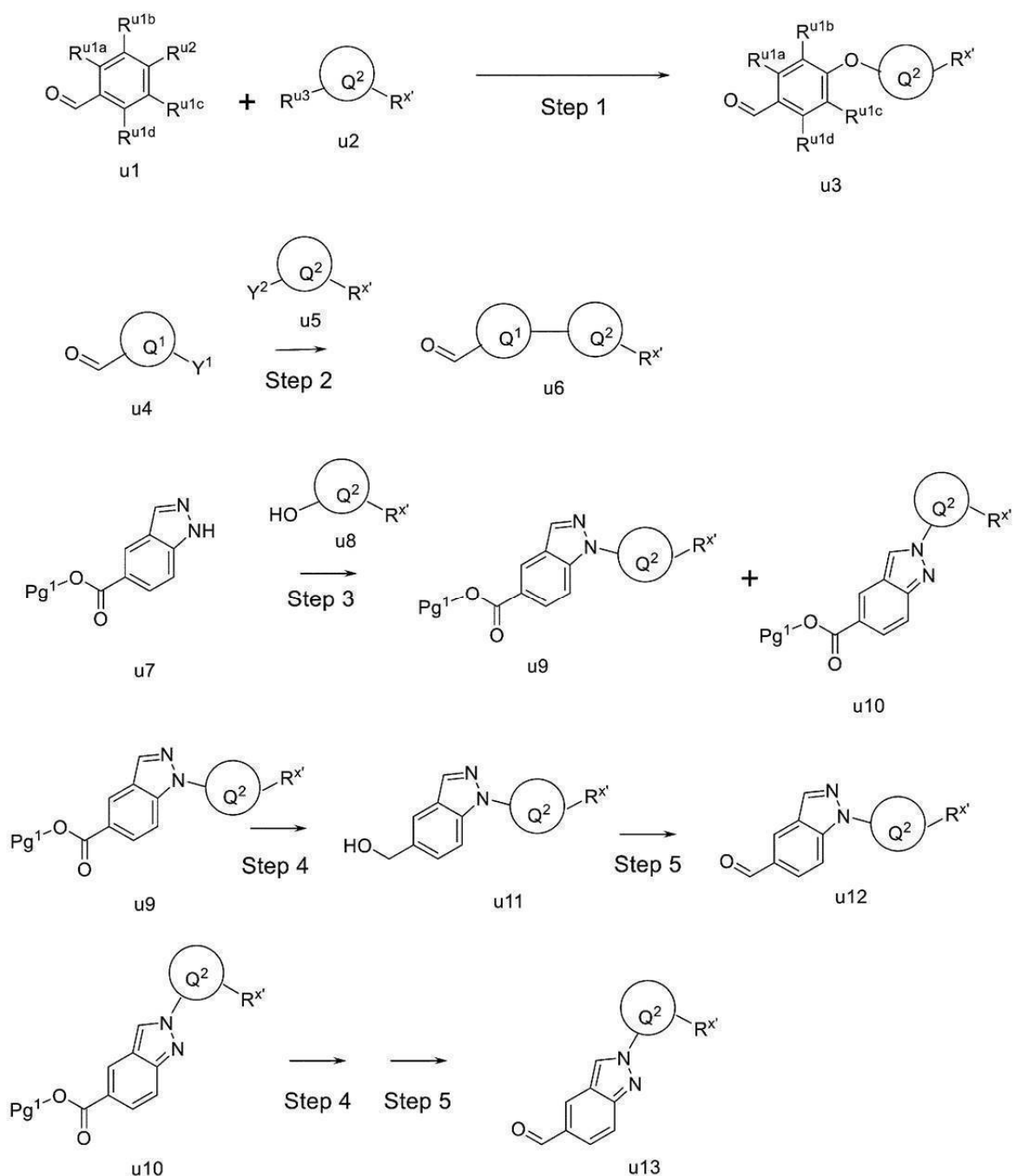
10 [0437]

(Method U)

Among the starting compounds (9), compound u3 wherein L¹
is oxygen atom, compound u6 wherein L¹ is a single bond, and
compounds u12 and u13 wherein Q¹ is a 7-azaspiro[3.5]nonane
15 ring, can be respectively produced according to the following
methods.

[0438]

[Chem. 79]



[0439]

wherein R^{u1a} , R^{u1b} , R^{u1c} , and R^{u1d} are each independently a hydrogen atom, a halogen atom, or a C_{1-6} alkyl group,

5 R^{u2} is a hydroxy group or a leaving group (when R^{u2} is a hydroxy group, R^{u3} is a hydroxy group or a leaving group, or when R^{u2} is a leaving group, R^{u3} is a hydroxy group),

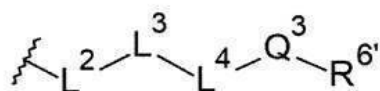
Y^1 is a halogen atom, a trifluoromethanesulfonyloxy group, a pinacolatoboryl group, or a dihydroxyboryl group (when
10 Y^1 is a halogen atom or a trifluoromethanesulfonyloxy group, Y^2

is a pinacolatoboryl group or a dihydroxyboryl group, or when Y^1 is a pinacolatoboryl group or a dihydroxyboryl group, Y^2 is a halogen atom or a trifluoromethanesulfonyloxy group),

$R^{*'}$ is a group that can be converted to a group
 5 represented by the following formula:

[0440]

[Chem. 80]



, and

[0441]

10 Pg^1 is a carboxy-protecting group.

[0442]

In the first step, compound u3 is obtained from compound u1 and compound u2. When R^{u2} is a hydroxy group and R^{u3} is a hydroxy group, this reaction can be performed by Mitsunobu
 15 reaction. The Mitsunobu reaction in this step can be performed, for example, by reacting compound u1 and compound u2 with phosphine such as triphenylphosphine and the like and azodicarboxylic acid ester such as diisopropyl azodicarboxylate and the like in a solvent such as tetrahydrofuran and the like.
 20 When either R^{u2} or R^{u3} is a leaving group, this reaction can be performed by a nucleophilic substitution reaction. The nucleophilic substitution reaction in this step can be performed, for example, by reacting compound u1 and compound u2 with a base such as potassium carbonate, cesium carbonate and
 25 the like under heating in a solvent such as DMF, DMA and the like.

[0443]

In the second step, compound u6 is obtained by coupling reaction of compound u4 and compound u5. The coupling reaction
 30 in this step can be performed, for example, by heating compound u4 and compound u5 in a solvent such as aqueous 1,4-dioxane and the like, in the presence of a base such as potassium carbonate and the like and a metal catalyst such as [1,1'-

bis(diphenylphosphino)ferrocene]palladium(II) dichloride
dichloromethane adduct and the like.

[0444]

In the third step, compound u9 and compound u10 are
5 obtained from compound u7 and compound u8 by Mitsunobu
reaction. The Mitsunobu reaction in this step can be
performed, for example, by reacting compound u7 and compound u8
with a phosphorane reagent such as
cyanomethylenetributylphosphorane and the like under heating in
10 a solvent such as toluene and the like.

[0445]

In the fourth step, compound u11 is obtained by reduction
reaction of compound u9. The reduction reaction in this step
can be performed under the same conditions as in the first step
15 of Method M.

[0446]

In the fifth step, compound u12 is obtained by oxidation
reaction of compound u11. The oxidation reaction in this step
can be performed, for example, by reacting compound u11 with an
20 oxidizing agent such as 1,1,1-triacetoxy-1,1-dihydro-1,2-
benzoiodoxol-3-(1H)-one, manganese(IV) oxide and the like in a
solvent such as dichloromethane and the like.

[0447]

Compound u13 can be obtained by subjecting compound u10
25 to the same steps as the fourth step and the fifth step of this
method.

[0448]

<12. Activity>

In one embodiment of the present invention, the compound
30 or polyfunctional molecule of the present invention
specifically binds to SF-1. The binding activity to SF-1 can
be measured using any known method, for example, by reacting a
test substance, a molecule (e.g., DAX1 peptide) known to
specifically bind to SF-1 (particularly, SF-1 ligand binding
35 domain (LBD)), and SF-1 (particularly SF-1-LBD), and

quantifying a decrease in the binding rate to SF-1 by the molecule known to specifically bind to SF-1 (e.g., by calculating the IC₅₀ value). In general, in such a test system, a test substance with an IC₅₀ value of 100 μM or less is considered to specifically bind to SF-1. Thus, in one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has an IC₅₀ value of 100 μM or less, preferably an IC₅₀ value of 10 μM or less, particularly preferably an IC₅₀ value of 1 μM or less, in relation to the decrease in the binding rate to SF-1 by a molecule known to specifically bind to SF-1 (e.g., DAX1 peptide). In another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has an IC₅₀ value of 100 μM or less, preferably an IC₅₀ value of 10 μM or less, particularly preferably an IC₅₀ value of 1 μM or less, in relation to the decrease in the binding rate to SF-1-LBD by a DAX1 peptide, in the test system and test conditions disclosed in Experimental Example 1 of the present specification.

[0449]

In one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has SF-1 antagonist activity. The SF-1 antagonist activity can be measured using any known method. For example, the activity can be measured by adding a test substance to cells expressing SF-1, culturing the cells for a certain period of time, and quantifying a decrease in the expression level of a target gene of SF-1 (e.g., CYP11A1, CYP17A1, CYP21A2, STAR, etc.) (e.g., by calculating IC₅₀ values). In general, in such test system, a test substance having an IC₅₀ value of 100 μM or less for a target gene of SF-1 is considered to have antagonist activity against SF-1. Therefore, in one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has an IC₅₀ value of 100 μM or less, preferably an IC₅₀ value of 10 μM or less, particularly

preferably an IC₅₀ value of 1 μM or less for a target gene of SF-1 (e.g., CYP11A1, CYP17A1, CYP21A2, and/or STAR). In another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has an IC₅₀ value of 100 μM or less, preferably an IC₅₀ value of 10 μM or less, particularly preferably an IC₅₀ value of 1 μM or less, against CYP11A1, CYP17A1, CYP21A2 and/or STAR in the test system and test conditions disclosed in Experimental Example 2 of the present specification.

10 [0450]

In one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has SF-1 degradation inducing activity. The SF-1 degradation inducing activity can be measured using any known method, for example, by adding a test substance to cells expressing SF-1, culturing them for a certain period of time, and then quantifying the expression level of SF-1. The SF-1 degradation inducing activity can also be measured, for example, by knocking in an easily detectable peptide tag (e.g., HiBiT tag) at the endogenous SF-1 gene locus in cells expressing SF-1, adding a test substance to the cells, culturing them for a certain period of time, and then observing the expression level of the peptide tag. In general, in such test system, a test substance with a concentration (DC₅₀ value) of SF-1 of 100 μM or less that induces 50% degradation is considered to have SF-1 degradation inducing activity. Accordingly, in one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has a DC₅₀ value of 100 μM or less, preferably a DC₅₀ value of 10 μM or less, particularly preferably a DC₅₀ value of 1 μM or less, against SF-1. In another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has a DC₅₀ value of 100 μM or less, preferably a DC₅₀ value of 10 μM or less, particularly preferably a DC₅₀ value of 1 μM or less, against SF-1 in the test system and test conditions disclosed

in Experimental Example 3 of the present specification.

[0451]

In one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has growth
5 inhibitory activity against tumors in which SF-1 is involved in the development or progression of the tumor. In another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has growth inhibitory activity against adrenocortical carcinoma. In yet
10 another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has growth inhibitory activity against NCI-H295R cells, an adrenocortical carcinoma cell line. The growth inhibitory activity against tumor cells can be measured using any known method, and
15 typically can be measured by adding a test substance to a model cell of the target tumor, culturing the cell for a certain period of time, and then quantifying the growth rate of the tumor cells. In general, in such test system, a test substance with a concentration (GI_{50} value) of 100 μM or less that
20 inhibits 50% of tumor cell growth is considered to have growth inhibitory activity. Therefore, in one embodiment of the present invention, the compound or polyfunctional molecule of the present invention has a GI_{50} value of 100 μM or less, preferably a GI_{50} value of 10 μM or less, particularly
25 preferably a GI_{50} value of 1 μM or less, against tumor cells (e.g., NCI-H295R cells). In another embodiment of the present invention, the compound or polyfunctional molecule of the present invention has a GI_{50} value of 100 μM or less, preferably a GI_{50} value of 10 μM or less, particularly
30 preferably a GI_{50} value of 1 μM or less, against tumor cells (e.g., NCI-H295R cells) in the test system and test conditions disclosed in Experimental Example 4 of the present specification.

[0452]

35 In one embodiment of the present invention, the compound

or polyfunctional molecule of the present invention has antitumor activity against an animal model (e.g., mice) in which a tumor cell in which SF-1 is involved in the development or progression, such as NCI-H295R cell (adrenocortical carcinoma cell line), VCaP cell (prostate cancer cell line), or a tumor derived from a prostate cancer patient, has been subcutaneously transplanted. The antitumor activity in the transplant model can be measured using any known method, for example, using the protocols described in Experimental Example 5 and Experimental Example 6 of the present specification. In addition, the therapeutic effect of the compound or polyfunctional molecule of the present invention against breast cancer can be measured using the protocol described in Experimental Example 7 of the present specification.

[Example]
[0453]

The present invention is described in detail by the following examples, which are merely an implementation and do not limit the present invention, and may be varied to the extent not departing from the scope of the present invention. In the following examples, "%" indicates mol/mol% for yield, volume % for solvents used in chromatography, and weight % for others.

Nuclear magnetic resonance spectra (¹H-NMR, resonance frequency 400 MHz or 500 MHz) are listed as δ values (ppm) with tetramethylsilane as the standard or with the chemical shift value of the deuterated solvent used as the reference value. Other abbreviations used in the text have the following meanings.

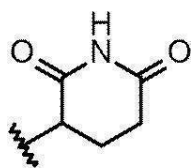
s: singlet
d: doublet
dd: doublet of doublets
t: triplet
dt: doublet of triplets
q: quartet

m: multiplet
 br: broad
 J: coupling constant
 Hz: hertz
 5 CDCl₃: deuteriochloroform
 DMSO-d₆: deuterodimethyl sulfoxide
 CD₃OD: deuterated methanol
 1H-NMR: proton nuclear magnetic resonance
 HPLC: high performance liquid chromatography
 10 SFC: supercritical fluid chromatography
 sCO₂: supercritical carbon dioxide
 APCI: atmospheric pressure chemical ionization
 ESI: electrospray ionization
 THF: tetrahydrofuran
 15 DMF: N,N-dimethylformamide
 HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-
 triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
 DIPEA: N,N-diisopropylethylamine
 RuPhos Pd G3: (2-dicyclohexylphosphino-2',6'-
 20 diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-
 biphenyl)]palladium(II) methanesulfonate
 BrettPhos Pd G3: [(2-dicyclohexylphosphino-3,6-dimethoxy-
 2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-
 biphenyl)]palladium(II) methanesulfonate methanesulfonate
 25 (S)-(-)-Tol-BINAP: (S)-(-)-2,2'-bis(di-p-tolylphosphino)-
 1,1'-binaphthyl
 XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
 (CAS Registry Number: 161265-03-8)
 IPA: isopropyl alcohol
 30 DCM: dichloromethane
 DMSO: dimethyl sulfoxide
 TLC: thin layer chromatography
 [0454]

In the following Examples, the structure represented by
 35 the formula:

[0455]

[Chem. 81]



[0456]

5 indicates that the asymmetric carbon in the structure has a mixture of α -configuration and β -configuration.

[0457]

The reagents, solvents, devices, and the like used in the following Examples are commercially available unless otherwise
10 specified. Furthermore, the raw material compounds used are known compounds and commercially available, or compounds synthesized and identified according to a method known per se or a method analogous thereto, unless otherwise specified.

[0458]

15 <Example A1> Ethyl cyano(2,2-dimethyltetrahydro-4H-pyran-4-ylidene)acetate

Under ice-cooling, to 2,2-dimethyltetrahydro-4H-pyran-4-one (CAS Registry Number: 1194-16-7) (200 g, 1.56 mol) was added dropwise ethyl cyanoacetate (175 mL, 1.65 mol) over 10
20 min, acetic acid (18 mL, 0.32 mol) was added dropwise over 5 min, and then piperidine (31 mL, 0.31 mol) was added dropwise over 10 min. The reaction mixture was warmed to room temperature and stirred for 41 hr. The reaction mixture was diluted with ethyl acetate (2 L), and washed successively with
25 1 mol/L aqueous sodium hydroxide solution (1.5 L), water (1.5 L), and saturated brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure and further dried under reduced pressure to give the title compound (324 g, 1.45 mol,
30 yield 93%).

[0459]

<Example A2> Ethyl [4-(4-chlorophenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl] (cyano)acetate

Using the compound obtained in <Example A1> and 4-chlorophenylmagnesium bromide (CAS Registry Number: 873-77-8), the title compound was obtained by the same method as in <Example C3>.

5 [0460]

<Example A3> 2-[4-(4-Chlorophenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine

Using the compound obtained in <Example A2>, the title compound was obtained by sequentially performing the same
10 operations as in <Example C4> and <Example C5>.

[0461]

<Example A4> Ethyl trans-4-(4-formylphenoxy)cyclohexanecarboxylate

To a solution of 4-hydroxybenzaldehyde (CAS Registry
15 Number: 123-08-0) (10.0 g, 81.9 mmol), ethyl cis-4-hydroxycyclohexanecarboxylate (WO 2011143645 A1) (14.8 g, 86.0 mmol), and tri-n-butylphosphine (24.5 mL, 98.3 mmol) in toluene (400 mL) was added at room temperature 1,1'-(azodicarbonyl)dipiperidine (24.8 g, 98.3 mmol) by small portions, and the
20 mixture was stirred at room temperature for 1 hr, and at 95°C for 3 hr. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (600 mL), and washed successively with water and saturated brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was
25 concentrated under reduced pressure. The precipitated solid was collected by filtration and washed with a mixed solvent of hexane/ethyl acetate (1/1). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the
30 title compound (5.94 g, 21.5 mmol, yield 26%).

[0462]

<Example A5> Ethyl trans-4-{4-[(2-[4-(4-chlorophenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]phenoxy}cyclohexanecarboxylate

35 Using the compounds obtained in <Example A4> and <Example

A3>, the title compound was obtained by the same method as in
<Example D1>.

[0463]

<Example A6> Trans-4-(4-{{2-[4-(4-chlorophenyl)-2,2-
5 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(2,2-
dimethylpropanoyl)amino]methyl}phenoxy)cyclohexanecarboxylic
acid

Using the compound obtained in <Example A5>, the title
compound was obtained by sequentially performing the same
10 operations as in <Example D2> and <Example S4>.

[0464]

<Example B1> Ethyl cyano{2,2-dimethyl-4-[4-
(trifluoromethoxy)phenyl]tetrahydro-2H-pyran-4-yl}acetate

Using the compound obtained in <Example A1> and 4-
15 (trifluoromethoxy)phenylmagnesium bromide (CAS Registry Number:
169222-42-8, 0.50 mol/L THF solution), the title compound was
obtained by the same method as in <Example C3>.

[0465]

<Example B2> 2-{2,2-Dimethyl-4-[4-
20 (trifluoromethoxy)phenyl]tetrahydro-2H-pyran-4-yl}ethanamine

Using the compound obtained in <Example B1>, the title
compound was obtained by sequentially performing the same
operations as in <Example C4> and <Example C5>.

[0466]

25 <Example B3> Ethyl trans-4-(4-{{(2-{2,2-dimethyl-4-[4-
(trifluoromethoxy)phenyl]tetrahydro-2H-pyran-4-
yl}ethyl)amino]methyl}phenoxy)cyclohexanecarboxylate

Using the compounds obtained in <Example A4> and <Example
B2>, the title compound was obtained by the same method as in
30 <Example D1>.

[0467]

<Example B4> Ethyl trans-4-(4-{{(2,2-dimethylpropanoyl)(2-{2,2-
dimethyl-4-[4-(trifluoromethoxy)phenyl]tetrahydro-2H-pyran-4-
yl}ethyl)amino]methyl}phenoxy)cyclohexanecarboxylate

35 Using the compound obtained in <Example B3>, the title

compound was obtained by the same method as in <Example D2>.

[0468]

<Example B5> Trans-4-(4-{{(2,2-dimethylpropanoyl)(2-{2,2-dimethyl-4-[4-(trifluoromethoxy)phenyl]tetrahydro-2H-pyran-4-yl}ethyl)amino)methyl}phenoxy)cyclohexanecarboxylic acid

Using the compound obtained in <Example B4>, the title compound was obtained by the same method as in <Example S4>.

[0469]

<Example C1> Ethyl (cis-4-hydroxycyclohexyl)acetate

To a solution of cis-2-(4-hydroxycyclohexyl)acetic acid (CAS Registry Number: 68592-22-3) (2.53 g, 16.0 mmol) in ethanol (46 mL) was added sulfuric acid (0.086 mL, 1.60 mmol), and the mixture was heated under reflux for 7 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was diluted with ethyl acetate, and washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give the title compound (2.66 g, 14.3 mmol, yield 89%).

[0470]

<Example C2> Ethyl [trans-4-(2-chloro-4-formylphenoxy)cyclohexyl]acetate

Using the compound obtained in <Example C1> and 3-chloro-4-hydroxybenzaldehyde (CAS Registry Number: 2420-16-8), the title compound was obtained by the same method as in <Example A4>.

[0471]

<Example C3> Ethyl cyano[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]acetate

To a solution of ethyl cyano(2,2-dimethyltetrahydro-4H-pyran-4-ylidene)acetate (8.92 g, 40.0 mmol) in THF (131 mL) was added at -78°C copper(I) bromide-dimethyl sulfide complex (0.805 g, 3.92 mmol) and, after stirring at said temperature for 2 hr, 4-methoxyphenylmagnesium bromide (CAS Registry

Number: 13139-86-1) (0.50 mol/L THF solution, 100 mL, 50 mmol) was added dropwise over 20 min at said temperature. The reaction mixture was stirred for 1.5 hr while raising the temperature to room temperature and left standing at room temperature overnight. To the reaction mixture was added at -78°C copper(I) bromide-dimethyl sulfide complex (0.805 g, 3.92 mmol), and the mixture was stirred at said temperature for 5 min. Then, 4-methoxyphenylmagnesium bromide (0.50 mol/L THF solution, 47 mL, 23.5 mmol) was added dropwise thereto over 5 min at said temperature, and the mixture was stirred for 6 hr while raising the temperature to room temperature. To the reaction mixture was added 1 mol/L hydrochloric acid (80 mL) under ice-cooling, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.72 g, 20.3 mmol, yield 51%).

[0472]

<Example C4> [4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]acetonitrile

To a solution of ethyl cyano[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]acetate (10.8 g, 32.6 mmol) in ethylene glycol (109 mL) was added sodium hydroxide (3.26 g, 81.5 mmol) at room temperature, and the mixture was stirred at 150°C for 7 hr and left standing at room temperature overnight. To the reaction mixture was added, under ice-cooling, ice, water and 1 mol/L hydrochloric acid and, after adjusting the pH to 1-2, the mixture was extracted with DCM. The obtained organic layer was washed successively with water and saturated brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title

compound (5.91 g, 22.8 mmol, yield 70%).

[0473]

<Example C5> 2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine

5 To a solution of [4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]acetonitrile (8.72 g, 33.6 mmol) in THF (224 mL) was added lithium aluminum hydride (3.19 g, 84.1 mmol) under ice-cooling over 10 min, and the mixture was stirred for 1.5 hr while raising the temperature to room
10 temperature, at 35°C for 4 hr, and at 50°C for 2 hr. After cooling, water (3.2 mL) was added to the reaction mixture under ice-cooling, 1 mol/L aqueous sodium hydroxide solution (3.2 mL) and water (9.0 mL) were added, the resulting precipitate was collected by filtration through celite and washed with THF.
15 The filtrate was concentrated under reduced pressure, the obtained residue was purified by amine-modified silica gel column chromatography (hexane/ethyl acetate and ethyl acetate/methanol) to give the title compound (1.74 g, 6.61 mmol, yield 20%).

20 [0474]

<Example C6> Ethyl (trans-4-{2-chloro-4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]phenoxy)cyclohexyl)acetate

 Using the compounds obtained in <Example C2> and <Example
25 C5>, the title compound was obtained by the same method as in <Example D1>.

[0475]

<Example C7> Ethyl [trans-4-(2-chloro-4-{[(2,2-dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-
30 dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino]methyl}phenoxy)cyclohexyl]acetate

 Using the compound obtained in <Example C6>, the title compound was obtained by the same method as in <Example D2>.

[0476]

35 <Example C8> [Trans-4-(2-chloro-4-{[(2,2-dimethylpropanoyl){2-

[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)cyclohexyl]acetic acid

Using the compound obtained in <Example C7>, the title compound was obtained by the same method as in <Example S4>.

5 [0477]

<Example D1> Ethyl trans-4-{4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)cyclohexanecarboxylate

To a solution of 2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine (3.89 g, 14.8 mmol) in toluene (72.4 mL) was added ethyl trans-4-(4-formylphenoxy)cyclohexanecarboxylate (4.00 g, 14.5 mmol) at room temperature, and the mixture was heated under reflux under a Dean-Stark apparatus. The mixture was stirred for 7 hr while gradually removing the solvent and left standing at room temperature overnight. The reaction mixture was heated under reflux under a Dean-Stark apparatus. The mixture was stirred for 1 hr while gradually removing the solvent and, after cooling, the organic solvent was evaporated under reduced pressure. The obtained residue was dissolved in methanol (145 mL), sodium borohydride (0.714 g, 17.4 mmol) was added thereto, under ice-cooling, and the mixture was stirred at said temperature for 5 min, and stirred for 1.5 hr while raising the temperature to room temperature. To the reaction mixture were added saturated aqueous ammonium chloride solution and water under ice-cooling, and the mixture was left standing overnight. The reaction mixture was extracted with DCM, and the obtained organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (5.13 g, 9.79 mmol, yield 68%).

[0478]

<Example D2> Ethyl trans-4-(4-{[(2,2-dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

yl}ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate

To a solution of ethyl trans-4-{4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl}amino)methyl}phenoxy)cyclohexanecarboxylate (1.11 g, 2.12 mmol) in DCM (21 mL) were added, under ice-cooling, triethylamine (0.588 mL, 4.24 mmol) and pivaloyl chloride (421 mg, 3.49 mmol), and the mixture was stirred at room temperature for 2.5 hr. To the reaction mixture was added, under ice-cooling, water, and the mixture was extracted with DCM. The obtained organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.19 g, 1.96 mmol, yield 92%).

[0479]

<Example D3> Trans-4-(4-{[(2,2-dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid

To a solution of ethyl trans-4-(4-{[(2,2-dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate (1.18 g, 1.94 mmol) in methanol (19.4 mL) was added at room temperature 1 mol/L aqueous sodium hydroxide solution (9.71 mL, 9.71 mmol), and the mixture was stirred at said temperature for 30 min and left standing overnight. To the reaction mixture was neutralized, under ice-cooling, with 1 mol/L hydrochloric acid (9.71 mL, 9.71 mmol), and the organic solvent was evaporated under reduced pressure. The mixture was extracted with DCM, and the obtained organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (943 mg, 1.63 mmol, yield 84%).

[0480]

<Example E1> Ethyl trans-4-(4-{{(2,2-dimethylpropanoyl){2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate

The racemic ethyl trans-4-(4-{{(2,2-dimethylpropanoyl){2-
5 [4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate was
optically resolved by chiral HPLC [column: CHIRALPAK IC
(registered trademark, Daicel Corporation), mobile phase:
hexane/ethanol = 50/50 (V/V)] to obtain the title compound as
10 the component eluted first.

[0481]

<Example E2> Trans-4-(4-{{(2,2-dimethylpropanoyl){2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid

15 Using the compound obtained in <Example E1>, the title
compound was obtained by the same method as in <Example S4>.

[0482]

<Example F1> Trans-4-(4-{{(2,2-dimethylpropanoyl){2-[4-(4-
hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
20 yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid

To a solution of trans-4-(4-{{(2,2-dimethylpropanoyl){2-
[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid (200
mg, 0.345 mmol) in DMF (3.45 mL) was added sodium thiomethoxide
25 (0.484 g, 6.90 mmol) at room temperature, and the mixture was
stirred at 100°C for 8 hr and left standing at room temperature
overnight. To the reaction mixture were added saturated
aqueous ammonium chloride solution and water at room
temperature, and the mixture was extracted with ethyl acetate
30 and DCM. The obtained organic layer was dried over anhydrous
sodium sulfate and filtered, and the filtrate was concentrated
under reduced pressure. The obtained residue was purified by
silica gel column chromatography (DCM/methanol) to give the
title compound (117 mg, 0.207 mmol, yield 60%).

35 [0483]

<Example F2> Ethyl trans-4-(4-{{(2,2-dimethylpropanoyl){2-[4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate

To a solution of trans-4-(4-{{(2,2-dimethylpropanoyl){2-[4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid (1.33 g, 2.35 mmol) in DMF (23.5 mL) were added DIPEA (2.05 mL, 11.8 mmol) and iodoethane (0.940 mL, 11.8 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hr and
10 left standing at room temperature overnight. To the reaction mixture were added DIPEA (0.819 mL, 4.70 mmol) and iodoethane (0.376 mL, 4.70 mmol) at room temperature, and the mixture was stirred at said temperature for 10 hr and left standing at room temperature for 2 days. To the reaction mixture was added
15 water at room temperature, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed successively with water and saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was
20 purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.43 g, 2.41 mmol, yield: quantitative).

[0484]

<Example F3> Ethyl trans-4-(4-{{(2,2-dimethylpropanoyl)(2-{2,2-dimethyl-4-[4-(propan-2-yloxy)phenyl]tetrahydro-2H-pyran-4-yl}ethyl)amino}methyl}phenoxy)cyclohexanecarboxylate

To a solution of ethyl trans-4-(4-{{(2,2-dimethylpropanoyl){2-[4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate (80.0 mg, 0.135 mmol) in DMF (1.32 mL) were added potassium carbonate (146 mg, 1.06 mmol) and 2-bromopropane (0.0991 mL, 1.06 mmol) at room temperature, and the mixture was stirred at 130°C for 4.5 hr and left standing at room temperature for 4 days. To
35 the reaction mixture was added water at room temperature, and

the mixture was extracted with ethyl acetate. The obtained organic layer was washed with water, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (78.7 mg, 0.124 mmol, yield 92%).

[0485]

<Example F4> Trans-4-(4-((2,2-dimethylpropanoyl)(2-(2,2-dimethyl-4-[4-(propan-2-yloxy)phenyl]tetrahydro-2H-pyran-4-yl)ethyl)amino)methyl)phenoxy)cyclohexanecarboxylic acid

Using the compound obtained in <Example F3>, the title compound was obtained by the same method as in <Example S4>.

[0486]

<Example G1> Ethyl trans-4-(4-((2,2-dimethylpropanoyl)(2-[2,2-dimethyl-4-(4-((trifluoromethyl)sulfonyl)oxy)phenyl]tetrahydro-2H-pyran-4-yl)ethyl)amino)methyl)phenoxy)cyclohexanecarboxylate

To a solution of ethyl trans-4-(4-((2,2-dimethylpropanoyl)(2-[4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethyl)amino)methyl)phenoxy)cyclohexanecarboxylate (800 mg, 1.32 mmol) in DCM (6.59 mL) was added, under ice-cooling, pyridine (1.32 mL, 16.3 mmol), then, trifluoromethanesulfonic anhydride (0.333 mL, 1.98 mmol) was added thereto by small portions, and the mixture was stirred at said temperature for 30 min and at room temperature for 1 hr. To the reaction mixture was added, under ice-cooling, water, and the mixture was extracted with mixed solvent of hexane/ethyl acetate (ratio 2/1). The obtained organic layer was washed successively with water and saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (915 mg, 1.26 mmol, yield 96%).

[0487]

<Example G2> Ethyl trans-4-(4-{{(2,2-dimethylpropanoyl) (2-{2,2-dimethyl-4-[4-(pyrrolidin-1-yl) phenyl]tetrahydro-2H-pyran-4-yl}ethyl)amino}methyl}phenoxy)cyclohexanecarboxylate

To a solution of ethyl trans-4-(4-{{(2,2-dimethylpropanoyl) {2-[2,2-dimethyl-4-(4-{{(trifluoromethyl)sulfonyl}oxy}phenyl)tetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylate (50.0 mg, 0.0689 mmol) in 1,4-dioxane (1.38 mL) were added tris(dibenzylideneacetone)dipalladium(0) (6.3 mg, 0.0069 mmol),
10 2-(di-tert-butylphosphino)biphenyl (4.1 mg, 0.0138 mmol), pyrrolidine (CAS Registry Number: 123-75-1) (0.0085 mL, 0.103 mmol) and tripotassium phosphate (20.5 mg, 0.0964 mmol) at room temperature, and the mixture was stirred at 95°C for 9 hr and left standing at room temperature for 3 days. To the reaction
15 mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed with water, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel
20 column chromatography (hexane/ethyl acetate) to give the title compound (36.2 mg, 0.0560 mmol, yield 81%).

[0488]

<Example G3> Trans-4-(4-{{(2,2-dimethylpropanoyl) (2-{2,2-dimethyl-4-[4-(pyrrolidin-1-yl) phenyl]tetrahydro-2H-pyran-4-yl}ethyl)amino}methyl}phenoxy)cyclohexanecarboxylic acid
25

Using the compound obtained in <Example G2>, the title compound was obtained by the same method as in <Example S4>.

[0489]

<Example H1> Trans-4-(4-{{(2,2-dimethylpropanoyl) {2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)-N-(dimethylsulfamoyl)cyclohexanecarboxamide
30

To a solution of trans-4-(4-{{(2,2-dimethylpropanoyl) {2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid (85
35

mg, 0.15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (CAS Registry Number: 25952-53-8) (56 mg, 0.29 mmol), and 4-dimethylaminopyridine (54 mg, 0.44 mmol) in DCM (2 mL) was added N,N-dimethylsulfamide (CAS Registry Number: 3984-14-3) (36 mg, 0.29 mmol) at room temperature, and the mixture was stirred at room temperature for one day. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and washed successively with 1 mol/L hydrochloric acid, water and saturated brine. The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (64 mg, 0.093 mmol, yield 62%).

[0490]

<Example I1> Ethyl trans-4-(4-([2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(pyridin-2-yl)amino)methyl]phenoxy)cyclohexanecarboxylate

To a mixture of ethyl trans-4-(4-([2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]phenoxy)cyclohexanecarboxylate (60 mg, 0.11 mmol) and 1,4-dioxane (1 mL) were successively added 2-bromopyridine (CAS Registry Number: 109-04-6) (0.030 mL, 0.31 mmol), cesium carbonate (120 mg, 0.368 mmol), and RuPhos Pd G3 (4 mg, 0.005 mmol), and the mixture was stirred at 100°C for 2 hr. To the reaction mixture were added tripotassium phosphate (100 mg, 0.471 mmol), 2-bromopyridine (0.030 mL, 0.31 mmol), and RuPhos Pd G3 (4 mg, 0.005 mmol), and the mixture was stirred at 100°C for 8 hr. To the reaction mixture was added RuPhos Pd G3 (4 mg, 0.005 mmol), and the mixture was stirred at 100°C for 3 hr. To the reaction mixture were added BrettPhos Pd G3 (4 mg, 0.004 mmol) and cesium carbonate (120 mg, 0.368 mmol), and the mixture was stirred at 100°C for 4 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The obtained organic layers were all

combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
5 compound (29.6 mg, 0.0493 mmol, yield 43%).

[0491]

<Example I2> trans-4-(4-{{2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(pyridin-2-yl)amino]methyl}phenoxy)cyclohexanecarboxylic acid

10 Using the compound obtained in <Example I1>, the title compound was obtained by the same method as in <Example S4>.

[0492]

<Example J1> Methyl 3-[4-(4-formylphenoxy)phenyl]-2,2-dimethylpropanoate

15 Using methyl 3-(4-hydroxyphenyl)-2,2-dimethylpropanoate (WO2008130514 A1) and 4-fluorobenzaldehyde (CAS Registry Number: 459-57-4), the title compound was obtained by the same method as in <Example P1>.

[0493]

20 <Example J2> Methyl 3-(4-{4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino]methyl}phenoxy)phenyl)-2,2-dimethylpropanoate
2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine (309 mg, 1.17 mmol) and methyl 3-[4-(4-
25 formylphenoxy)phenyl]-2,2-dimethylpropanoate (367 mg, 1.17 mmol) were dissolved in 1,2-dichloroethane (6.0 mL), acetic acid (0.60 mL) was added, and the mixture was stirred at room temperature for 1 hr. Thereto was added sodium triacetoxymethylborohydride (324 mg, 1.53 mmol), and the mixture was
30 stirred at room temperature for 20 hr. To the reaction mixture were added water and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced
35 pressure. The obtained residue was purified by silica gel

column chromatography (ethyl acetate/methanol) to give the title compound (462 mg, 0.825 mmol, yield 70%).

[0494]

<Example J3> Methyl 3-[4-(4-{{(2,2-dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)phenyl]-2,2-dimethylpropanoate
Methyl 3-(4-(4-{{(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)phenyl)-2,2-dimethylpropanoate
10 (241 mg, 0.431 mmol) and pivalic acid (52.8 mg, 0.517 mmol) were dissolved in DMF (6.0 mL), HATU (205 mg, 0.538 mmol) and DIPEA (0.187 mL, 1.08 mmol) were added, and the mixture was stirred under a nitrogen atmosphere at room temperature for 3 days. Water was added to the reaction mixture, and the mixture
15 was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
20 compound (247 mg, 0.384 mmol, yield 89%).

[0495]

<Example J4> 3-[4-(4-{{(2,2-Dimethylpropanoyl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)phenyl]-2,2-dimethylpropanoic
25 acid

Using the compound obtained in <Example J3>, the title compound was obtained by the same method as in <Examples 4>.

[0496]

<Example K1> Benzyl (cis-4-hydroxycyclohexyl)acetate

30 To a solution of 4-hydroxyphenylacetic acid (CAS Registry Number: 156-38-7) (10.0 g, 65.7 mmol) in ethanol (200 mL) was added rhodium-alumina (10.0 g), and the mixture was stirred under a hydrogen atmosphere at 50°C for 8 hr. Insoluble materials were filtered off through celite and washed with
35 ethanol. The obtained solution was concentrated to about 200

mL, rhodium-alumina (10.0 g) was added thereto, and the mixture was stirred under a hydrogen atmosphere at 50°C for 4 hr. Insoluble materials were filtered off through celite and washed with ethanol. The filtrate was concentrated under reduced
5 pressure. The residue was dissolved in DMF (130 mL) and potassium carbonate (18.2 g, 131 mmol) was added at room temperature. Under water cooling, benzyl bromide (11.7 mL, 98.6 mmol) was added dropwise thereto, and the mixture was stirred at room temperature overnight. The reaction mixture
10 was diluted with diethyl ether, washed successively with water, 1 mol/L hydrochloric acid, and saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to
15 give the title compound (7.65 g, 30.8 mmol, yield 47%).

[0497]

<Example K2> Benzyl [trans-4-(4-formylphenoxy)cyclohexyl]acetate

Using the compound obtained in <Example K1> and 4-
20 hydroxybenzaldehyde (CAS Registry Number: 123-08-0), the title compound was obtained by the same method as in <Example A4>.

[0498]

<Example K3> Benzyl (trans-4-{4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]phenoxy}cyclohexyl)acetate
25

Using the compounds obtained in <Example K2> and <Example C5>, the title compound was obtained by the same method as in <Example D1>.

[0499]

<Example K4> Benzyl [trans-4-(4-{[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)(3,3,3-trifluoropropyl)amino]methyl}phenoxy)cyclohexyl]acetate
30

Using the compound obtained in <Example K3> and 3,3,3-trifluoropropionaldehyde (CAS Registry Number: 460-40-2), the
35 title compound was obtained by the same method as in <Example

T1>.

[0500]

<Example K5> [Trans-4-(4-{[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)}(3,3,3-

5 trifluoropropyl)amino]methyl}phenoxy)cyclohexyl]acetic acid

Using the compound obtained in <Example K4>, the title compound was obtained by the same method as in <Example S4>.

[0501]

<Example L1> Ethyl trans-4-(4-{[(2-{2,2-dimethyl-4-[4-

10 (methylamino)phenyl]tetrahydro-2H-pyran-4-yl]ethyl)(2,2-dimethylpropanoyl)amino]methyl}phenoxy)cyclohexanecarboxylate

Using the compound obtained in <Example G1> and methylamine (2.0 mol/L THF solution), the title compound was obtained by the same method as in <Example G2>.

15 [0502]

<Example L2> Trans-4-(4-{[(2-{2,2-dimethyl-4-[4-

(methylamino)phenyl]tetrahydro-2H-pyran-4-yl]ethyl)(2,2-dimethylpropanoyl)amino]methyl}phenoxy)cyclohexanecarboxylic acid

20 Using the compound obtained in <Example L1>, the title compound was obtained by the same method as in <Example S4>.

[0503]

<Example M1> 2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine

25 The racemic 2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine was optically resolved by chiral HPLC [column: CHIRALCEL OZ-H (registered trademark, Daicel Corporation), mobile phase: hexane/IPA=60/40(V/V)] to obtain the title compound as the
30 component eluted later.

Analysis conditions column: CHIRALCEL OJ-H (registered trademark, Daicel Corporation), size: 0.46 cm×25 cm, flow rate: 1.0 mL/min, temperature: 30°C, mobile phase: hexane/isopropyl alcohol/diethylamine=70/30/0.2 (V/V/V), retention time: R form

35 <Example M1> 5.1 min, S form 6.7 min

[0504]

<Example M2> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide

5 To a solution of 3,3,3-trifluoro-2,2-dimethylpropanoic acid (CAS Registry Number: 889940-13-0) (18.0 g, 115 mmol) in DMF (150 mL) was added HATU (43.8 g, 115 mmol), and the mixture was stirred at room temperature for 20 min. The reaction mixture was cooled to 0°C, and stirred for 5 min. To the
10 reaction mixture were successively added dropwise a solution of 2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine (25.2 g, 95.7 mmol) in DMF (150 mL) and DIPEA (50 mL, 287 mmol), and the mixture was stirred at room temperature for 24 hr. The reaction mixture was diluted with ethyl
15 acetate, washed successively with aqueous sodium hydrogen carbonate solution, water, and saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) and
20 dried under reduced pressure to give the title compound (36.2 g, 90.2 mmol, yield 94%).

[0505]

<Example M3> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-
25 1-amine

To a solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide (24.7 g, 61.5 mmol) in THF (60 mL) was added borane-THF complex (0.89 mol/L THF solution, 240 mL, 210
30 mmol), and the mixture was stirred with heating under reflux for 9 hr. The reaction mixture was cooled to room temperature, methanol (60 mL) was added, and the mixture was stirred with heating under reflux for 3 hr. The reaction mixture was cooled to room temperature and concentrated under reduced pressure.
35 To the residue was added ethyl acetate, and the mixture was

washed successively with water and saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) and dried under reduced pressure to give the title compound (22.1 g, 57.0 mmol, yield 93%).

[0506]

<Example M4> Ethyl trans-4-(4-({2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)cyclohexanecarboxylate

Using the compounds obtained in <Example M3> and <Example A4>, the title compound was obtained by the same method as in <Example T1>.

[0507]

<Example M5> Trans-4-(4-({2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)cyclohexanecarboxylic acid

Using the compound obtained in <Example M4>, the title compound was obtained by the same method as in <Example S4>.

[0508]

<Example N1> N-[4-(4-Bromophenoxy)benzyl]-N-{2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide

Using the compound obtained in <Example C5> and 4-(4-bromophenoxy)benzaldehyde (Bioorg. Med. Chem. Lett., 2004, 14, 4179-4183.), the title compound was obtained by sequentially performing the same operations as in <Example D1> and <Example D2>.

[0509]

<Example N2> N-{4-[4-({Dimethyl(oxide)- λ^6 -sulfanilidene}amino)cyclohexyl]oxy}benzyl}-N-{2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide

To a solution of N-[4-(4-bromophenoxy)benzyl]-N-{2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-

dimethylpropanamide (150 mg, 0.246 mmol) in toluene (5 mL) were added dimethylsulfoximine (CAS Registry Number: 1520-31-6) (35 mg, 0.38 mmol), (S)-(-)-Tol-BINAP (26 mg, 0.038 mmol), cesium carbonate (161 mg, 0.494 mmol), and palladium(II) acetate (6 mg, 0.03 mmol), and the mixture was stirred with heating under reflux for 9 hr under a nitrogen atmosphere. To the reaction mixture were added dimethylsulfoximine (40 mg, 0.429 mmol), cesium carbonate (170 mg, 0.522 mmol), (S)-(-)-Tol-BINAP (28 mg, 0.041 mmol), and palladium(II) acetate (7 mg, 0.03 mmol), and the mixture was stirred with heating under reflux for 8 hr under a nitrogen atmosphere. To the reaction mixture were further added (S)-(-)-Tol-BINAP (27 mg, 0.040 mmol) and palladium(II) acetate (8 mg, 0.04 mmol), and the mixture was stirred with heating under reflux for 4 hr under a nitrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/methanol) to give the title compound (7 mg, 0.01 mmol, yield 4%).

[0510]

<Example 01> Ethyl trans-4-(4-((5-fluoropyrimidin-2-yl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)cyclohexanecarboxylate

To a mixture of ethyl trans-4-(4-((2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino)methyl}phenoxy)cyclohexanecarboxylate (65.5 mg, 0.125 mmol) and 2-butanol (1.5 mL, 16 mmol) were successively added 2-chloro-5-fluoropyrimidine (CAS Registry Number: 62802-42-0) (0.030 mL, 0.24 mmol), 1,8-diazabicyclo[5.4.0]-7-undecene (0.040 mL, 0.27 mmol), and cesium fluoride (1 mg, 0.007 mmol), and the mixture was stirred at 150°C for 1.5 hr under microwave irradiation. To the reaction mixture were added water and saturated brine, and the mixture was extracted with ethyl acetate. The obtained organic layers were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (47.4 mg, 0.0765 mmol, yield 61%).

[0511]

<Example O2> Trans-4-(4-{{(5-fluoropyrimidin-2-yl){2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino}methyl}phenoxy)cyclohexanecarboxylic acid

Using the compound obtained in <Example O1>, the title compound was obtained by the same method as in <Example S4>.

[0512]

10 <Example P1> Methyl 2-[4-(4-formylphenoxy)phenyl]propanoate

4-Fluorobenzaldehyde (CAS Registry Number: 459-57-4) (0.637 mL, 5.94 mmol) and methyl 2-(4-hydroxyphenyl)propanoate (J. Med. Chem., 2007, 50, 3984-4002.) (1.07 g, 5.94 mmol) were dissolved in N,N-dimethylacetamide (10 mL), potassium carbonate
15 (2.46 g, 17.8 mmol) was added, and the mixture was stirred at 130°C for 8 hr, cooled to room temperature, and left standing overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium
20 sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (878 mg, 3.09 mmol, yield 52%).

[0513]

25 <Example P2> Methyl 2-[4-(4-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino}methyl}phenoxy)phenyl]propanoate

Using the compounds obtained in <Example M3> and <Example P1>, the title compound was obtained by the same method as in

30 <Example T1>.

[0514]

<Example P3> 2-[4-(4-{{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino}methyl}phenoxy)phenyl]propanoic acid

35 Using the compound obtained in <Example P2>, the title

compound was obtained by the same method as in <Example S4>.

[0515]

<Example Q1> Methyl 4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]-2-

5 methylbenzoate

Using the compound obtained in <Example C5> and methyl 4-formyl-2-methylbenzoate (CAS Registry Number: 74733-23-6), the title compound was obtained by the same method as in <Example J2>.

10 [0516]

<Example Q2> Methyl 4-[(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)(3,3,3-trifluoro-2,2-dimethylpropanoyl)amino]methyl]-2-methylbenzoate

3,3,3-Trifluoro-2,2-dimethylpropanoic acid (CAS Registry
15 Number: 889940-13-0) (1.25 g, 8.04 mmol) was dissolved in DCM (10 mL), DMF (0.05 mL) was added, and the mixture was stirred at room temperature. Oxalyl chloride (0.748 mL, 8.84 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hr. The solution was added to a solution of methyl 4-
20 [(2-[4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)amino)methyl]-2-methylbenzoate (1.14 g, 2.68 mmol) and triethylamine (2.23 mL, 16.1 mmol) in DCM (15 mL), and the mixture was stirred at room temperature for 24 hr. To the reaction mixture were added water and saturated aqueous sodium
25 hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
30 compound (1.12 g, 1.99 mmol, yield 74%).

[0517]

<Example Q3> 4-[(2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)(3,3,3-trifluoro-2,2-dimethylpropanoyl)amino]methyl]-2-methylbenzoic acid

35 Using the compound obtained in <Example Q2>, the title

compound was obtained by the same method as in <Example S4>. [0518]

<Example Q4> 3-[4-(4-{{2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropanoyl)amino)methyl}-2-methylbenzoyl)phenyl]propanoic acid

4-{{2-[4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropanoyl)amino)methyl}-2-methylbenzoic acid (1.06 g, 1.93 mmol) was dissolved in DCM (10 mL), DMF (0.05 mL) was added, and the mixture was stirred at room temperature. Oxalyl chloride (0.539 mL, 6.36 mmol) was added thereto, and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated to give the corresponding acid chloride (1.06 g, 1.87 mmol, yield 97%). To the obtained acid chloride (191 mg, 0.336 mmol) were added [4-(2-ethoxycarbonyl)phenyl]boronic acid (CAS Registry Number: 660440-57-3) (60.0 mg, 0.270 mmol), toluene (8.0 mL), cesium carbonate (225 mg, 0.692 mmol) and tetrakis(triphenylphosphine)palladium(0) (40.6 mg, 0.0351 mmol), and the mixture was stirred at 80°C for 6 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate). The obtained crudely purified product was dissolved in ethanol (4.0 mL), 1 mol/L aqueous sodium hydroxide solution (0.754 mL, 0.754 mmol) was added, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure, and the residue was neutralized by adding water and 2 mol/L hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and filtered, and

the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (15.0 mg, 0.0220 mmol, yield 15%).

5 [0519]

<Example R1> Ethyl (2S)-2-ethoxy-3-[4-(4-formylphenoxy)phenyl]propanoate

Using 4-fluorobenzaldehyde (CAS Registry Number: 459-57-4) and ethyl (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (CAS
10 Registry Number: 222555-06-8), the title compound was obtained by the same method as in <Example P1>.

[0520]

<Example R2> Ethyl (2S)-2-ethoxy-3-[4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)phenyl]propanoate
15

Using the compounds obtained in <Example M3> and <Example R1>, the title compound was obtained by the same method as in <Example T1>.

20 [0521]

<Example R3> (2S)-2-Ethoxy-3-[4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)phenyl]propanoic acid

25 Using the compound obtained in <Example R2>, the title compound was obtained by the same method as in <Example S4>.

[0522]

<Example S1> Ethyl (cis-4-hydroxycyclohexyl)acetate

Under a nitrogen atmosphere, to a solution of ethyl 2-(4-oxocyclohexyl)acetate (CAS Registry Number: 58012-34-3) (7.75
30 g, 42.1 mmol) in THF (170 mL) was added dropwise at -78°C lithium tri(sec-butyl)borohydride (1.07 mol/L THF solution, 39.3 mL, 42.1 mmol) over 30 min. After dropwise addition, the mixture was stirred at -78°C for 2 hr. To the reaction mixture
35 were added saturated aqueous ammonium chloride solution and

water, the mixture was returned to room temperature, THF was evaporated under reduced pressure, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and
5 filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.13 g, 32.9 mmol, yield 78%).

[0523]

10 <Example S2> Ethyl {trans-4-[(5-formylpyridin-2-yl)oxy]cyclohexyl}acetate

Using the compound obtained in <Example S1> and 6-hydroxynicotinaldehyde (CAS Registry Number: 106984-91-2), the title compound was obtained by the same method as in <Example
15 A4>.

[0524]

<Example S3> Ethyl {trans-4-[(5-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}pyridin-2-
20 yl)oxy]cyclohexyl}acetate

Using the compounds obtained in <Example S2> and <Example M3>, the title compound was obtained by the same method as in <Example T1>.

[0525]

25 <Example S4> {Trans-4-[(5-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}pyridin-2-yl)oxy]cyclohexyl}acetic acid

To a solution of ethyl {trans-4-[(5-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
30 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}pyridin-2-yl)oxy]cyclohexyl}acetate (390 mg, 0.588 mmol) in methanol (11.8 mL) was added 1 mol/L aqueous sodium hydroxide solution (2.94 mL, 2.94 mmol) at room
35 temperature, and the mixture was stirred at 50°C for 30 min and

left standing at room temperature overnight. To the reaction mixture was added 1 mol/L hydrochloric acid (2.94 mL, 2.94 mmol) at room temperature, and the mixture was extracted with DCM. The organic layer was dried over anhydrous sodium sulfate
5 and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (265 mg, 0.418 mmol, yield 71%).

[0526]

10 <Example T1> Benzyl [trans-4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenoxy)cyclohexyl]acetate

To a solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-
15 dimethylpropan-1-amine (450 mg, 1.16 mmol) in methanol (11.6 mL) were added benzyl [trans-4-(4-formylphenoxy)cyclohexyl]acetate (450 mg, 1.28 mmol) and acetic acid (0.199 mL, 3.48 mmol) at room temperature, and the mixture was stirred at 50°C for 1 hr. After cooling, to the reaction
20 mixture was added sodium cyanoborohydride (137 mg, 2.18 mmol) under ice-cooling, and the mixture was stirred at room temperature 3 hr and left standing for 2 days. The reaction mixture was stirred at 50°C for 1.5 hr. After cooling the reaction mixture, ice, water and sodium hydrogen carbonate were
25 added under ice-cooling, and the mixture was extracted with DCM. The obtained organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography
30 (hexane/ethyl acetate) to give the title compound (569 mg, 0.785 mmol, yield 68%).

[0527]

<Example T2> [Trans-4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
35 dimethylpropyl)amino]methyl}phenoxy)cyclohexyl]acetic acid

Using the compound obtained in <Example T1>, the title compound was obtained by the same method as in <Examples 4>.
[0528]

<Example U1> N-[4-(Benzyloxy)benzyl]-2-[(4R)-4-(4-

5 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethanamine

Using the compound obtained in <Example M1> and 4-benzyloxybenzaldehyde (CAS Registry Number: 4397-53-9), the title compound was obtained by the same method as in <Example D1>.

10 [0529]

<Example U2> N-[4-(Benzyloxy)benzyl]-3,3-difluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide

Using the compound obtained in <Example U1> and 3,3-difluoro-2,2-dimethylpropanoic acid (CAS Registry Number: 1022154-50-2), the title compound was obtained by the same method as in <Example Q2>.

[0530]

<Example U3> 3,3-Difluoro-N-(4-hydroxybenzyl)-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide

To a solution of N-[4-(benzyloxy)benzyl]-3,3-difluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropanamide (920 mg, 1.59 mmol) in
25 ethanol (30 mL) was added 10% palladium carbon (400 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, insoluble materials were filtered off through celite. The filtrate was concentrated under reduced pressure,
30 and the residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (714 mg, 1.46 mmol, yield 92%).

[0531]

<Example U4> (cis-4-{[tert-

35 Butyl(diphenyl)silyl]oxy}cyclohexyl)methyl 4-

methylbenzenesulfonate

To a solution of (cis-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)methanol (WO2007126041 A1) (8.20 g, 22.2 mmol) in DCM (200 mL) were added triethylamine (4.63 mL, 33.4 mmol) and para-toluenesulfonyl chloride (4.67 g, 24.5 mmol), and the mixture was stirred with heating under reflux for 7 hr. The reaction mixture was cooled to room temperature, ethanol (2 mL) was added, and the mixture was stirred at room temperature for 10 hr. Water and saturated brine were added thereto, and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (8.89 g, 17.0 mmol, yield 76%).

[0532]

<Example U5> tert-Butyl({cis-4-[(methylsulfonyl)methyl]cyclohexyl}oxy)diphenylsilane

To a solution of (cis-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)methyl 4-methylbenzenesulfonate (8.89 g, 17.0 mmol) in THF (400 mL) was added sodium thiomethoxide (9.54 g, 136 mmol), and the mixture was stirred with heating under reflux for 10 hr. The reaction mixture was cooled to room temperature, water and saturated brine were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.28 g, 15.8 mmol, yield 93%).

[0533]

<Example U6> tert-Butyl({cis-4-[(methylsulfinyl)methyl]cyclohexyl}oxy)diphenylsilane

To a solution of tert-butyl({cis-4-
[(methylsulfanyl)methyl]cyclohexyl}oxy)diphenylsilane (6.28 g,
15.8 mmol) in methanol (100 mL) and water (25 mL) was added
sodium periodate (4.04 g, 18.9 mmol), and the mixture was
5 stirred at room temperature for 15 hr. To the reaction mixture
were added saturated brine and water, and the mixture was
extracted with ethyl acetate. The organic layers were
combined, washed with saturated brine, dried over anhydrous
sodium sulfate, filtered, and concentrated under reduced
10 pressure. The residue was purified by silica gel column
chromatography (DCM/methanol) to give the title compound (6.41
g, 15.5 mmol, yield 98%).

[0534]

<Example U7> Benzyl {[cis-4-{[tert-
15 butyl(diphenyl)silyl]oxy}cyclohexyl)methyl](methyl)oxide- λ^6 -
sulfanilidene}carbamate

To a solution of tert-butyl({cis-4-
[(methylsulfinyl)methyl]cyclohexyl}oxy)diphenylsilane (6.41 g,
15.5 mmol) and benzyl carbamate (CAS Registry Number: 621-84-
20 1) (7.01 g, 46.4 mmol) in DCM (250 mL) were added, under a
nitrogen atmosphere, magnesium oxide (4.98 g, 124 mmol),
iodobenzene diacetate (14.9 g, 46.4 mmol), and rhodium(II)
acetate dimer (1.37 g, 3.09 mmol), and the mixture was stirred
with heating under reflux for 7 hr. Insoluble materials were
25 filtered off, and concentrated under reduced pressure. The
residue was purified by silica gel column chromatography
(hexane/ethyl acetate) to give the title compound (3.97 g, 7.04
mmol, yield 46%).

[0535]

30 <Example U8> Benzyl {[cis-4-
hydroxycyclohexyl)methyl](methyl)oxide- λ^6 -
sulfanilidene}carbamate

To a solution of benzyl {[cis-4-{[tert-
butyl(diphenyl)silyl]oxy}cyclohexyl)methyl](methyl)oxide- λ^6 -
35 sulfanilidene}carbamate (3.97 g, 7.04 mmol) in THF (30 mL) was

added tetrabutylammonium fluoride (1.0 mol/L THF solution, 30 mL, 30 mmol), and the mixture was stirred at 65°C for 2 hr. The reaction mixture was cooled to room temperature, water and saturated brine were added, and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (1.70g, 5.22 mmol, yield 74%).

[0536]

<Example U9> Benzyl {(R) or (S)-[(cis-4-hydroxycyclohexyl)methyl](methyl)oxide- λ^6 -sulfanilidene}carbamate

The racemic benzyl{[(cis-4-hydroxycyclohexyl)methyl](methyl)oxide- λ^6 -sulfanylidene}carbamate was optically resolved by chiral HPLC [column: CHIRALPAK IC (registered trademark, Daicel Corporation), mobile phase: hexane/ethanol = 40/60 (V/V)] to obtain the title compound as the component eluted first.

[0537]

<Example U10> Benzyl [(R) or (S)-{[trans-4-(4-{[(3,3-difluoro-2,2-dimethylpropanoyl){2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}amino]methyl}phenoxy)cyclohexyl]methyl}(methyl)oxide- λ^6 -sulfanilidene]carbamate

Using the compounds obtained in <Example U9> and <Example U3>, the title compound was obtained by the same method as in <Example A4>.

[0538]

<Example U11> 3,3-Difluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{4-[(trans-4-{[(R) or (S)-S-methylsulfonimidoyl]methyl}cyclohexyl)oxy]benzyl}propanamide

Using the compound obtained in <Example U10>, the title

compound was obtained by the same method as in <Example U3>.

[0539]

<Example V1> tert-Butyl 2'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

5 4-Bromo-3-fluorobenzaldehyde (CAS Registry Number: 133059-43-5) (4.00 g, 19.7 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1562375-30-7) (6.38 g, 20.7 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride DCM adduct (0.804 g, 0.985 mmol), and sodium carbonate (6.27 g, 59.2 mmol) were dissolved in a mixed solvent of 1,4-dioxane (45 mL) and water (5 mL), and the mixture was stirred with heating under a nitrogen atmosphere at 85°C for 4 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.03 g, 19.8 mmol, yield: quantitative).

[0540]

<Example V2> tert-Butyl (4R)-2'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

25 <Example V3> tert-butyl (4S)-2'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

The racemic tert-butyl 2'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate was purified by chiral HPLC [column: CHIRALPAK IG (registered trademark, Daicel Corporation), mobile phase: acetonitrile] to obtain R form <Example V2> as the component eluted first and S form <Example V3> as the component eluted later. Analysis conditions column: CHIRALPAK IG (registered trademark, Daicel Corporation), size: 0.46 cm×25 cm, flow rate: 1.0 mL/min, temperature: 40°C, mobile phase: acetonitrile,

retention time: R form <Example V2> 4.8 min, S form <Example V3> 5.6 min

[0541]

<Example V4> tert-Butyl (4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

tert-Butyl (4R)-2'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (0.115 g, 0.378 mmol) and
10 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine (0.147 g, 0.379 mmol) were dissolved in DCM (4 mL), sodium triacetoxyborohydride (0.157 g, 0.741 mmol) was added, and the mixture was stirred at room temperature for 20 hr. To
15 the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column
20 chromatography (hexane/ethyl acetate) to give the title compound (0.196 g, 0.290 mmol, yield 77%).

[0542]

<Example V5> (4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride

tert-Butyl (4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
30 2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (0.196 g, 0.290 mmol) was dissolved in DCM (2 mL), 4 mol/L hydrogen chloride/1,4-dioxane solution (1.2 mL, 4.8 mmol) was added, and the mixture was stirred at room temperature for 24 hr. The reaction mixture was concentrated under reduced pressure to
35 give the title compound (0.237 g, 0.361 mmol, yield:

quantitative).

[0543]

<Example W1> tert-Butyl 4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

5 A suspension of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1562375-30-7) (WO2017051355) (1.14 g, 3.70 mmol), 4-bromobenzaldehyde (CAS Registry Number: 1122-91-4) (694 mg, 3.75 mmol), [1,1'-
10 bis(diphenylphosphino)ferrocene]dichloropalladium(II) DCM adduct (306 mg, 0.375 mmol), and potassium carbonate (2.0 mol/L aqueous solution, 3.5 mL, 7.0 mmol) in 1,4-dioxane (7.5 mL) was stirred under a nitrogen atmosphere at 90°C for 2 hr. The reaction mixture was cooled to room temperature, ethyl acetate
15 and water were added, insoluble materials were filtered off through celite, and two layers were separated. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl
20 acetate) to give the title compound (836 mg, 2.92 mmol, yield 79%).

[0544]

<Example W2> tert-Butyl (4R)-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

25 <Example W3> tert-Butyl (4S)-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

 The racemic tert-butyl 4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate was purified by chiral SFC [column: CHIRALPAK IG (registered trademark, Daicel
30 Corporation), mobile phase: sCO₂/acetonitrile = 60/40 (V/V)] to obtain R form <Example W2> as the component eluted first and S form <Example W3> as the component eluted later.
Analysis conditions column: CHIRALPAK IG-3 (registered trademark, Daicel Corporation), size: 0.46 cm×5 cm, flow rate:
35 3.0 mL/min, temperature: 35°C, mobile phase: sCO₂/acetonitrile

(0.05% diethylamine)=60/40 (V/V), retention time: R form

<Example W2> 0.9 min, S form <Example W3> 1.4 min

[0545]

<Example W4> tert-Butyl (4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
5 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-
4-carboxylate

A solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-
10 dimethylpropan-1-amine (16.7 g, 43.1 mmol) and tert-butyl (4R)-
4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (12.8 g,
44.7 mmol) in DCM (200 mL) was stirred at room temperature for
15 min. To the reaction mixture was added sodium
triacetoxyborohydride (18.6 g, 87.8 mmol), and the mixture was
stirred for 5 hr. To the reaction mixture were added saturated
aqueous sodium hydrogen carbonate solution and water, and the
mixture was extracted with DCM. The organic layer was dried
over sodium sulfate and filtered, and the filtrate was
concentrated under reduced pressure. The residue was purified
20 by silica gel column chromatography (hexane/ethyl acetate) to
give the title compound (26.2 g, 39.8 mmol, yield 92%).

[0546]

<Example W5> [(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
25 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
yl]methanol

Under ice-cooling, to a suspension of lithium aluminum
hydride (3.01 g, 79.3 mmol) in THF (170 mL) was added dropwise
a solution of tert-butyl (4R)-4'-{[{2-[(4R)-4-(4-
30 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (26.2 g, 39.8 mmol)
in THF (200 mL), and the mixture was stirred at the said
temperature for 2.5 hr. To the reaction mixture were added
35 sodium sulfate decahydrate and ethyl acetate, and the mixture

was stirred at room temperature. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (23.8 g, 40.5 mmol, yield: quantitative).

5 [0547]

<Example X1> [(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl methanesulfonate

10 [(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methanol (0.783 g, 1.33 mmol) and triethylamine (0.56 mL, 4.0 mmol) were dissolved in THF (13 mL), methanesulfonic anhydride
15 (0.473 g, 2.71 mmol) was added at 0°C, and the mixture was stirred at room temperature for 16 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous
20 sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (0.878 g, 1.32 mmol, yield 99%).

[0548]

<Example X2> tert-Butyl 4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazine-1-carboxylate

30 [(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl methanesulfonate (0.878 g, 1.32 mmol) and 1-(tert-butoxycarbonyl)piperazine (CAS Registry Number: 57260-71-6) (1.37 g, 7.37 mmol) were dissolved in DMF (6 mL), sodium iodide
35 (0.0425 g, 0.284 mmol) was added, and the mixture was stirred

with heating at 110°C for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, 5 dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.877 g, 1.16 mmol, yield 88%).

10 [0549]

<Example Y1> tert-Butyl (2-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}ethyl)carbamate

To a suspension of 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-15 1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1) (391 mg, 1.43 mmol) and N-Boc-2-aminoacetaldehyde (CAS Registry Number: 89711-08-0) (364 mg, 2.29 mmol) in methanol (7 mL) and N,N-dimethylacetamide (7 mL) was added acetic acid (0.245 mL, 4.28 mmol), and the mixture was stirred at room temperature for 20 30 min. To the reaction mixture was added sodium cyanoborohydride (365 mg, 5.81 mmol), and the mixture was stirred at room temperature for 15 hr. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate solution and water, and the mixture was extracted with ethyl acetate. 25 The organic layers were combined, washed successively with water and saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (375 30 mg, 0.898 mmol, yield 63%).

[0550]

<Example Y2> 3-{5-[(2-Aminoethyl)amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione dihydrochloride

35 Using the compound obtained in <Example Y1>, the title

compound was obtained by the same method as in <Example A05>.
[0551]

<Example Y3> Methyl (4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetate

5 Using 4-bromobenzaldehyde (CAS Registry Number: 1122-91-4) and methyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexen-1-yl]acetate (CAS Registry Number: 1109277-66-8), the title compound was obtained by the same method as in <Example W1>.

10 [0552]

<Example Y4> Methyl (4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetate

15 To a solution of methyl (4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetate (283 mg, 1.0956 mmol) and 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine (300 mg, 0.774 mmol) in methanol (4 mL) was added acetic
20 acid (0.133 mL, 2.32 mmol), and the mixture was stirred at room temperature for 25 min. To the reaction mixture was added sodium cyanoborohydride (158 mg, 2.51 mmol), and the mixture was stirred for 19 hr at room temperature. To the reaction mixture was added sodium cyanoborohydride (210 mg, 3.34 mmol),
25 and the mixture was stirred for 5 hr at room temperature. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced
30 pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (233 mg, 0.370 mmol, yield 48%).

[0553]

<Example Y5> (4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-

35

dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetic acid

To a solution of methyl (4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetate (233 mg, 0.370 mmol) in THF (2 mL) and methanol (3 mL) was added 1 mol/L aqueous sodium hydroxide solution (1 mL, 1 mmol), and the mixture was stirred at room temperature for 20 hr. To the reaction mixture
10 were added 1 mol/L hydrochloric acid (1 mL, 1 mmol), and the mixture was extracted with DCM. The organic layer dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dried under reduced pressure to give the title compound (219 mg, 0.357 mmol, yield
15 96%).

[0554]

<Example Y6> N-(2-{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}ethyl)-2-(4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)acetamide
20

Using the compounds obtained in <Example Y5> and <Example Y2>, the title compound was obtained by the same method as in <Example BM9>.

25 [0555]

<Example Z1> tert-Butyl [4-(4-formylphenoxy)piperidin-1-yl]acetate

Using tert-butyl 4-(4-formylphenoxy)piperidine-1-carboxylate (WO2015069110 A1), the title compound was obtained
30 by the same method as in <Example AK7>.

[0556]

<Example Z2> tert-Butyl [4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetate
35

Using the compounds obtained in <Example M3> and <Example

Z1>, the title compound was obtained by the same method as in
<Example Y4>.

[0557]

<Example Z3> [4-(4-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-
5 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetic acid
dihydrochloride

Using the compound obtained in <Example Z2>, the title
compound was obtained by the same method as in <Example V5>.

10 [0558]

<Example Z4> 3-Bromo-1-{[2-
(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

To a suspension of 3-bromopiperidine-2,6-dione (CAS
Registry Number: 62595-74-8) (25.5 g, 133 mmol) in DCM (250 mL)
15 were successively added, under ice-cooling, DIPEA (45 mL, 258
mmol) and [2-(chloromethoxy)ethyl]trimethylsilane (29 mL, 170
mmol), and the mixture was stirred at said temperature for 40
min. The reaction mixture was warmed to room temperature and
stirred for 16 hr. The reaction mixture was washed with water,
20 and the organic layer was dried over sodium sulfate and
filtered, and the filtrate was concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography (hexane/ethyl acetate) to give the title
compound (36.5 g, 113 mmol, yield 85%).

25 [0559]

<Example Z5> 3-(3-Methyl-4-nitro-2-oxo-2,3-dihydro-1H-
benzimidazol-1-yl)-1-{[2-
(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

A suspension of 1-methyl-7-nitro-1,3-dihydro-2H-
30 benzimidazol-2-one (WO2020200291 A1) (3.29 g, 17.0 mmol), 3-
bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione
(11.38 g, 35.31 mmol), and cesium carbonate (16.7 g, 51.3 mmol)
in DMF (80 mL) was stirred under a nitrogen atmosphere at room
temperature for 26 hr. The reaction mixture was diluted with
35 ethyl acetate and washed successively with water and saturated

brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
5 compound (6.76 g, 15.6 mmol, yield 91%).

[0560]

<Example Z6> 3-(4-Amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

10 Using the compound obtained in <Example Z5>, the title compound was obtained by the same method as in <Example BK5>.
[0561]

<Example Z7> N-[1-(2,6-Dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3-methyl-2-oxo-
15 2,3-dihydro-1H-benzimidazol-4-yl]-2-[4-(4-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetamide

Using the compounds obtained in <Example Z6> and <Example
20 Z3>, the title compound was obtained by the same method as in <Example BM9>.
[0562]

<Example Z8> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]-2-[4-(4-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetamide

Using the compound obtained in <Example Z7>, the title compound was obtained by the same method as in <Example BK9>.
30 [0563]

<Example AA1> Ethyl (4'-formyl[biphenyl]-3-yl)acetate

Using 4-bromobenzaldehyde (CAS Registry Number: 1122-91-4) and [3-(2-ethoxy-2-oxoethyl)phenyl]boronic acid (CAS Registry Number: 1256345-69-3), the title compound was obtained
35 by the same method as in <Example W1>.

[0564]

<Example AA2> Ethyl (4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}[biphenyl]-3-yl)acetate

5 Using the compounds obtained in <Example AA1> and <Example M3>, the title compound was obtained by the same method as in <Example Y4>.

[0565]

<Example AA3> (4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}[biphenyl]-3-yl)acetic acid

10 Using the compound obtained in <Example AA2>, the title compound was obtained by the same method as in <Example Y5>.

[0566]

<Example AA4> N-(2-{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}ethyl)-2-(4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}[biphenyl]-3-yl)acetamide

15 Using the compounds obtained in <Example AA3> and <Example Y2>, the title compound was obtained by the same method as in <Example BM9>.

[0567]

<Example AB1> Ethyl cyano(4,4-difluorocyclohexylidene)acetate

25 Using 4,4-difluorocyclohexanone (CAS Registry Number: 22515-18-0), the title compound was obtained by the same method as in <Example A1>.

[0568]

<Example AB2> N-{2-[4,4-Difluoro-1-(4-methoxyphenyl)cyclohexyl]ethyl}-3,3,3-trifluoro-2,2-dimethylpropan-1-amine

30 Using the compound obtained in <Example AB1>, the title compound was obtained by sequentially performing the same operations as in <Example C3>, <Example C4>, <Example C5>, <Example M2> and <Example M3>.

[0569]

<Example AB3> Methyl [4-(4-formylphenoxy)piperidin-1-yl]acetate

Using tert-butyl 4-(4-formylphenoxy)piperidine-1-

carboxylate (WO2015069110 A1) and methyl bromoacetate (CAS

5 Registry Number: 96-32-2), the title compound was obtained by the same method as in <Example AK7>.

[0570]

<Example AB4> Methyl [4-(4-{{2-[4,4-difluoro-1-(4-methoxyphenyl)cyclohexyl]ethyl}}(3,3,3-trifluoro-2,2-

10 dimethylpropyl)amino)methyl}phenoxy)piperidin-1-yl]acetate

Using the compounds obtained in <Example AB3> and

<Example AB2>, the title compound was obtained by the same method as in <Example Y4>.

[0571]

15 <Example AB5> [4-(4-{{2-[4,4-Difluoro-1-(4-

methoxyphenyl)cyclohexyl]ethyl}}(3,3,3-trifluoro-2,2-

dimethylpropyl)amino)methyl}phenoxy)piperidin-1-yl]acetic acid

Using the compound obtained in <Example AB4>, the title compound was obtained by the same method as in <Example Y5>.

20 [0572]

<Example AB6> 2-[4-(4-{{2-[4,4-Difluoro-1-(4-

methoxyphenyl)cyclohexyl]ethyl}}(3,3,3-trifluoro-2,2-

dimethylpropyl)amino)methyl}phenoxy)piperidin-1-yl]-N-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-

25 benzimidazol-4-yl]acetamide

Using the compound obtained in <Example AB5> and 3-(4-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-

yl)piperidine-2,6-dione (WO2021170109 A1), the title compound was obtained by the same method as in <Example BM9>.

30 [0573]

<Example AC1> Ethyl cyano(tetrahydro-4H-pyran-4-ylidene)acetate

Using tetrahydro-4H-pyran-4-one (CAS Registry Number:

29943-42-8), the title compound was obtained by the same method as in <Example A1>.

35 [0574]

<Example AC2> 3,3,3-Trifluoro-N-{2-[4-(4-methoxyphenyl)tetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine

Using the compound obtained in <Example AC1>, the title
5 compound was obtained by sequentially performing the same
operations as in <Example C3>, <Example C4>, <Example C5>,
<Example M2> and <Example M3>.

[0575]

<Example AC3> Methyl [4-(4-{[2-[4-(4-methoxyphenyl)tetrahydro-
10 2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetate

Using the compounds obtained in <Example AB3> and
<Example AC2>, the title compound was obtained by the same
method as in <Example Y4>.

15 [0576]

<Example AC4> [4-(4-{[2-[4-(4-Methoxyphenyl)tetrahydro-2H-
pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenoxy)piperidin-1-yl]acetic acid

Using the compound obtained in <Example AC3>, the title
20 compound was obtained by the same method as in <Example Y5>.

[0577]

<Example AC5> N-[1-(2,6-Dioxo-1-{[2-
(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3-methyl-2-oxo-
2,3-dihydro-1H-benzimidazol-4-yl]-2-[4-(4-{[2-[4-(4-
25 methoxyphenyl)tetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}phenoxy)piperidin-1-
yl]acetamide

Using the compounds obtained in <Example AC4> and
<Example Z6>, the title compound was obtained by the same
30 method as in <Example BM9>.

[0578]

<Example AC6> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-
2,3-dihydro-1H-benzimidazol-4-yl]-2-[4-(4-{[2-[4-(4-
methoxyphenyl)tetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
35 2,2-dimethylpropyl)amino]methyl}phenoxy)piperidin-1-

yl]acetamide

Using the compound obtained in <Example AC5>, the title compound was obtained by the same method as in <Example BK9>. [0579]

5 <Example AD1> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]-2-[2-(4-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetamide

Using the compound obtained in <Example AK9> and 3-(4-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1), the title compound was obtained by the same method as in <Example BM9>.

15 [0580]

<Example AE1> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]-2-[2-(4-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetamide

Using the compound obtained in <Example AK9> and 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1), the title compound was obtained by the same method as in <Example BM9>. [0581]

<Example AF1> N-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-2-[2-(4-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetamide

Using the compound obtained in <Example AK9> and 3-(5-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (ACS Med. Chem. Lett., 2021, 12, 1733.), the title compound was obtained by the same method as in <Example BM9>.

[0582]

<Example AG1> Ethyl 4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using 4-bromobenzaldehyde (CAS Registry Number: 1122-91-4) and ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1), the title compound was obtained by the same method as in <Example W1>.

[0583]

10 <Example AG2> Ethyl 4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example AG1>, the title compound was obtained by the same method as in <Example W4>.

[0584]

<Example AG3> (4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methanol

To a solution of ethyl 4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (439 mg, 0.697 mmol) in toluene (3.5 mL) was added, under ice-cooling, diisobutylaluminum hydride (1 mol/L toluene solution, 1.7 mL, 1.7 mmol), and the mixture was stirred at said temperature for 20 min. To the reaction mixture were added saturated Rochelle salt solution, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was extracted with ethyl acetate, the organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (388 mg, 0.660 mmol, yield 94%).

[0585]

<Example AG4> (4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl methanesulfonate

Using the compound obtained in <Example AG3>, the title compound was obtained by the same method as in <Example X1>.

[0586]

<Example AG5> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{[4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride

Using the compound obtained in <Example AG4>, the title compound was obtained by sequentially performing the same operations as in <Example X2> and <Example A05>.

[0587]

<Example AG6> 2,4,6-Trichlorophenyl 2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindole-5-carboxylate

Using 3-(5-bromo-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-2,6-piperidinedione (WO2019038717 A1), the title compound was obtained by the same method as in <Example BY5>.

[0588]

<Example AG7> 3-[5-({4-[(4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl}carbonyl)-1-oxo-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione

Using the compounds obtained in <Example AG6> and <Example AG5>, the title compound was obtained by the same method as in <Example BI1>.

[0589]

<Example AH1> 3-(4-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using 7-bromo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one

(CAS Registry Number: 913297-44-6), the title compound was obtained by the same method as in <Example Z5>.

[0590]

<Example AH2> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy]methyl)piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-4-carboxylate

Using the compound obtained in <Example AH1>, the title compound was obtained by the same method as in <Example BY5>.

[0591]

<Example AH3> 3-[4-([4-([4'-([2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl)-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-1-([2-(trimethylsilyl)ethoxy]methyl)piperidine-2,6-dione

Using the compounds obtained in <Example AH2> and <Example AG5>, the title compound was obtained by the same method as in <Example BI1>.

[0592]

<Example AH4> 3-[4-([4-([4'-([2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl)-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

Using the compound obtained in <Example AH3>, the title compound was obtained by the same method as in <Example BK9>.

[0593]

<Example AI1> Ethyl cis-4-(4-formylphenyl)cyclohexanecarboxylate

<Example AI2> Ethyl trans-4-(4-formylphenyl)cyclohexanecarboxylate

Under a hydrogen atmosphere, a suspension of ethyl 4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (1.1 g, 4.30 mmol) and 7.5% palladium carbon (350 mg) in ethanol (30 mL) was stirred for 1.5 hr. The catalyst was filtered off through

celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform (30 mL), manganese(IV) oxide (1.9 g) was added and the mixture was heated under reflux for 1 hr. Insoluble materials were
5 filtered off from the reaction mixture through celite, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane/ethyl acetate) to give the title cis isomer (730 mg, 2.80 mmol, yield 66%) and trans isomer (320 mg, 1.22 mmol,
10 yield 29%).

[0594]

<Example AI3> Ethyl cis-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenyl)cyclohexanecarboxylate

15 Using the compounds obtained in <Example M3> and <Example AI1>, the title compound was obtained by the same method as in <Example W4>.

[0595]

<Example AI4> [Cis-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenyl)cyclohexyl]methanol
20

Using the compound obtained in <Example AI3>, the title compound was obtained by the same method as in <Example W5>.

[0596]

25 <Example AI5> Cis-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenyl)cyclohexanecarbaldehyde

Under ice-cooling, to a solution of [cis-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenyl)cyclohexyl]methanol (520 mg, 0.88 mmol) in DCM (10 mL) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3-(1H)-one (CAS Registry Number: 87413-09-0) (490 mg, 1.15 mmol), and the mixture was stirred
30 for 1 hr. To the reaction mixture was added aqueous sodium

hydrogen carbonate solution, and the mixture was stirred and then extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The
5 residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (346 mg, 0.58 mmol, yield 66 %).

[0597]

<Example AI6> tert-Butyl 4-{{[cis-4-(4-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methyl}piperazine
10 -1-carboxylate

Using the compound obtained in <Example AI5> and 1-(tert-butoxycarbonyl)piperazine (CAS Registry Number: 57260-71-6),
15 the title compound was obtained by the same method as in <Example W4>.

[0598]

<Example AI7> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{4-[cis-4-(piperazin-1-ylmethyl)cyclohexyl]benzyl}propan-1-amine
20

At room temperature, to a solution of tert-butyl 4-{{[cis-4-(4-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methyl}piperazine
25 -1-carboxylate (390 mg, 0.51 mmol) in DCM (5 mL) was added 4 mol/L hydrogen chloride/1,4-dioxane solution (3 mL, 12 mmol). After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was basified
30 by adding aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (320 mg, 0.49 mmol, yield 94%).

35 [0599]

<Example AI8> tert-Butyl 3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

Using tert-butyl 4-amino-3-(methylamino)benzoate (Bioorg. Med. Chem. Lett., 2002, 12, 3129.), the title compound was
5 obtained by the same method as in <Example AN2>.

[0600]

<Example AI9> tert-Butyl 1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

Under ice-cooling, to a solution of tert-butyl 3-methyl-
10 2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (260 mg, 0.46 mmol) in THF (5 mL) was added sodium hydride (55% oil, 50 mg, 1.15 mmol), and the mixture was stirred for 30 min. Then, 3-bromopiperidine-2,6-dione (CAS Registry Number: 62595-74-8) (200 mg, 1.04 mmol) was added thereto, and the mixture was
15 stirred at 60°C for 1.5 hr. After cooling, to the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue
20 was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (165 mg, 0.46 mmol, yield 44%).

[0601]

<Example AI10> 1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-
25 dihydro-1H-benzimidazole-5-carboxylic acid

At room temperature, to a solution of tert-butyl 1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (165 mg, 0.46 mmol) in DCM (3 mL) was added trifluoroacetic acid (3 mL), and the mixture was
30 stirred for 2 hr. The reaction mixture was concentrated under reduced pressure to give a crude crystal, and the crystal was washed with a small amount of chloroform/ethyl acetate to give the title compound (74 mg, 0.24 mmol, yield 53%).

[0602]

35 <Example AI11> 3-{5-[4-{[Cis-4-(4-{[2-(4R)-4-(4-

methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

At room temperature, to a solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{4-[cis-4-(piperazin-1-ylmethyl)cyclohexyl]benzyl}propan-1-amine (45 mg, 0.066 mmol) and 1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (20 mg, 0.066 mmol) in DMF (2 mL) was added 3H-1,2,3-triazolo[4,5-b]pyridin-3-ol (CAS Registry Number: 39968-33-7) (10 mg, 0.066 mmol), and dissolved. Then, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (CAS Registry Number: 25952-53-8) (25 mg, 0.099 mmol) was added thereto, and the mixture was stirred for 15 hr. The reaction mixture was diluted with chloroform, and washed successively with water and saturated brine. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (55 mg, 0.058 mmol, yield 88%).

[0603]

<Example AJ1> Ethyl trans-4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenyl)cyclohexanecarboxylate

Using the compounds obtained in <Example M3> and <Example AI2>, the title compound was obtained by the same method as in <Example W4>.

[0604]

<Example AJ2> [Trans-4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methanol

Using the compound obtained in <Example AJ1>, the title

compound was obtained by the same method as in <Example W5>.
[0605]

<Example AJ3> Trans-4-(4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-
5 dimethylpropyl)amino]methyl}phenyl)cyclohexanecarbaldehyde

Using the compound obtained in <Example AJ2>, the title
compound was obtained by the same method as in <Example AI5>.
[0606]

<Example AJ4> tert-Butyl 4-{[trans-4-(4-{[2-[(4R)-4-(4-
10 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methyl}piperazine
-1-carboxylate

Using the compound obtained in <Example AJ3> and 1-(tert-
15 butoxycarbonyl)piperazine (CAS Registry Number: 57260-71-6),
the title compound was obtained by the same method as in
<Example W4>.

[0607]

<Example AJ5> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-
20 2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{4-
[trans-4-(piperazin-1-ylmethyl)cyclohexyl]benzyl}propan-1-amine

Using the compound obtained in <Example AJ4>, the title
compound was obtained by the same method as in <Example AI7>.
[0608]

<Example AJ6> 3-{5-[(4-{[Trans-4-(4-{[2-[(4R)-4-(4-
25 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}phenyl)cyclohexyl]methyl}piperazin-
1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-
30 yl}piperidine-2,6-dione

Using the compounds obtained in <Example AJ5> and
<Example AI10>, the title compound was obtained by the same
method as in <Example AI11>.

[0609]

35 <Example AK1> tert-Butyl 7-amino-8-bromo-3,4-

dihydroisoquinoline-2(1H)-carboxylate

A solution of tert-butyl 7-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (CAS Registry Number: 171049-41-5) (1.13 g, 4.55 mmol) in acetonitrile (50 mL) was cooled to 0°C, N-bromosuccinimide (0.83 g, 4.66 mmol) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.43 g, 4.37 mmol, yield 96%).

[0610]

<Example AK2> tert-Butyl 8-bromo-7-[(methylcarbamoyl)amino]-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of tert-butyl 7-amino-8-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.8 g, 5.5 mmol) in DCM (28 mL) was added DIPEA (3.8 mL, 22 mmol), N-methylcarbamoyl chloride (CAS Registry Number: 6452-47-7) (1.5 g, 17 mmol) was added at 0°C, and the mixture was stirred at room temperature for 17 hr. To the reaction mixture were added N-methylcarbamoyl chloride (1.0 g, 11 mmol) and DIPEA (1.9 mL, 11 mmol), and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (1.86 g, 4.84 mmol, yield 88%).

[0611]

<Example AK3> tert-Butyl 1-methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-h]isoquinoline-8-carboxylate

To a solution of tert-butyl 8-bromo-7-[(methylcarbamoyl)amino]-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.57 g, 4.09 mmol) in DMSO (41 mL) were added copper(I) iodide (160 mg, 0.817 mmol), trans-4-hydroxy-L-proline (230 mg, 1.75 mmol), and tripotassium phosphate (1.73 g, 8.17 mmol) at room temperature, and the mixture was stirred at 160°C for 5 hr. The reaction mixture was cooled to room

temperature, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The
5 residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (540 mg, 1.78 mmol, yield 44%).

[0612]

<Example AK4> tert-Butyl 3-[2,6-bis(benzyloxy)pyridin-3-yl]-1-
10 methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-h]isoquinoline-8-carboxylate

To a suspension of tert-butyl 1-methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-h]isoquinoline-8-carboxylate (540 mg, 1.78 mmol), 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-
15 dioxaborolan-2-yl)pyridine (WO2021262812 A1) (1.11 g, 2.66 mmol), and copper(II) acetate (644 mg, 3.56 mmol) in acetonitrile (3.6 mL) was added triethylamine (0.74 mL, 5.34 mmol), and the mixture was stirred at 80°C for 10 hr. The reaction mixture was purified by silica gel column
20 chromatography (hexane/ethyl acetate) to give the title compound (1.0 g, 1.7 mmol, yield 95%).

[0613]

<Example AK5> tert-Butyl 3-(2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-h]isoquinoline-8-
25 carboxylate

To a solution of tert-butyl 3-[2,6-bis(benzyloxy)pyridin-3-yl]-1-methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-h]isoquinoline-8-carboxylate (1.0 g, 1.7 mmol) in ethyl acetate (16 mL)-ethanol (16 mL) was added ASCA-2 (manufactured by N.E.
30 Chemcat Corporation) (670 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 6 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl
35 acetate, ethyl acetate/methanol) to give the title compound

(380 mg, 0.92 mmol, yield 54%).

[0614]

<Example AK6> tert-Butyl 2-(4-formylphenoxy)-7-azaspiro[3.5]nonane-7-carboxylate

5 A suspension of tert-butyl 2-[(methylsulfonyl)oxy]-7-azaspiro[3.5]nonane-7-carboxylate (J. Med. Chem., 2014, 57, 3, 733.) (7.02 g, 22.0 mmol), 4-hydroxybenzaldehyde (CAS: 123-08-0) (2.66 g, 21.8 mmol), and cesium carbonate (13.8 g, 42.4 mmol) in DMF (45 mL) was stirred at 100°C for 4 hr. The
10 reaction mixture was cooled to room temperature and diluted with ethyl acetate (150 mL). The mixture was washed successively with water (150 mL) and saturated brine (100 mL), dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified
15 by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (6.63 g, 19.2 mmol, yield 87%).

[0615]

<Example AK7> tert-Butyl [2-(4-formylphenoxy)-7-azaspiro[3.5]nonan-7-yl]acetate

20 To a solution of tert-butyl 2-(4-formylphenoxy)-7-azaspiro[3.5]nonane-7-carboxylate (6.63 g, 19.2 mmol) in DCM (50 mL) was added 4 mol/L hydrogen chloride/1,4-dioxane solution (50 mL, 200 mmol), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated
25 under reduced pressure. After drying, to a suspension of the residue and potassium carbonate (12.4 g, 89.7 mmol) in DMF (40 mL) was added tert-butyl bromoacetate (3.22 mL, 22.0 mmol), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate (100 mL), and
30 washed successively with water (100 mL) and saturated brine (100 mL). The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
35 compound (6.57 g, 18.3 mmol, yield 92%).

[0616]

<Example AK8> tert-Butyl [2-(4-{{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-
5 7-yl]acetate

Using the compounds obtained in <Example M3> and <Example
AK7>, the title compound was obtained by the same method as in
<Example W4>.

[0617]

10 <Example AK9> [2-(4-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-
yl]acetic acid dihydrochloride

Using the compound obtained in <Example AK8>, the title
15 compound was obtained by the same method as in <Example V5>.

[0618]

<Example AK10> 3-(8-{{2-(4-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-
20 yl]acetyl}-1-methyl-2-oxo-1,2,6,7,8,9-hexahydro-3H-imidazo[4,5-
h]isoquinolin-3-yl)piperidine-2,6-dione

To a solution of tert-butyl 3-(2,6-dioxopiperidin-3-yl)-
1-methyl-2-oxo-1,2,3,6,7,9-hexahydro-8H-imidazo[4,5-
h]isoquinoline-8-carboxylate (21.4 mg, 0.0516 mmol) in DCM (1
25 mL) was added trifluoroacetic acid (0.5 mL) at room
temperature, and the mixture was stirred at room temperature
for 2 hr. The reaction mixture was concentrated under reduced
pressure, and the obtained residue was diluted with ethanol (2
mL) and THF (2 mL). Then, [2-(4-{{2-[(4R)-4-(4-
30 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-
yl]acetic acid dihydrochloride (36.0 mg, 0.0483 mmol), DIPEA
(0.100 mL, 0.584 mmol), and 4-(4,6-dimethoxy-1,3,5-triazin-2-
35 yl)-4-methylmorpholinium chloride (CAS Registry Number: 3945-

69-5) (30.0 mg, 0.0794 mmol) were added thereto, and the mixture was stirred at room temperature for 19 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by amine-modified silica gel column chromatography (ethyl acetate/methanol) to give the title compound (27.9 mg, 0.0287 mmol, yield 60%).

10 [0619]

<Example AL1> tert-Butyl 5-amino-4,6-dibromo-1,3-dihydro-2H-isoindole-2-carboxylate

tert-Butyl 5-amino-1,3-dihydro-2H-isoindole-2-carboxylate (CAS Registry Number: 264916-06-5) (200 mg, 0.85 mmol) was dissolved in a mixed solvent of DCM (12 mL)-methanol (6 mL), calcium carbonate (230 mg, 2.30 mmol) and benzyltrimethylammonium tribromide (700 mg, 1.80 mmol) were added at room temperature, and the mixture was stirred for 30 min. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (340 mg, 0.87 mmol, yield: quantitative).

[0620]

25 <Example AL2> tert-Butyl 5-amino-4-bromo-1,3-dihydro-2H-isoindole-2-carboxylate

To a mixture of tert-butyl 5-amino-4,6-dibromo-1,3-dihydro-2H-isoindole-2-carboxylate (33 mg, 0.084 mmol), palladium(II) acetate (2.1 mg, 0.0094 mmol), and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (5.1 mg, 0.084 mmol) was added THF (1 mL), and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added N,N'-dimethylethylenediamine (0.020 mL, 0.019 mmol), and the mixture was stirred for 10 min. Then, sodium borohydride (4.0 mg, 0.11 mmol) was added thereto, and the mixture was stirred

at room temperature for 17 hr. To the reaction mixture was added a small amount of methanol, and the mixture was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.022 g, 0.070 mmol, yield 83%).

5 [0621]

<Example AL3> tert-Butyl 3-(2,6-dioxopiperidin-3-yl)-1-methyl-2-oxo-2,3,6,8-tetrahydroimidazo[4,5-e]isoindole-7(1H)-carboxylate

Using the compound obtained in <Example AL2>, the title
10 compound was obtained by sequentially performing the same operations as in <Example AK2>, <Example AK3>, <Example AK4> and <Example AK5>.

[0622]

<Example AL4> 3-[7-{[2-(4-{[2-(4R)-4-(4-Methoxyphenyl)-2,2-
15 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetyl}-1-methyl-2-oxo-1,6,7,8-tetrahydroimidazo[4,5-e]isoindole-3(2H)-yl]piperidine-2,6-dione

Using the compound obtained in <Example AL3>, the title
20 compound was obtained by the same method as in <Example AK10>.

[0623]

<Example AM1> 4-[(4R)-2,2-Dimethyl-4-{2-[(3,3,3-trifluoro-2,2-dimethylpropyl)amino]ethyl}tetrahydro-2H-pyran-4-yl]phenol

A suspension of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine (2.00 g, 5.16 mmol) and sodium
25 thiomethoxide (1.16 g, 16.6 mmol) in DMF (10 mL) was stirred under microwave irradiation at 150°C for 1 hr. The reaction mixture was diluted with ethyl acetate, and washed successively
30 with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (1.97 g, 5.27 mmol, yield: quantitative).

35 [0624]

<Example AM2> tert-Butyl {2-[(4R)-4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)carbamate

To a solution of 4-[(4R)-2,2-dimethyl-4-{2-[(3,3,3-trifluoro-2,2-dimethylpropyl)amino]ethyl}tetrahydro-2H-pyran-4-yl]phenol (1.97 g, 5.27 mmol) and triethylamine (2 mL, 14 mmol) in THF (25 mL) was added di-tert-butyl dicarbonate (1.79 g, 8.20 mmol), and the mixture was stirred at room temperature for 4.5 hr. The reaction mixture was concentrated under reduced
10 pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.92 g, 4.05 mmol, yield 77%).

[0625]

<Example AM3> tert-Butyl (2-{(4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)carbamate

To a solution of tert-butyl {2-[(4R)-4-(4-hydroxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)carbamate (443 mg, 0.935 mmol) in
20 acetonitrile (5 mL)-water (1 mL) were successively added, under ice-cooling, 50% aqueous potassium hydroxide solution (0.348 mL, 4.68 mmol) and diethyl (bromodifluoromethyl)phosphonate (CAS Registry Number: 65094-22-6) (0.250 mL, 1.40 mmol), and the mixture was stirred at said temperature for 40 min. The
25 reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl
30 acetate) to give the title compound (356 mg, 0.680 mmol, yield 73%).

[0626]

<Example AM4> N-(2-{(4R)-4-[4-(Difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl)-3,3,3-trifluoro-2,2-dimethylpropan-1-amine

To a solution of tert-butyl (2-((4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethyl) (3,3,3-trifluoro-2,2-dimethylpropyl)carbamate (426 mg, 0.812 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.5 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (297 mg, 0.701 mmol, yield 86%).

[0627]

<Example AM5> Ethyl 4'-{[(2-((4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethyl) (3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example AG1> and <Example AM4>, the title compound was obtained by the same method as in <Example W4>.

[0628]

<Example AM6> tert-Butyl 4-[(4'-{[(2-((4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethyl) (3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazine-1-carboxylate

Using the compound obtained in <Example AM5>, the title compound was obtained by sequentially performing the same operations as in <Example AG3>, <Example X1> and <Example X2>.

[0629]

<Example AM7> 3-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

A solution of 6-bromo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (CAS Registry Number: 305790-48-1) (23.8 g,

105 mmol), 3-bromo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (68.3 g, 212 mmol), and cesium carbonate (102 g, 313 mmol) in DMF (300 mL) was stirred at room temperature for 45 hr. The reaction mixture was diluted with ethyl acetate (600 mL), and washed with water (600 mL). The aqueous layer was extracted with ethyl acetate, and the organic layers were combined and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate), and the obtained solid was washed with hexane to give the title compound (32.7 g, 69.8 mmol, yield 67%).

[0630]

15 <Example AM8> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

To a mixture of 3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (1.13 g, 2.41 mmol), 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) (816 mg, 3.62 mmol), palladium(II) acetate (27.1 mg, 0.121 mmol), and XantPhos (140 mg, 0.241 mmol) were added toluene (24.0 mL) and triethylamine (0.592 mL, 4.27 mmol) at room temperature, and the mixture was stirred under a carbon monoxide atmosphere at 100°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.48 g, 2.27 mmol, yield 94%).

[0631]

<Example AM9> 3-[5-([4-([4'-([2-((4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl)-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-

yl}carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-
1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

To a solution of tert-butyl 4-[(4'-{[(2-{(4R)-4-[4-(difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazine-1-carboxylate (51.3 mg, 0.0648 mmol) in DCM (0.5 mL) was added 4 mol/L hydrogen chloride/1,4-dioxane solution (0.5 mL, 2 mmol), and the mixture was stirred at room temperature for 2 hr and
10 concentrated under reduced pressure. To the residue were added 2,4,6-trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (45.8 mg, 0.0747 mmol), 4-dimethylaminopyridine (2.1 mg, 0.017 mmol),
15 acetonitrile (1 mL), and DIPEA (0.0564 mL, 0.324 mmol), and the mixture was stirred at room temperature for 22 hr. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and
20 the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (68.0 mg, 0.0614 mmol, yield 95%).

[0632]

25 <Example AM10> 3-[5-({4-[(4'-{[(2-{(4R)-4-[4-(Difluoromethoxy)phenyl]-2,2-dimethyltetrahydro-2H-pyran-4-yl}ethyl)(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl}carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione
30

Using the compound obtained in <Example AM9>, the title compound was obtained by the same method as in <Example BK9>.

[0633]

<Example AN1> 1,2,3,4-Tetrahydroquinoxalin-5-amine

35 To a solution of 5-aminoquinoxaline (CAS Registry Number:

16566-20-4) (450 mg, 3.10 mmol) in THF (15 mL) was added borane-THF complex (1 mol/L THF solution, 7.5 mL, 7.5 mmol) at room temperature, and the mixture was stirred for 15 min. To the reaction mixture was added methanol (15 mL), and the
5 mixture was stirred at room temperature for 2 hr and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (414 mg, 2.77 mmol, yield 90%).

[0634]

10 <Example AN2> 5,6-Dihydro-4H-imidazo[1,5,4-de]quinoxalin-2(1H)-one

A solution of 1,2,3,4-tetrahydroquinoxalin-5-amine (414 mg, 2.77 mmol) in THF (10 mL) was cooled to 0°C, 1,1'-carbonyldiimidazole (550 mg, 3.39 mmol) was added and the
15 mixture was stirred at room temperature for 17 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (403 mg, 2.30 mmol, yield 83%).

20 [0635]

<Example AN3> 6-{[2-(4-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetyl}-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxaline-2(1H)-
25 one

Using the compounds obtained in <Example AK9> and <Example AN2>, the title compound was obtained by the same method as in <Example BM9>.

[0636]

30 <Example AN4> 3-[6-{[2-(4-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetyl}-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-
35 dione

Using the compound obtained in <Example AN3>, the title compound was obtained by the same method as in <Example Z5>. [0637]

<Example AN5> 3-[6-{[2-(4-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetyl}-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione

Using the compound obtained in <Example AN4>, the title compound was obtained by the same method as in <Example BK9>. [0638]

<Example A01> Benzyl 4-{[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]amino}-3-nitrobenzoate

A suspension of tert-butyl D- α -glutamate monohydrochloride (CAS Registry Number: 66575-26-6) (460 mg, 1.93 mmol), benzyl 4-fluoro-3-nitrobenzoate (Org. Lett., 2016, 18, 3706.) (633 mg, 2.30 mmol), and potassium carbonate (814 mg, 5.89 mmol) in DMF (4 mL) was stirred at room temperature for 5 hr. The reaction mixture was diluted with ethyl acetate and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (368 mg, 0.804 mmol, yield 42%).

[0639]

<Example A02> Benzyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

To a solution of benzyl 4-{[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]amino}-3-nitrobenzoate (317 mg, 0.693 mmol) in acetone (5 mL)-water (1 mL) were added ammonium chloride (369 mg, 6.90 mmol) and zinc powder (426 mg, 6.52 mmol), and the mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with ethyl acetate,

insoluble materials were filtered off through celite, washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (7 mL), 1,1'-carbonyldiimidazole (186 mg, 1.15 mmol) was added, and the mixture was stirred at room temperature for 5 hr. To the reaction mixture was added 1,1'-carbonyldiimidazole (117 mg, 0.722 mmol), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added 1,1'-carbonyldiimidazole (66.5 mg, 0.410 mmol), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with methanol and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (226 mg, 0.498 mmol, yield 72%).

[0640]

<Example A03> Benzyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

To a suspension of benzyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (226 mg, 0.498 mmol) and potassium carbonate (205 mg, 1.48 mmol) in DMF (1 mL) was added iodomethane (0.062 mL, 1.0 mmol), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure and further dried under reduced pressure to give the title compound (207 mg, 0.443 mmol, yield 89%).

[0641]

<Example A04> 1-[(2R)-1-Amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid

A suspension of benzyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-

5-carboxylate (195 mg, 0.417 mmol), and 10% palladium carbon (223 mg) in ethyl acetate (2 mL)-ethanol (2 mL) was stirred under a hydrogen atmosphere at room temperature for 2 hr. The reaction mixture was diluted with chloroform, insoluble materials were filtered off through celite, and the filtrate was concentrated under reduced pressure to give the title compound (150 mg, 0.397 mmol, yield 95%).

[0642]

<Example A05> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-[[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride

To a solution of tert-butyl 4-[[(4R)-4'-[[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazine-1-carboxylate (13.8 g, 18.3 mmol) in DCM (50 mL) was added 4 mol/L hydrogen chloride/1,4-dioxane solution (50 mL, 200 mmol), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, the precipitated solid was washed with diethyl ether, and dried under reduced pressure at 60°C to give the title compound (13.8 g, 18.9 mmol, yield: quantitative).

[0643]

<Example A06> tert-Butyl (4R)-5-amino-4-{5-[(4-[[(4R)-4'-[[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-5-oxopentanoate

3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-[[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride (0.15 g, 0.21 mmol), 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-

oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.075 g, 0.20 mmol), and DIPEA (0.17 mL, 1.0 mmol) were dissolved in DMF (1.0 mL), HATU (0.11 g, 0.29 mmol) was added, and the mixture was stirred at room temperature for 20 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (0.17 g, 0.16 mmol, yield 83%).

[0644]

<Example A07> (3R)-3-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione
tert-Butyl (4R)-5-amino-4-{5-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-5-oxopentanoic acid (0.167 g, 0.164 mmol) were dissolved in acetonitrile (2.0 mL), benzenesulfonic acid (0.0552 g, 0.349 mmol) was added, and the mixture was stirred with heating at 90°C for 7 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (0.104 g, 0.110 mmol, yield 67%).

[0645]

<Example AP1> Benzyl 4-{[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]amino}-3-nitrobenzoate

A suspension of tert-butyl L- α -glutamate
5 monohydrochloride (CAS Registry Number: 108607-02-9) (280 mg, 1.17 mmol), benzyl 4-fluoro-3-nitrobenzoate (Org. Lett., 2016, 18, 3706.) (433 mg, 1.57 mmol), and potassium carbonate (482 mg, 3.49 mmol) in DMF (2 mL) was stirred at room temperature for 4.5 hr. The reaction mixture was diluted with ethyl
10 acetate, and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
15 compound (299 mg, 0.654 mmol, yield 56%).

[0646]

<Example AP2> Benzyl 1-[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

20 To a solution of benzyl 4-{[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]amino}-3-nitrobenzoate (1.09 g, 2.38 mmol) in acetone (15 mL)-water (3 mL) were added ammonium chloride (1.10 g, 20.6 mmol) and zinc powder (1.36 g, 20.8 mmol), and the mixture was stirred at room temperature for 5 min. The
25 reaction mixture was diluted with ethyl acetate, insoluble materials were filtered off through celite, and the filtrate was washed with saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved
30 in THF (24 mL), 1,1'-carbonyldiimidazole (580 mg, 3.58 mmol) was added, and the mixture was stirred at room temperature for 5 hr. To the reaction mixture was added 1,1'-carbonyldiimidazole (366 mg, 2.26 mmol), and the mixture was stirred for 1.5 hr. To the reaction mixture was added 1,1'-
35 carbonyldiimidazole (222 mg, 1.37 mmol), and the mixture was

stirred for 1.5 hr. The reaction mixture was diluted with methanol, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (839 mg, 1.85 mmol, yield 78%).

5 [0647]

<Example AP3> Benzyl 1-[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate

To a suspension of benzyl 1-[(2S)-1-amino-5-tert-butoxy-
10 1,5-dioxopentan-2-yl]-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (839 mg, 1.85 mmol) and potassium carbonate (757 mg, 5.48 mmol) in DMF (4 mL) was added iodomethane (0.230 mL, 3.69 mmol), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with ethyl acetate, and
15 washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure and successively dried under reduced pressure to give the title compound (783 mg, 1.67 mmol, yield 91%).

20 [0648]

<Example AP4> 1-[(2S)-1-Amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid

To a suspension of benzyl 1-[(2S)-1-amino-5-tert-butoxy-
25 1,5-dioxopentan-2-yl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (780 mg, 1.67 mmol) in ethyl acetate (8 mL)-ethanol (8 mL) was added 10% palladium carbon (859 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hr. The reaction mixture
30 was diluted with chloroform, and insoluble materials were filtered off through celite. The filtrate was concentrated under reduced pressure, and successively dried under reduced pressure to give the title compound (647 mg, 1.71 mmol, yield: quantitative).

35 [0649]

<Example AP5> tert-Butyl (4S)-5-amino-4-{5-[(4-{ [(4R)-4'-{ [{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-
5 yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-
5-oxopentanoate

3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{ [(4'R)-
4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-
10 yl)methyl}propan-1-amine dihydrochloride (0.155 g, 0.213 mmol),
1-[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-3-methyl-2-
oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid (0.0761 g,
0.202 mmol), and DIPEA (0.173 mL, 1.01 mmol) were dissolved in
DMF (1.0 mL), HATU (0.116 g, 0.304 mmol) was added, and the
15 mixture was stirred at room temperature for 19 hr. To the
reaction mixture was added saturated aqueous sodium hydrogen
carbonate solution, and the mixture was extracted with
hexane/ethyl acetate. The organic layer was washed
successively with water and saturated brine, dried over sodium
20 sulfate and filtered, and the filtrate was concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (DCM/methanol) to give the title compound
(0.164 g, 0.161 mmol, yield 80%).

[0650]

25 <Example AP6> (3S)-3-{5-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-
Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-
yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-
30 yl}piperidine-2,6-dione

tert-Butyl (4S)-5-amino-4-{5-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-
(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-
35 yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-

5-oxopentanoate (0.164 g, 0.161 mmol) was dissolved in acetonitrile (2.0 mL), benzenesulfonic acid (0.0536 g, 0.339 mmol) was added, and the mixture was stirred with heating at 90°C for 24 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) to give the title compound (0.105 g, 0.112 mmol, yield 69%).

[0651]

<Example AQ1> N-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-2-[2-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)-7-azaspiro[3.5]nonan-7-yl]acetamide

Using the compound obtained in <Example AK9> and 5-amino-2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione (CAS Registry Number: 191732-76-0), the title compound was obtained by the same method as in <Example BM9>.

[0652]

<Example AR1> N-{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-1-(trifluoromethyl)cyclobutanecarboxamide

Using the compound obtained in <Example M1> and 1-(trifluoromethyl)cyclobutanecarboxylic acid (CAS Registry Number: 277756-45-3), the title compound was obtained by the same method as in <Example M2>.

[0653]

<Example AR2> 2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]-N-{{1-(trifluoromethyl)cyclobutyl}methyl}ethanamine

Using the compound obtained in <Example AR1>, the title

compound was obtained by the same method as in <Example M3>.

[0654]

<Example AR3> Ethyl 4'-[({2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}{[1-

5 (trifluoromethyl)cyclobutyl)methyl}amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example AR2> and <Example AG1>, the title compound was obtained by the same method as in <Example W4>.

10 [0655]

<Example AR4> tert-Butyl 4-({4'-[({2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}{[1-(trifluoromethyl)cyclobutyl)methyl}amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl)piperazine-1-carboxylate

15 Using the compound obtained in <Example AR3>, the title compound was obtained by sequentially performing the same operations as in <Example AG3>, <Example X1> and <Example X2>.

[0656]

<Example AR5> 2-[(4R)-4-(4-Methoxyphenyl)-2,2-

20 dimethyltetrahydro-2H-pyran-4-yl]-N-{[4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl)methyl}-N-{[1-(trifluoromethyl)cyclobutyl)methyl}ethanamine dihydrochloride

Using the compound obtained in <Example AR4>, the title compound was obtained by the same method as in <Example A05>.

25 [0657]

<Example AR6> 3-(5-{[4-({4'-[({2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}{[1-

(trifluoromethyl)cyclobutyl)methyl}amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl)piperazin-1-yl]carbonyl}-3-

30 methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compounds obtained in <Example AR5> and <Example AM8>, the title compound was obtained by the same method as in <Example BI1>.

35 [0658]

<Example AR7> 3-(5-{[4-({4'-[({2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}){[1-(trifluoromethyl)cyclobutyl)methyl]amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl)piperazin-1-yl}carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione

Using the compound obtained in <Example AR6>, the title compound was obtained by the same method as in <Example BK9>. [0659]

10 <Example AS1> 1-(2,6-Dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde

A suspension of 3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (5.71 g, 12.2 mmol), triethylsilane (4.0 mL, 25 mmol), triethylamine (5.0 mL, 36 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.37 g, 1.87 mmol) in DMF (60 mL) was stirred under a carbon monoxide atmosphere at 95°C for 7 hr. The reaction mixture was diluted with ethyl acetate, and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (2.12 g, 5.08 mmol, yield 42%).

[0660]

<Example AS2> Benzyl 4-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)methyl]piperazine-1-carboxylate

To a solution of 1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde (1.36 g, 3.26 mmol), 1-carbobenzoxypiperazine (CAS Registry Number: 31166-44-

6) (0.811 mL, 4.23 mmol), and acetic acid (0.559 mL, 9.76 mmol) in DCM (15 mL) was added sodium triacetoxyborohydride (1.48 g, 6.98 mmol), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (1.64 g, 2.64 mmol, yield 81%).

[0661]

<Example AS3> Benzyl 4-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]methyl}piperazine-1-carboxylate

Using the compound obtained in <Example AS2>, the title compound was obtained by the same method as in <Example BK9>.

[0662]

<Example AS4> 3-[3-Methyl-2-oxo-5-(piperazin-1-ylmethyl)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

To a solution of benzyl 4-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]methyl}piperazine-1-carboxylate (917 mg, 1.87 mmol) in ethyl acetate (20 mL) was added 10% palladium carbon (2.33 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1.5 hr. The reaction mixture was purged with nitrogen, diluted with 10% IPA/chloroform (30 mL) and IPA (4 mL), and insoluble materials were filtered off through celite, and washed with 33% IPA/chloroform. The filtrate and washing were combined, and concentrated under reduced pressure. The precipitated solid was washed with ethyl acetate to give the title compound (317 mg, 0.887 mmol, yield 48%).

[0663]

<Example AS5> Ethyl 4'-formyl-2'-methyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1) and 4-bromo-3-methylbenzaldehyde (CAS Registry Number: 78775-11-8), the title compound was obtained by the same method as in <Example W1>.

5 [0664]

<Example AS6> Ethyl 4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2'-methyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

10 Using the compounds obtained in <Example M3> and <Example AS5>, the title compound was obtained by the same method as in <Example W4>.

[0665]

<Example AS7> 3-[5-({4-[(4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2'-methyl-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

20 Using the compounds obtained in <Example AS6> and <Example AS4>, the title compound was obtained by the same method as in <Example AU2>.

[0666]

<Example AT1> Ethyl 3'-fluoro-4'-formyl-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

25 Using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1) and 4-bromo-2-fluorobenzaldehyde (CAS Registry Number: 57848-46-1), the title compound was obtained by the same method as in <Example W1>.

[0667]

<Example AT2> Ethyl 3'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example AT1>, the title compound was obtained by the same method as in <Example W4>.

[0668]

5 <Example AT3> 3-[5-({4-[(3'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

Using the compounds obtained in <Example AT2> and <Example AS4>, the title compound was obtained by the same method as in <Example AU2>.

[0669]

15 <Example AU1> Ethyl 2',6'-difluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using 4-bromo-3,5-difluorobenzaldehyde (CAS Registry
20 Number: 135564-22-6) and ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1), the title compound was obtained by sequentially performing the same operations as in <Example W1> and <Example W4>.

25 [0670]

<Example AU2> tert-Butyl 4-[(2',6'-difluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazine-1-carboxylate

Ethyl 2',6'-difluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate (0.124 g, 0.186 mmol) was dissolved in a mixed
35 solvent of THF (0.60 mL)-ethanol (0.60 mL), 1 mol/L aqueous

sodium hydroxide solution (0.60 mL, 0.60 mmol) was added, and the mixture was stirred at room temperature for 22.5 hr. To the reaction mixture were added 1 mol/L hydrochloric acid (0.60 mL, 0.60 mmol) and water, and the mixture was extracted with
 5 ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (2 mL), DIPEA (0.109 mL, 0.637 mmol), HATU (0.113 g, 0.298 mmol), and 1-(tert-butoxycarbonyl)piperazine (CAS Registry Number: 57260-71-
 10 6) (0.060 g, 0.322 mmol) were added, and the mixture was stirred at room temperature for 22 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the
 15 filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.149 g, 0.185 mmol, yield 99%).

[0671]

20 <Example AU3> 3-[5-({4-[(2',6'-Difluoro-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]-1-
 25 {[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione
 tert-Butyl 4-[(2',6'-difluoro-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazine-1-
 30 carboxylate (0.149 g, 0.185 mmol) was dissolved in DCM (1 mL), trifluoroacetic acid (0.5 mL) was added, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with DCM. The organic layer was
 35 dried over sodium sulfate and filtered, and the filtrate was

concentrated under reduced pressure. To the residue were added 1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde (0.091 g, 0.218 mmol), DCM (1 mL), acetic acid (0.032 mL, 0.56 mmol), and sodium triacetoxyborohydride (0.092 g, 0.43 mmol), and the mixture was stirred at room temperature for 1.5 hr. To the reaction mixture was added 1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde (0.020 g, 0.048 mmol), and the mixture was stirred at room temperature for 6 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (0.146 g, 0.132 mmol, yield 71%).

[0672]

15 <Example AU4> 3-[5-({4-[(2',6'-Difluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

Using the compound obtained in <Example AU3>, the title compound was obtained by the same method as in <Example BK9>.

[0673]

<Example AV1> Ethyl 2',3'-difluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1) and 4-bromo-2,3-difluorobenzaldehyde (CAS Registry Number: 644985-24-0), the title compound was obtained by sequentially performing the same operations as in <Example W1> and <Example W4>.

[0674]

35 <Example AV2> 3-[5-({4-[(2',3'-Difluoro-4'-{[2-[(4R)-4-(4-

methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl)-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

Using the compound obtained in <Example AV1>, the title compound was obtained by sequentially performing the same operations as in <Example AU2>, <Example AU3> and <Example BK9>.

10 [0675]

<Example AW1> 7-Iodo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-2(1H)-one

Under ice-cooling, to a solution of 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-2(1H)-one (CAS Registry Number: 4024-28-6) (3.80 g, 22.1 mmol) in DMF (150 mL) was added N-iodosuccinimide (5.5 g, 24 mmol), and the mixture was stirred at 40°C for 10 hr. N-Iodosuccinimide (2.5 g, 11 mmol) was added, and the mixture was further stirred for 5 hr. The reaction mixture was added to water, and the precipitated solid was collected by filtration, washed with water, and dried to give the title compound (5.49 g, 18.3 mmol, yield 82%).

[0676]

<Example AW2> 3-(7-Iodo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

At room temperature, to a solution of 7-iodo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline-2(1H)-one (5.0 g, 17 mmol) and 3-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione (11 g, 34 mmol) in DMF (80 mL) was added cesium carbonate (11 g, 34 mmol), and the mixture was stirred with heating at 50°C for 6 hr. After cooling, the reaction mixture was diluted with ethyl acetate, washed successively with an aqueous citric acid solution and saturated brine. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified

by amine-modified silica gel column chromatography (hexane/ethyl acetate) to give the title compound (5.1 g, 9.4 mmol, yield 57%).

[0677]

5 <Example AW3> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate

At room temperature, to a solution of 3-(7-iodo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (2.2 g, 4.1 mmol) in toluene (30 mL) were added 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) (1.4 g, 6.1 mmol) and XantPhos (250 mg, 0.41 mmol), and then palladium(II) acetate (50 mg, 0.20 mmol) and triethylamine (1.0 mL, 7.2 mmol) were added, and the mixture was stirred under heating under a carbon monoxide atmosphere at 100°C for 3 hr. After cooling, the reaction mixture was diluted with ethyl acetate, insoluble materials were filtered off through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.9 g, 3.1 mmol, yield 75%).

[0678]

<Example AW4> 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

At room temperature, to a suspension of 2,4,6-trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate (407 mg, 0.637 mmol) and 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-

2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-
{[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-
tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride
(527 mg, 0.724 mmol) in acetonitrile (5 mL) were added 4-
5 dimethylaminopyridine (25 mg, 0.19 mmol) and DIPEA (0.8 mL, 3.8
mmol), and the mixture was stirred for 18 hr. Water was added
to the reaction mixture, and the mixture was extracted with
chloroform. The organic layer was washed with saturated brine,
dried over magnesium sulfate and filtered, and the filtrate was
10 concentrated under reduced pressure. The residue was purified
by silica gel column chromatography (chloroform/methanol) to
give the title compound (654 mg, 0.596 mmol, yield 94%).

[0679]

<Example AW5> 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-
15 Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-
yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-
1(2H)-yl}piperidine-2,6-dione

20 At room temperature, to a solution of 3-{7-[(4-{[(4R)-4'-
{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-
4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-
yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-
25 1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-
dione (651 mg, 0.594 mmol) in DCM (2 mL) was added
trifluoroacetic acid (0.5 mL), and the mixture was stirred for
1 hr. The reaction mixture was concentrated under reduced
pressure, and the residue was neutralized by adding aqueous
30 sodium hydrogen carbonate solution, and extracted with
chloroform. The organic layer was washed with saturated brine,
dried over magnesium sulfate and filtered, and the filtrate was
concentrated under reduced pressure. The residue was dissolved
in ethyl acetate (2 mL), N,N'-dimethylethylenediamine (0.13 mL,
35 1.2 mmol) was added, and the mixture was stirred for 1 hr. The

reaction mixture was diluted with ethyl acetate, was washed successively with water and saturated brine, the organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was
5 purified by silica gel column chromatography (chloroform/methanol) to give the title compound (547 mg, 0.566 mmol, yield 95%).

[0680]

<Example AX1> N-{[4'-(Bromomethyl)-2',3',4',5'-

10 tetrahydro[biphenyl]-4-yl)methyl}-3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine

To a solution of (4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
15 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl methanesulfonate (53.0 mg, 0.0796 mmol) in acetone (1 mL) was added lithium bromide (20.0 mg, 0.230 mmol), and the mixture was stirred at 70°C for 4 hr. To the reaction mixture was added acetone (1 mL), and the mixture was stirred again at
20 70°C for 4 hr, and cooled to room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure, and
25 successively dried under reduced pressure to give the title compound (42.1 mg, 0.0647 mmol, yield 81%).

[0681]

<Example AX2> tert-Butyl 4-[(4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-
30 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]-3-oxopiperazine-1-carboxylate

To a solution of N-{[4'-(bromomethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl)methyl}-3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-
35 2,2-dimethylpropan-1-amine (42.1 mg, 0.0647 mmol) and 1-Boc-3-

oxopiperazine (CAS Registry Number: 76003-29-7) (26.5 mg, 0.132 mmol) in DMF (1 mL) was added sodium hydride (55% oil, 9.0 mg, 0.21 mmol), and the mixture was stirred at room temperature for 20 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The obtained organic layers were combined, washed successively with water and saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (34.8 mg, 0.0452 mmol, yield 70%).

[0682]

<Example AX3> 3-[5-({4-[(4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]-3-oxopiperazin-1-yl)methyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

Using the compound obtained in <Example AX2>, the title compound was obtained by sequentially performing the same operations as in <Example AU3> and <Example BK9>.

[0683]

<Example AY1> 3-(3-Methyl-5-nitro-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using 1-methyl-6-nitro-1,3-dihydro-2H-benzimidazol-2-one (WO2019060693 A1), the title compound was obtained by the same method as in <Example Z5>.

[0684]

<Example AY2> 3-(5-Amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compound obtained in <Example AY1>, the title compound was obtained by the same method as in <Example BK5>.

[0685]

<Example AY3> N-[1-(2,6-Dioxo-1-{[2-

(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]-2-nitrobenzenesulfonamide

Using the compound obtained in <Example AY2>, the title compound was obtained by the same method as in <Example CC1>.

5 [0686]

<Example AY4> tert-Butyl (trans-3-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]}(2-nitrophenyl)sulfonyl]amino}cyclobutyl)carbamate

10 N-[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]-2-nitrobenzenesulfonamide (0.367 g, 0.622 mmol), cis-tert-butyl 3-hydroxycyclobutylcarbamate (CAS Registry Number: 389890-43-1) (0.175 g, 0.934 mmol), and triphenylphosphine (0.245 g, 0.934 mmol) were dissolved in THF (2 mL), diisopropyl azodicarboxylate (0.20 mL, 0.93 mmol) was added at 0°C, and the mixture was stirred at room temperature for 51 hr. To the reaction mixture were added cis-tert-butyl 3-hydroxycyclobutylcarbamate (0.175 g, 0.934 mmol), triphenylphosphine (0.245 g, 0.934 mmol), and diisopropyl azodicarboxylate (0.20 mL, 0.93 mmol) at 0°C, and the mixture was stirred at room temperature for 43 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.366 g, 0.482 mmol, yield 78%).

[0687]

<Example AY5> tert-Butyl (trans-3-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]}amino}cyclobutyl)carbamate
tert-Butyl (trans-3-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]}(2-nitrophenyl)sulfonyl]amino}cyclobutyl)carbamate (0.366 g, 0.482

35

mmol) was dissolved in DMF (2 mL), 4-bromobenzenethiol (0.182 g, 9.65 mmol) and potassium carbonate (0.200 g, 1.45 mmol) were added, and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.164 g, 0.286 mmol, yield 59%).

[0688]

<Example AY6> 3-{5-[(Trans-3-aminocyclobutyl)amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-1-(hydroxymethyl)piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example AY5>, the title compound was obtained by the same method as in <Example AO5>.

[0689]

<Example AY7> 4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid

Using the compound obtained in <Example AG2>, the title compound was obtained by the same method as in <Example Y5>.

[0690]

<Example AY8> N-(Trans-3-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}cyclobutyl)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxamide

Using the compounds obtained in <Example AY6> and <Example AY7>, the title compound was obtained by the same method as in <Example BM9>.

[0691]

<Example AZ1> Methyl 1-[7-(tert-butoxycarbonyl)-7-azaspiro[3.5]nonan-2-yl]-1H-indazole-5-carboxylate

<Example AZ2> Methyl 2-[7-(tert-butoxycarbonyl)-7-azaspiro[3.5]nonan-2-yl]-2H-indazole-5-carboxylate

5 To a suspension of methyl indazole-5-carboxylate (CAS Registry Number: 473416-12-5) (327 mg, 1.86 mmol), and tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (CAS Registry Number: 240401-28-9) (470 mg, 1.95 mmol) in toluene (9 mL) was added cyanomethylenetriethylphosphorane (CAS Registry
10 Number: 157141-27-0) (1.0 mL, 3.8 mmol), and the mixture was stirred at 90°C for 1.5 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give <Example AZ1> (500 mg, 1.25
15 mmol, yield 67%), and <Example AZ2> (235 mg, 0.588 mmol, yield 32%).

[0692]

<Example AZ3> tert-Butyl 2-[5-(hydroxymethyl)-2H-indazol-2-yl]-7-azaspiro[3.5]nonane-7-carboxylate

20 Using the compound obtained in <Example AZ2>, the title compound was obtained by the same method as in <Example W5>.
[0693]

<Example AZ4> tert-Butyl 2-(5-formyl-2H-indazol-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate

25 To a solution of tert-butyl 2-[5-(hydroxymethyl)-2H-indazol-2-yl]-7-azaspiro[3.5]nonane-7-carboxylate (233 mg, 0.627 mmol) in chloroform (6 mL) was added manganese(IV) oxide (291 mg), and the mixture was stirred at room temperature for 22 hr. To the reaction mixture was added manganese(IV) oxide
30 (345 mg), and the mixture was stirred for 5.5 hr. The reaction mixture was diluted with ethyl acetate, insoluble materials were filtered off through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to
35 give the title compound (120 mg, 0.325 mmol, yield 52%).

[0694]

<Example AZ5> tert-Butyl 2-(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2H-indazol-2-yl)-7-

5 azaspiro[3.5]nonane-7-carboxylate

Using the compounds obtained in <Example M3> and <Example AZ4>, the title compound was obtained by the same method as in <Example W4>.

[0695]

10 <Example AZ6> tert-Butyl [2-(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2H-indazol-2-yl)-7-azaspiro[3.5]nonan-7-yl]acetate

To a solution of tert-butyl 2-(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2H-indazol-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate (115 mg, 0.155 mmol) in DCM (1 mL) was added 4 mol/L hydrogen chloride/1,4-dioxane solution (1 mL, 4 mmol), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile (1 mL), potassium carbonate (103 mg, 0.745 mmol) and tert-butyl bromoacetate (CAS Registry Number: 5292-43-3) (0.0341 mL, 0.233 mmol) were added, and the mixture was stirred at room temperature for 20 hr. To the reaction mixture was added DMF (1 mL), and the mixture was stirred at room temperature for 5 hr. The reaction mixture was diluted with ethyl acetate and washed successively with water and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (110 mg, 0.146 mmol, yield 94%).

[0696]

35 <Example AZ7> [2-(5-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-

dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2H-indazol-2-yl)-7-azaspiro[3.5]nonan-7-yl]acetic acid dihydrochloride

Using the compound obtained in <Example AZ6>, the title
5 compound was obtained by the same method as in <Example V5>.
[0697]

<Example AZ8> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]-2-[2-(5-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2H-indazol-2-yl)-7-azaspiro[3.5]nonan-7-yl]acetamide
10

Using the compound obtained in <Example AZ7> and 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1), the title compound
15 was obtained by the same method as in <Example BM9>.
[0698]

<Example BA1> tert-Butyl 2-[5-(hydroxymethyl)-1H-indazol-1-yl]-7-azaspiro[3.5]nonane-7-carboxylate

Using the compound obtained in <Example AZ1>, the title
20 compound was obtained by the same method as in <Example W5>.
[0699]

<Example BA2> tert-Butyl 2-(5-formyl-1H-indazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate

Using the compound obtained in <Example BA1>, the title
25 compound was obtained by the same method as in <Example AZ4>.
[0700]

<Example BA3> tert-Butyl 2-(5-{[2-(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-1H-indazol-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate
30

Using the compounds obtained in <Example M3> and <Example BA2>, the title compound was obtained by the same method as in <Example W4>.
[0701]

35 <Example BA4> tert-Butyl [2-(5-{[2-(4R)-4-(4-methoxyphenyl)-

2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-1H-indazol-1-yl)-7-azaspiro[3.5]nonan-7-yl]acetate

Using the compound obtained in <Example BA3>, the title compound was obtained by the same method as in <Example AZ6>. [0702]

<Example BA5> [2-(5-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-1H-indazol-1-yl)-7-azaspiro[3.5]nonan-7-yl]acetic acid dihydrochloride

Using the compound obtained in <Example BA4>, the title compound was obtained by the same method as in <Example V5>. [0703]

<Example BA6> N-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]-2-[2-(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-1H-indazol-1-yl)-7-azaspiro[3.5]nonan-7-yl]acetamide

Using the compound obtained in <Example BA5> and 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1), the title compound was obtained by the same method as in <Example BM9>. [0704]

<Example BB1> tert-Butyl 3-fluoro-4-oxocyclohexanecarboxylate
tert-Butyl 4-Oxocyclohexanecarboxylate (CAS Registry Number: 38446-95-6) (1.01 g, 5.09 mmol) and triethylamine (1.4 mL, 10 mmol) were dissolved in DCM (17 mL), trimethylsilyl trifluoromethanesulfonate (1.1 mL, 6.1 mmol) was added at 0°C, and the mixture was stirred for 20 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetonitrile (17 mL), 1-chloromethyl-

4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
bis(tetrafluoroborate) (CAS Registry Number: 140681-55-6) (2.17
g, 6.11 mmol) was added at 0°C, and the mixture was stirred at
room temperature for 2.5 hr. To the reaction mixture was added
5 saturated aqueous sodium hydrogen carbonate solution, and the
mixture was extracted with ethyl acetate. The organic layer
was washed with saturated brine, dried over sodium sulfate and
filtered, and the filtrate was concentrated under reduced
pressure. The residue was purified by silica gel column
10 chromatography (hexane/ethyl acetate) to give the title
compound (0.849 g, 3.93 mmol, yield 77%).

[0705]

<Example BB2> tert-Butyl 6-fluoro-4'-formyl-2,3,4,5-
tetrahydro[biphenyl]-4-carboxylate

15 tert-Butyl 3-fluoro-4-oxocyclohexanecarboxylate (0.436 g,
2.02 mmol) was dissolved in THF (4 mL), lithium
bis(trimethylsilyl)amide (1.12 mol/L THF solution, 2.0 mL, 2.2
mmol) was added under a nitrogen atmosphere at -78°C, and the
mixture was stirred for 30 min. To the reaction mixture was
20 added a solution of N-phenylbis(trifluoromethanesulfonimide)
(0.792 g, 2.22 mmol) in THF (4 mL) at -78°C, and the mixture
was stirred at room temperature for 1 hr. The reaction mixture
was diluted with ethyl acetate and washed successively with 1
mol/L aqueous sodium hydroxide solution, saturated aqueous
25 ammonium chloride solution, and saturated brine. The organic
layer was dried over sodium sulfate and filtered, and the
filtrate was concentrated under reduced pressure. The residue
and (4-formylphenyl)boronic acid (CAS Registry Number: 87199-
17-5) (0.363 g, 2.42 mmol) were dissolved in a mixed solvent of
30 1,4-dioxane (10 mL)-water (1 mL), sodium carbonate (0.641 g,
6.05 mmol) and [1,1'-
bis(diphenylphosphino)ferrocene]palladium(II) dichloride DCM
adduct (0.165 g, 0.202 mmol) were added, and the mixture was
stirred with heating under a nitrogen atmosphere at 85°C for 1
35 hr. The reaction mixture was cooled to room temperature,

saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under
5 reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.212 g, 0.697 mmol, yield 35%).

[0706]

<Example BB3> tert-Butyl 6-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
10 2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example BB2>, the title compound was obtained by the same method as in
15 <Example W4>.

[0707]

<Example BB4> 6-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
20 carboxylic acid monohydrochloride

Using the compound obtained in <Example BB3>, the title compound was obtained by the same method as in <Example V5>.

[0708]

<Example BB5> tert-Butyl 4-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]methyl}piperazine-1-carboxylate

Using the compound obtained in <Example AW2>, the title compound was obtained by the same method as in <Example BQ1>.

30 [0709]

<Example BB6> 1-(Hydroxymethyl)-3-[2-oxo-7-(piperazin-1-ylmethyl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example BB5>, the title
35 compound was obtained by the same method as in <Example AO5>.

[0710]

<Example BB7> 3-[7-({4-[(6-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl})-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperazin-1-yl)methyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione

Using the compounds obtained in <Example BB4> and <Example BB6>, the title compound was obtained by the same method as in <Example BW3>.

[0711]

<Example BC1> 6-Bromo-N²-methylpyridine-2,3-diamine

To a solution of 6-bromo-N-methyl-3-nitropyridin-2-amine (CAS Registry Number: 924293-34-5) (300 mg, 1.29 mmol) in THF (9 mL) was added a solution of ammonium chloride (280 mg, 5.17 mmol) in water (4.5 mL). After ice-cooling, zinc powder (850 mg, 12.9 mmol) was gradually added and, after stirring for 30 min, insoluble materials were filtered off through celite. The filtrate was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (225 mg, 1.11 mmol, yield 86%).

[0712]

<Example BC2> 5-Bromo-3-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

Using the compound obtained in <Example BC1>, the title compound was obtained by the same method as in <Example AN2>.

[0713]

<Example BC3> 3-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compound obtained in <Example BC2>, the title compound was obtained by the same method as in <Example Z5>.

[0714]

<Example BC4> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-5-carboxylate

Using the compound obtained in <Example BC3>, the title
5 compound was obtained by the same method as in <Example BY5>.
[0715]

<Example BC5> 3-[5-({4-[(4'-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
10 yl)methyl}piperazin-1-yl}carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compounds obtained in <Example AG5> and
<Example BC4>, the title compound was obtained by the same
15 method as in <Example BI1>.
[0716]

<Example BC6> 3-[5-({4-[(4'-{{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-
20 yl)methyl}piperazin-1-yl}carbonyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl]piperidine-2,6-dione

Using the compound obtained in <Example BC5>, the title
compound was obtained by the same method as in <Example BK9>.
[0717]

25 <Example BD1> N-{{Trans-4-(4-chlorophenyl)cyclohexyl)methyl}-3,3,3-trifluoro-N-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropan-1-amine

Using the compound obtained in <Example M3> and trans-4-
30 (4-chlorophenyl)cyclohexanecarbaldehyde (Org. Process Res. Dev., 2012, 16, 10, 1607-1617.), the title compound was
obtained by the same method as in <Example W4>.
[0718]

<Example BD2> tert-Butyl [4-(trans-4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
35

yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl)cyclohexyl)phenyl]carbamate

To N-{[trans-4-(4-chlorophenyl)cyclohexyl]methyl}-3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethylpropane-1-amine (300 mg, 0.505 mmol), tert-butyl carbamate (CAS Registry Number: 4248-19-5) (95 mg, 0.81 mmol), 1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene (80 mg, 0.112 mmol), tris(dibenzylideneacetone)dipalladium(0) (60 mg, 0.066 mmol),
10 and cesium carbonate (310 mg, 0.95 mmol) was added tert-butyl alcohol (4 mL), and the mixture was stirred with heating under a nitrogen atmosphere at 100°C for 5 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel
15 column chromatography (hexane/ethyl acetate) to give the title compound (200 mg, 0.30 mmol, yield 59%).

[0719]

<Example BD3> 4-(Trans-4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl)cyclohexyl)aniline dihydrochloride
20

Using the compound obtained in <Example BD2>, the title compound was obtained by the same method as in <Example A05>.

[0720]

<Example BD4> tert-Butyl 3-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}cyclobutanecarboxylate
25

Using 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1) and tert-butyl 3-oxocyclobutanecarboxylate (CAS Registry Number: 145549-76-4), the title compound was obtained by the same
30 method as in <Example BM7>.

[0721]

<Example BD5> 3-{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}cyclobutanecarboxylic
35 acid

At room temperature, to a solution of tert-butyl 3-{{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}cyclobutanecarboxylate (245 mg, 0.57 mmol) in DCM (2 mL) was added trifluoroacetic acid (2 mL).

5 After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was azeotropically distilled with chloroform, and the obtained solid was dried under reduced pressure to give the title compound (210 mg, 0.56 mmol, yield 98%).

10 [0722]

<Example BD6> 3-{{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}-N-[4-(trans-4-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-

15 dimethylpropyl)amino]methyl}cyclohexyl)phenyl]cyclobutanecarboxamide

Using the compounds obtained in <Example BD5> and <Example BD3>, the title compound was obtained by the same method as in <Example BM9>.

20 [0723]

<Example BE1> Ethyl 4'-[(tert-butoxycarbonyl)amino]-3'-fluoro-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using tert-butyl (4-bromo-2-fluorophenyl)carbamate (CAS Registry Number: 209958-42-9) and ethyl 4-(4,4,5,5-tetramethyl-25 1,3,2-dioxaborolan-2-yl)-3-cyclohexene-1-carboxylate (CAS Registry Number: 1049004-32-1), the title compound was obtained by the same method as in <Example W1>.

[0724]

<Example BE2> tert-Butyl [3-fluoro-4'-(hydroxymethyl)-

30 2',3',4',5'-tetrahydro[biphenyl]-4-yl]carbamate

Using the compound obtained in <Example BE1>, the title compound was obtained by the same method as in <Example AG3>.

[0725]

<Example BE3> tert-Butyl (3-fluoro-4'-{{[2-[(4R)-4-(4-

35 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2',3',4',5'-tetrahydro[biphenyl]-4-yl)carbamate

Using the compound obtained in <Example BE2>, the title
compound was obtained by sequentially performing the same
5 operations as in <Example AI5> and <Example W4>.

[0726]

<Example BE4> 3-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-
dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2',3',4',5'-tetrahydro[biphenyl]-
10 4-amine dihydrochloride

Using the compound obtained in <Example BE3>, the title
compound was obtained by the same method as in <Example A05>.

[0727]

<Example BE5> 3-{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-
15 2,3-dihydro-1H-benzimidazol-5-yl]amino}-N-(3-fluoro-4'-{[{2-
[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2',3',4',5'-tetrahydro[biphenyl]-4-yl)cyclobutanecarboxamide

Using the compounds obtained in <Example BE4> and
20 <Example BD5>, the title compound was obtained by the same
method as in <Example BM9>.

[0728]

<Example BF1> 5,8-Dibromo-1,2,3,4-tetrahydroquinoline

A suspension of 5,8-dibromoquinoline (CAS Registry
25 Number: 81045-39-8) (3.49 g, 12.2 mmol), diethyl 1,4-dihydro-
2,6-dimethyl-3,5-pyridinedicarboxylate (CAS Registry Number:
1149-23-1) (7.69 g, 30.4 mmol), and boric acid (121 mg, 1.96
mmol) in 1,2-dichloroethane (50 mL) was stirred at 60°C for 5
hr. The reaction mixture was cooled to room temperature,
30 ethanol (40 mL) and 10 mol/L aqueous sodium hydroxide solution
(10 mL, 100 mmol) were added, and the mixture was stirred at
room temperature for 2 hr. Water was added to the reaction
mixture, and the mixture was extracted with DCM. The obtained
organic layer was washed with saturated aqueous sodium hydrogen
35 carbonate solution, dried over sodium sulfate and filtered, and

the filtrate was concentrated under reduced pressure. To the residue was added diethyl ether, insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/DCM) to give the title compound (2.28 g, 7.84 mmol, yield 64%).

[0729]

<Example BF2> tert-Butyl N²-[(5,8-dibromo-3,4-dihydroquinolin-1(2H)-yl)carbonyl]-L- α -glutamate

Under ice-cooling, to a solution of triphosgene (1.39 g, 4.68 mmol) in DCM (15 mL) was added dropwise a solution of 5,8-dibromo-1,2,3,4-tetrahydroquinoline (2.28 g, 7.84 mmol) in DCM (6 mL) over 5 min. To the reaction mixture was added pyridine (1 mL, 12 mmol), and the mixture was stirred at said temperature for 40 min. To the reaction mixture was added 1 mol/L hydrochloric acid, and the mixture was extracted with DCM. The obtained organic layers were combined and washed with 1 mol/L hydrochloric acid, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetonitrile (20 mL), tert-butyl L- α -glutamate hydrochloride (CAS Registry Number: 108607-02-9) (1.93 g, 8.09 mmol) and triethylamine (3 mL, 21.5 mmol) were added, and the mixture was stirred at 50°C for 2 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution and water were added, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (2.25 g, 4.33 mmol, yield 55%).

[0730]

<Example BF3> tert-Butyl (4S)-5-amino-4-(7-bromo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-5-oxopentanoate

A suspension of tert-butyl N²-[(5,8-dibromo-3,4-

dihydroquinolin-1(2H)-yl)carbonyl]-L- α -glutamate (2.25 g, 4.33 mmol), trans-4-hydroxy-L-proline (229 mg, 1.75 mmol), tripotassium phosphate (2.66 g, 12.5 mmol), and copper(I) iodide (155 mg, 0.814 mmol) in DMSO (15 mL) was stirred under a nitrogen atmosphere at 50°C for 80 min. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (1.81 g, 4.13 mmol, yield 95%).

[0731]

<Example BF4> 2,4,6-Trichlorophenyl 1-[(2S)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate

To a suspension of tert-butyl (4S)-5-amino-4-(7-bromo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-5-oxopentanoate (387 mg, 0.883 mmol), 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) (304 mg, 1.35 mmol), palladium(II) acetate (23.8 mg, 0.106 mmol), and XantPhos (101 mg, 0.175 mmol) in toluene (4 mL) was added triethylamine (0.246 mL, 1.76 mmol), and the mixture was stirred under a carbon monoxide atmosphere at 80°C for 2 hr, and at 90°C for 2.5 hr. The reaction mixture was cooled to room temperature, and purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (480 mg, 0.824 mmol, yield 93%).

[0732]

<Example BF5> tert-Butyl (4S)-5-amino-4-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-5-oxopentanoate

To a solution of 2,4,6-trichlorophenyl 1-[(2S)-1-amino-5-

tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate (70.5 mg, 0.0967 mmol), 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-[[4'R)-4'-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride (75.4 mg, 0.104 mmol), and DIPEA (0.0842 mL, 0.483 mmol) in acetonitrile (1 mL) was added 4-dimethylaminopyridine (catalytic amount), and the mixture was stirred at room temperature for 25 hr. The
10 reaction mixture was heated to 60°C, and stirred for 4.5 hr. The reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The
15 residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (58.4 mg, 0.0561 mmol, yield 58%).

[0733]

<Example BF6> (3S)-3-{7-[(4-{[(4R)-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione

25 To a solution of tert-butyl (4S)-5-amino-4-{7-[(4-{[(4R)-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-5-oxopentanoate (58.4 mg, 0.0561 mmol) in acetonitrile (1 mL) was added benzenesulfonic acid (23.1 mg, 0.146 mmol), and the mixture was stirred at 80°C for 4 hr. To the reaction mixture was added benzenesulfonic acid (23.1 mg, 0.146 mmol), and the mixture was stirred at 80°C
35 for 3.5 hr. The reaction mixture was cooled to room

temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol), and the obtained solid was washed with hexane/ethyl acetate and dried under reduced pressure at 50°C to give the title compound (36.7 mg, 0.0379 mmol, yield 68%).

10 [0734]

<Example BG1> tert-Butyl N²-[(5,8-dibromo-3,4-dihydroquinolin-1(2H)-yl)carbonyl]-D-α-glutamate

To a solution of triphosgene (984 mg, 3.32 mmol) in DCM (15 mL) was added dropwise, under ice-cooling, a solution of 15 5,8-dibromo-1,2,3,4-tetrahydroquinoline (1.66 g, 5.70 mmol) in DCM (4 mL) over 5 min. To the reaction mixture was added dropwise pyridine (0.65 mL, 8.1 mmol) over 10 min, and the mixture was stirred at said temperature for 40 min. To the reaction mixture was added 1 mol/L hydrochloric acid, and the 20 mixture was extracted with DCM. The organic layers were combined, washed with 1 mol/L hydrochloric acid, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetonitrile (14 mL), tert-butyl D-α-glutamate 25 monohydrochloride (CAS Registry Number: 66575-26-6) (1.37 g, 5.74 mmol) and triethylamine (2.5 mL, 18 mmol) were added, and the mixture was stirred at room temperature for 2.5 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. 30 The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (2.45 g, 4.72 mmol, yield 83%).

35 [0735]

<Example BG2> tert-Butyl (4R)-5-amino-4-(7-bromo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-5-oxopentanoate

A suspension of tert-butyl N²-[(5,8-dibromo-3,4-dihydroquinolin-1(2H)-yl)carbonyl]-D-α-glutamate (2.45 g, 4.72 mmol), trans-4-hydroxy-L-proline (244 mg, 1.86 mmol), tripotassium phosphate (3.12 g, 14.7 mmol), and copper(I) iodide (171 mg, 0.898 mmol) in DMSO (15 mL) was stirred at 60°C for 1.5 hr. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate. The mixture was washed successively with water and saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, DCM/methanol) to give the title compound (1.02 g, 2.33 mmol, yield 49%).

[0736]

<Example BG3> 2,4,6-Trichlorophenyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate

To a solution of tert-butyl (4R)-5-amino-4-(7-bromo-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-5-oxopentanoate (312 mg, 0.712 mmol), 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) (199 mg, 0.883 mmol), palladium(II) acetate (16.2 mg, 0.0722 mmol), and XantPhos (73.3 mg, 0.127 mmol) in toluene (3 mL) was added triethylamine (0.198 mL, 1.42 mmol), and the mixture was stirred under a carbon monoxide atmosphere at 90°C for 4 hr. The reaction mixture was cooled to room temperature, and purified by silica gel column chromatography (DCM/ethyl acetate) to give the title compound (363 mg, 0.623 mmol, yield 87%).

[0737]

<Example BG4> tert-Butyl (4R)-5-amino-4-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-

1(2H)-yl}-5-oxopentanoate

To a solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-[[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride (89.8 mg, 0.123 mmol), 2,4,6-trichlorophenyl 1-[(2R)-1-amino-5-tert-butoxy-1,5-dioxopentan-2-yl]-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline-7-carboxylate (92.5 mg, 0.159 mmol), and DIPEA (0.107 mL, 0.614 mmol) in acetonitrile (1 mL) was added 4-dimethylaminopyridine (catalytic amount), and the mixture was stirred at room temperature for 27 hr. The reaction mixture was heated to 60°C, and stirred for 4.5 hr. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (84.7 mg, 0.0813 mmol, yield 66%).

[0738]

<Example BG5> (3R)-3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione

To a solution of tert-butyl (4R)-5-amino-4-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-5-oxopentanoate (84.7 mg, 0.0813 mmol) in acetonitrile (1 mL) was added benzenesulfonic acid (36.8 mg, 0.233 mmol), and the mixture was stirred at 80°C for 3 hr. To the reaction mixture was added benzenesulfonic

acid (20.5 mg, 0.130 mmol), and the mixture was stirred for 3.5 hr. The reaction mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was successively extracted with DCM and ethyl acetate. The organic layers were combined, dried over sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol), and the obtained solid was washed with hexane/ethyl acetate, and dried under reduced pressure at 50°C to give the title compound (57.2 mg, 0.0591 mmol, yield 73%).

[0739]

<Example BH1> tert-Butyl 2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example V1>, the title compound was obtained by the same method as in <Example W4>.

[0740]

<Example BH2> 2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride

Using the compound obtained in <Example BH1>, the title compound was obtained by the same method as in <Example V5>.

[0741]

<Example BH3> 3-{7-[Methyl(piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

tert-Butyl 4-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino}piperidine-1-carboxylate (0.160 g, 0.261 mmol) was dissolved in DCM (4 mL), paraformaldehyde (0.078 g), acetic acid (0.045 mL, 0.79

mmol), and sodium triacetoxyborohydride (0.276 g, 1.30 mmol) were added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added 37% aqueous formaldehyde solution (0.097 mL, 1.3 mmol), and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetonitrile (2 mL), para-toluenesulfonic acid monohydrate (0.198 g, 1.04 mmol) was added, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (0.120 g, 0.227 mmol, yield 87%).

[0742]

<Example BH4> 3-{7-[[1-[(2'-Fluoro-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperidin-4-yl}(methyl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

Using the compounds obtained in <Example BH3> and <Example BH2>, the title compound was obtained by the same method as in <Example BM9>.

[0743]

<Example BH5> 3-{7-[[1-[(2'-Fluoro-4'-{[[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)carbonyl]piperidin-4-yl}(methyl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-

ij]quinolin-1(2H)-yl}piperidine-2,6-dione

Using the compound obtained in <Example BH4>, the title compound was obtained by the same method as in <Example BK9>.
[0744]

5 <Example BI1> 3-{5-[(4-{[(4R)-4'-{[2-(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-
10 1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

To a solution of 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl)methyl}propan-1-amine dihydrochloride
15 (210 mg, 0.289 mmol), 2,4,6-trichlorophenyl 1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate (194 mg, 0.317 mmol), and DIPEA (0.250 mL, 1.44 mmol) in acetonitrile (1.5 mL) was added 4-dimethylaminopyridine (catalytic amount), and the
20 mixture was stirred at room temperature for 18.5 hr. The reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The
25 residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (197 mg, 0.184 mmol, yield 64%).

[0745]

<Example BI2> 3-{5-[(4-{[(4R)-4'-{[2-(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione
30

To a solution of 3-{5-[(4-{[(4R)-4'-{[2-(4R)-4-(4-

methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-

5 1-([2-(trimethylsilyl)ethoxy]methyl)piperidine-2,6-dione (197 mg, 0.184 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.5 mL), and the mixture was stirred at room temperature for 50 min. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate

10 solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 mL), N,N'-dimethylethylenediamine (0.0217 mL, 0.202 mmol) was added, and the mixture was stirred at room temperature for 40 min.

15 The reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography

20 (DCM/methanol), and the obtained solid was washed with hexane/ethyl acetate, and dried under reduced pressure at 50°C to give the title compound (93.8 mg, 0.0997 mmol, yield 54%). [0746]

<Example BJ1> 6-Bromo-N-methylpyridine-3,4-diamine

25 At room temperature, to a solution of 2-bromo-N-methyl-5-nitropyridin-4-amine (CAS Registry Number: 1234014-33-5) (300 mg, 1.29 mmol) in acetic acid (10 mL) was added iron powder (290 mg, 5.17 mmol). After completion of the reaction, the reaction mixture was diluted with ethyl acetate, insoluble

30 materials were filtered off through celite, and the filtrate was concentrated under reduced pressure. The residue was neutralized with aqueous sodium hydrogen carbonate solution. Insoluble materials were collected again by filtration through celite, and the filtrate was diluted with ethyl acetate, and

35 washed with saturated brine. The organic layer was dried over

magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (240 mg, 1.18 mmol, yield 91%).

[0747]

5 <Example BJ2> 6-Bromo-1-methyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one

Using the compound obtained in <Example BJ1>, the title compound was obtained by the same method as in <Example AN2>.

[0748]

10 <Example BJ3> 3-(6-Bromo-1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-c]pyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compound obtained in <Example BJ2>, the title compound was obtained by the same method as in <Example Z5>.

15 [0749]

<Example BJ4> 2,4,6-Trichlorophenyl 3-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]pyridine-6-carboxylate

Using the compound obtained in <Example BJ3>, the title compound was obtained by the same method as in <Example BY5>.

[0750]

<Example BJ5> 3-[6-({4-[(4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl)-1-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-c]pyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compounds obtained in <Example AG5> and <Example BJ4>, the title compound was obtained by the same method as in <Example BI1>.

[0751]

<Example BJ6> 3-[6-({4-[(4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl)-1-methyl-2-oxo-1,2-dihydro-

35 yl)methyl]piperazin-1-yl)carbonyl)-1-methyl-2-oxo-1,2-dihydro-

3H-imidazo[4,5-c]pyridin-3-yl]piperidine-2,6-dione

Using the compound obtained in <Example BJ5>, the title compound was obtained by the same method as in <Example BK9>. [0752]

5 <Example BK1> 8-Bromo-5-nitro-1,2,3,4-tetrahydroquinoline

A suspension of 8-bromo-5-nitroquinoline (CAS Registry Number: 139366-35-1) (5.02 g, 19.8 mmol), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (CAS Registry Number: 1149-23-1) (11.1 g, 43.8 mmol), and para-toluenesulfonic acid
10 monohydrate (701 mg, 3.69 mmol) in 1,2-dichloroethane (80 mL) was stirred at 60°C for 80 min. The reaction mixture was cooled to room temperature, ethanol (40 mL), and 5 mol/L aqueous sodium hydroxide solution (20 mL, 100 mmol) were added, and the mixture was stirred at room temperature for 3 hr.
15 Ethanol (40 mL) was further added thereto, and the mixture was stirred for 3 hr. To the reaction mixture were added water and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was
20 concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/DCM) to give the title compound (2.83 g, 11.0 mmol, yield 56%).

[0753]

<Example BK2> 8-Bromo-N-(2,6-dioxopiperidin-3-yl)-5-nitro-3,4-
25 dihydroquinoline-1(2H)-carboxamide

Under ice-cooling, to a solution of triphosgene (1.90 g, 6.40 mmol) in DCM (20 mL) were successively added dropwise a solution of 8-bromo-5-nitro-1,2,3,4-tetrahydroquinoline (2.64 g, 10.3 mmol) in DCM (20 mL), and pyridine (2.0 mL, 25 mmol),
30 and the mixture was stirred at 0°C for 10 min, and warmed to room temperature, and stirred for 2 hr. To the reaction mixture was added 1 mol/L hydrochloric acid, and the mixture was extracted with DCM. The organic layers were combined, dried over sodium sulfate and filtered, and the filtrate was
35 concentrated under reduced pressure. To the residue were added

3-aminopiperidine-2,6-dione monohydrochloride (CAS Registry Number: 24666-56-6) (1.74 g, 10.6 mmol), acetonitrile (35 mL), and triethylamine (7 mL, 50 mmol), and the mixture was stirred at 60°C for 1 hr and left standing at room temperature overnight. To the reaction mixture were added water and ethyl acetate, insoluble materials were filtered off through celite, two layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (3.75 g, 9.12 mmol, yield 89%).

[0754]

<Example BK3> 8-Bromo-N-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-5-nitro-3,4-dihydroquinoline-1(2H)-carboxamide

To a solution of 8-bromo-N-(2,6-dioxopiperidin-3-yl)-5-nitro-3,4-dihydroquinoline-1(2H)-carboxamide (311 mg, 0.756 mmol) and DIPEA (0.254 mL, 1.46 mmol) in DCM (2.5 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (0.142 mL, 0.802 mmol) under ice-cooling, and the mixture was stirred at said temperature for 15 min, and then warmed to room temperature and stirred for 1.5 hr. To the reaction mixture was added 2-(trimethylsilyl)ethoxymethyl chloride (0.0402 mL, 0.227 mmol), and the mixture was stirred at room temperature for 1 hr. DIPEA (0.134 mL, 0.769 mmol) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (327 mg, 0.604 mmol, yield 80%).

[0755]

<Example BK4> 3-(7-Nitro-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

A suspension of 8-bromo-N-(2,6-dioxo-1-{[2-

(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-5-nitro-3,4-dihydroquinoline-1(2H)-carboxamide (4.22 g, 7.79 mmol), trans-4-hydroxy-L-proline (370 mg, 2.82 mmol), copper(I) iodide (269 mg, 1.41 mmol), and potassium triphosphate (5.00 g, 23.6 mmol) in DMSO (25 mL) was stirred at 60°C for 1 hr. The mixture was cooled to room temperature and left standing for 13 hr. The reaction mixture was diluted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (2.67 g, 5.80 mmol, yield 74%).

[0756]

<Example BK5> 3-(7-Amino-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione

To a solution of 3-(7-nitro-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione (2.67 g, 5.80 mmol) in ethyl acetate (60 mL) was added 10% palladium carbon (2.43 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate, insoluble materials were filtered off through celite, and the filtrate was concentrated under reduced pressure to give the title compound (2.26 g, 5.25 mmol, yield 91%).

[0757]

<Example BK6> tert-Butyl 4-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino}piperidine-1-carboxylate

Under ice-cooling, to a solution of 3-(7-amino-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl)piperidine-2,6-dione (1.65 g, 3.83 mmol) and tert-butyl 4-oxo-1-piperidinecarboxylate (CAS

Registry Number: 79099-07-3) (840 mg, 4.22 mmol) in DCM (20 mL) was gradually added sodium triacetoxyborohydride (1.62 g, 7.66 mmol), and the mixture was stirred for 1 hr. The reaction mixture was warmed to room temperature, further stirred for 2
5 hr, and the reaction was discontinued by adding water. The mixture was neutralized by adding aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under
10 reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (2.28 g, 3.71 mmol, yield 96%).

[0758]

<Example BK7> 3-[2-Oxo-7-(piperidin-4-ylamino)-5,6-dihydro-4H-
15 imidazo[4,5,1-ij]quinolin-1(2H)-yl]-1-[[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione
tert-Butyl 4-[[1-(2,6-dioxo-1-[[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-
tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino]piperidine-
20 1-carboxylate (0.505 g, 0.823 mmol) was dissolved in acetonitrile (6 mL), para-toluenesulfonic acid monohydrate (0.621 g, 3.26 mmol) was added, and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the
25 mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (0.427 g, 0.831 mmol, yield: quantitative).

30 [0759]

<Example BK8> 3-{7-[(1-[[(4R)-2'-Fluoro-4'-[[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-
35 yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-

yl}-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

To a solution of (4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride (17.9 g, 27.3 mmol), 3-[2-oxo-7-(piperidin-4-ylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (14.2 g, 27.6 mmol), and DIPEA (24 mL, 138 mmol) in DMF (135 mL) was added HATU (12.4 g, 32.6 mmol), and the mixture was stirred at room temperature for 22 hr. The reaction mixture was diluted with ethyl acetate and washed successively with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (27.0 g, 24.2 mmol, yield 89%).

[0760]

<Example BK9> 3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione

To a solution of 3-{7-[(1-{[(4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (27.0 g, 24.2 mmol) in DCM (30 mL) was added trifluoroacetic acid (30 mL), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was neutralized by adding

DCM, water, and sodium hydrogen carbonate. Two layers were separated and successively extracted with DCM and ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was suspended in ethyl acetate (240 mL), N,N'-dimethylethylenediamine (3 mL, 28 mmol) was added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate solution and water, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol) and the obtained solid was washed with diethyl ether, and dried under reduced pressure at 50°C to give the title compound (18.0 g, 18.3 mmol, yield 76%).

[0761]

<Example BL1> tert-Butyl (4S)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example V3>, the title compound was obtained by the same method as in <Example W4>.

[0762]

<Example BL2> (4S)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride

Using the compound obtained in <Example BL1>, the title compound was obtained by the same method as in <Example V5>.

[0763]

<Example BL3> 3-{7-[(1-{[(4S)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-

yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compounds obtained in <Example BK7> and <Example BL2>, the title compound was obtained by the same method as in <Example BM9>.

[0764]

<Example BL4> 3-{7-[1-{[(4S)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione

Using the compound obtained in <Example BL3>, the title compound was obtained by the same method as in <Example BK9>.

[0765]

<Example BM1> 6-Chloro-8-nitro-3,4-dihydro-2H-1,4-benzoxazine

At room temperature, to a suspension of 6-chloro-8-nitro-2H-1,4-benzoxazin-3(4H)-one (CAS Registry Number: 870064-73-6) (5.6 g, 24 mmol) in THF (20 mL) was added dropwise borane-THF complex (0.89 mol/L THF solution, 55 mL, 49 mmol). The reaction mixture was heated under reflux for 3 hr. After confirming the reaction by TLC, the reaction mixture was ice-cooled, 80% aqueous ethanol solution (30 mL) was gradually added. After the completion of foaming, triethylamine (3 mL) was added, and the mixture was heated under reflux for 1 hr. After cooling, the reaction mixture was concentrated under reduced pressure to about 1/3. To the residue was added water, and the precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give the title compound (4.8 g, 22 mmol, yield 91%).

[0766]

<Example BM2> 5,7-Dibromo-6-chloro-8-nitro-3,4-dihydro-2H-1,4-benzoxazine

6-Chloro-8-nitro-3,4-dihydro-2H-1,4-benzoxazine (4.8 g, 22 mmol) was dissolved in DMF (75 mL), and N-bromosuccinimide

(8.2 g, 45 mmol) and acetic acid (4 mL, 67 mmol) were added. After confirming the completion of the reaction by TLC, water was added to the reaction mixture, and the mixture was stirred. The precipitated solid was collected by filtration, washed with
5 water, and dried under reduced pressure to give the title compound (7.1 g, 19 mmol, yield 85%).

[0767]

<Example BM3> 5,7-Dibromo-6-chloro-N-(2,6-dioxopiperidin-3-yl)-8-nitro-2,3-dihydro-4H-1,4-benzoxazine-4-carboxamide

10 Under ice-cooling, to a solution of triphosgene (4.50 g, 15.0 mmol) in DCM (150 mL) was added dropwise a solution of 5,7-dibromo-6-chloro-8-nitro-3,4-dihydro-2H-1,4-benzoxazine (11.2 g, 30.1 mmol) in DCM (150 mL), and then pyridine (7.5 mL, 90 mmol) was added. After confirming the reaction by TLC, the
15 reaction mixture was added to ice-cooled 1 mol/L hydrochloric acid (95 mL), and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved
20 in acetonitrile (150 mL), 3-aminopiperidine-2,6-dione monohydrochloride (CAS Registry Number: 24666-56-6) (5.5 g, 33 mmol) and triethylamine (21 mL, 150 mmol) were added, and the mixture was stirred for 1 hr. Water was added to the reaction mixture, and the mixture was concentrated under reduced
25 pressure to half. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give the title compound (11.7 g, 22.2 mmol, yield 73%).

[0768]

<Example BM4> 5,7-Dibromo-6-chloro-N-(2,6-dioxo-1-[[2-(trimethylsilyl)ethoxy]methyl]piperidin-3-yl)-8-nitro-2,3-dihydro-4H-1,4-benzoxazine-4-carboxamide

Using the compound obtained in <Example BM3>, the title compound was obtained by the same method as in <Example BY3>.

[0769]

35 <Example BM5> 3-(8-Bromo-9-chloro-7-nitro-2-oxo-4,5-

dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

To a solution of 5,7-dibromo-6-chloro-N-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-8-nitro-2,3-dihydro-4H-1,4-benzoxazine-4-carboxamide (10.5 g, 16.0 mmol) in DMSO (80 mL) were added trans-4-hydroxy-L-proline (760 mg, 5.76 mmol) and tripotassium phosphate (10.5 g, 48.0 mmol), copper(I) iodide (610 mg, 3.20 mmol) was added, and the mixture was heated under a nitrogen atmosphere at 60°C for 5 hr. The reaction mixture was cooled, diluted with ethyl acetate, and insoluble materials were filtered off through celite. The filtrate was acidified by adding 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.83 g, 11.4 mmol, yield 71%).

[0770]

<Example BM6> 3-(7-Amino-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

To a solution of 3-(8-bromo-9-chloro-7-nitro-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (22.3 g, 38.7 mmol) in ethyl acetate (300 mL) were added triethylamine (20 mL, 155 mmol) and 10% palladium carbon (8.0 g) and, after being purged with hydrogen, the mixture was stirred for 2 hr. Insoluble materials were filtered off through celite, washed with ethyl acetate, and the filtrate was concentrated under reduced pressure to half. To the residue were added again 10% palladium carbon (8.0 g) and triethylamine (20 mL, 155 mmol) and, after being purged with hydrogen, the mixture was stirred for 2 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. To the residue was added

aqueous sodium hydrogen carbonate solution, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. To the
5 residue was added IPA, and the precipitated solid was collected by filtration to give the title compound (12.7 g, 29.4 mmol, yield 75%).

[0771]

<Example BM7> tert-Butyl 4-{[1-(2,6-dioxo-1-{[2-
10 (trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,4,5-tetrahydroimidazo[1,5,4-de][1,4]benzoxazin-7-yl]amino}piperidine-1-carboxylate

To a solution of 3-(7-amino-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl)-1-{[2-
15 (trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (12.7 g, 29.4 mmol) in DCM (75 mL) was added tert-butyl 4-oxo-1-piperidinecarboxylate (CAS Registry Number: 79099-07-3) (5.90 g, 29.4 mmol). After stirring for about 5 min, the reaction mixture was concentrated under reduced pressure. To the
20 residue was added chloroform, and the mixture was azeotropically distilled, dissolved again in DCM (150 mL), and ice-cooled. Sodium triacetoxyborohydride (12.5 g, 58.7 mmol) was gradually added thereto, and the mixture was stirred at said temperature for 1 hr, the ice bath was removed and the
25 temperature was raised to room temperature. After confirming the completion of the reaction by TLC, water was added to the reaction mixture and the mixture was stirred, basified by adding aqueous sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was dried over
30 magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (17.5 g, 28.4 mmol, yield 96%).

[0772]

35 <Example BM8> 3-[2-Oxo-7-(piperidin-4-ylamino)-4,5-

dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

At room temperature, to a solution of tert-butyl 4-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-2-oxo-1,2,4,5-tetrahydroimidazo[1,5,4-de][1,4]benzoxazin-7-yl]amino}piperidine-1-carboxylate (17.5 g, 28.4 mmol) in acetonitrile (300 mL) was added para-toluenesulfonic acid monohydrate (11.0 g, 56.8 mmol), and the mixture was heated at 50°C for 2 hr. After cooling, the reaction mixture was concentrated under reduced pressure to half. The residue was basified by adding aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by amine-modified silica gel column chromatography (chloroform/methanol) to give the title compound (13.1 g, 25.4 mmol, yield 89%).

[0773]

<Example BM9> 3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

At room temperature, to a solution of (4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride (18.0 g, 27.4 mmol) and 3-[2-oxo-7-(piperidin-4-ylamino)-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl]-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione (14.2 g, 27.4 mmol) in DMF (150 mL) was added HATU (12.6 g, 32.9 mmol), and DIPEA (24 mL, 137 mmol) was added. After completion of the

reaction, the reaction mixture was diluted with ethyl acetate and washed with water and saturated brine. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was
5 purified by silica gel column chromatography (chloroform/methanol) to give the title compound (30.0 g, 26.8 mmol, yield 97%).

[0774]

<Example BM10> 3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-
10 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl}piperidine-2,6-dione

15 Using the compound obtained in <Example BM9>, the title compound was obtained by the same method as in <Example BK9>.

[0775]

<Example BN1> 3-{7-[(1-{[(4S)-2'-Fluoro-4'-{[2-[(4R)-4-(4-
20 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

25 Using the compounds obtained in <Example BM8> and <Example BL2>, the title compound was obtained by the same method as in <Example BM9>.

[0776]

<Example BN2> 3-{7-[(1-{[(4S)-2'-Fluoro-4'-{[2-[(4R)-4-(4-
30 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl}piperidine-2,6-dione

35 Using the compound obtained in <Example BN1>, the title

compound was obtained by the same method as in <Example BK9>.
[0777]

<Example B01> (4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid

Using the compound obtained in <Example W4>, the title compound was obtained by the same method as in <Example V5>.
[0778]

10 <Example B02> tert-Butyl 4-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]amino}piperidine-1-carboxylate

Using 3-(5-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (ACS Med. Chem. Lett., 2021, 12, 1733.), the title compound was obtained by the same method as
15 in <Example BR1>.

[0779]

<Example B03> 3-[1-Oxo-5-(piperidin-4-ylamino)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example B02>, the title
20 compound was obtained by the same method as in <Example A05>.
[0780]

<Example B04> 3-{5-[(1-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
25 2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-1-oxo-1,3-dihydro-2H-isoindol-2-yl}piperidine-2,6-dione

Using the compounds obtained in <Example B03> and <Example B01>, the title compound was obtained by the same
30 method as in <Example BM9>.

[0781]

<Example BP1> 6-Bromo-4-fluoro-1-methyl-1,3-dihydro-2H-benzimidazol-2-one

Using 5-bromo-3-fluoro-N-methyl-2-nitroaniline
35 (WO2018039384 A1), the title compound was obtained by

sequentially performing the same operations as in <Example BJ1> and <Example AN2>.

[0782]

<Example BP2> 3-(5-Bromo-7-fluoro-3-methyl-2-oxo-2,3-dihydro-
5 1H-benzimidazol-1-yl)-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compound obtained in <Example BP1>, the title compound was obtained by the same method as in <Example Z5>.

[0783]

10 <Example BP3> tert-Butyl 4-{{1-(2,6-dioxo-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-7-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl}methyl}piperazine-1-carboxylate

Using the compound obtained in <Example BP2>, the title
15 compound was obtained by the same method as in <Example BQ1>.

[0784]

<Example BP4> 3-[7-Fluoro-3-methyl-2-oxo-5-(piperazin-1-ylmethyl)-2,3-dihydro-1H-benzimidazol-1-yl]-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

20 Using the compound obtained in <Example BP3>, the title compound was obtained by the same method as in <Example BM8>.

[0785]

<Example BP5> 3-{7-Fluoro-5-[(4-{{(4R)-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
25 yl}ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl}carbonyl}piperazin-1-yl)methyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compounds obtained in <Example BO1> and
30 <Example BP4>, the title compound was obtained by the same method as in <Example BM9>.

[0786]

<Example BP6> 3-{7-Fluoro-5-[(4-{{(4R)-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
35 yl}ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-

2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperazin-1-yl)methyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

Using the compound obtained in <Example BP5>, the title
5 compound was obtained by the same method as in <Example BK9>.
[0787]

<Example BQ1> tert-Butyl 4-{{[1-(2,6-dioxo-1-{{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]methyl}piperazine-1-
10 carboxylate
3-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione (0.201 g, 0.429 mmol), potassium (4-tert-butoxycarbonylpiperazin-1-yl)methyltrifluoroborate (CAS
15 Registry Number: 936329-97-4) (0.261 g, 0.852 mmol), cesium carbonate (0.433 g, 1.33 mmol), and (SP-4-3)-[dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine] (methanesulfonate-KO) [2'-(methylamino-KN) [1,1'-biphenyl]-2-yl-KC]palladium(II) (CAS Registry Number: 1599466-
20 81-5) (0.018 g, 0.021 mmol) were dissolved in a mixed solvent of 1,4-dioxane (4 mL) and water (0.4 mL), and the mixture was stirred with heating under a nitrogen atmosphere at 85°C for 3 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate.
25 The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (0.219 g, 3.73 mmol, yield 87%).

30 [0788]

<Example BQ2> 3-[3-Methyl-2-oxo-5-(piperazin-1-ylmethyl)-2,3-dihydro-1H-benzimidazol-1-yl]-1-{{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compound obtained in <Example BQ1>, the title
35 compound was obtained by the same method as in <Example BM8>.

[0789]

<Example BQ3> 3-{5-[(4-{ [(4R)-2'-Fluoro-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
5 2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperazin-1-yl)methyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

Using the compounds obtained in <Example V5> and <Example BQ2>, the title compound was obtained by the same method as in
10 <Example BM9>.

[0790]

<Example BQ4> 3-{5-[(4-{ [(4R)-2'-Fluoro-4'-{ [{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl} (3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-
15 2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperazin-1-yl)methyl]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

Using the compound obtained in <Example BQ3>, the title compound was obtained by the same method as in <Example BK9>.

20 [0791]

<Example BR1> tert-Butyl 4-{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate

To a suspension of 3-(5-amino-3-methyl-2-oxo-2,3-dihydro-
25 1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1) (0.606 g, 2.21 mmol), tert-butyl 4-oxo-1-piperidinecarboxylate (CAS Registry Number: 79099-07-3) (0.880 g, 4.42 mmol) in DCM (18 mL)-acetic acid (6 mL) was added dropwise borane-THF complex (0.89 mol/L THF solution, 5.0 mL, 4.5 mmol) at 0°C, and
30 the mixture was stirred at said temperature for 3 hr. To the reaction mixture were added ice and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced
35 pressure. The residue was purified by silica gel column

chromatography (ethyl acetate/methanol) to give the title compound (0.951 g, 2.08 mmol, yield 94%).

[0792]

<Example BR2> 3-[3-Methyl-2-oxo-5-(piperidin-4-ylamino)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example BR1>, the title compound was obtained by the same method as in <Example A05>.

[0793]

10 <Example BR3> 3-{5-[(1-[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl]amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

Using the compounds obtained in <Example V5> and <Example BR2>, the title compound was obtained by the same method as in <Example BM9>.

[0794]

20 <Example BS1> tert-Butyl 4-{[2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-1H-isoindol-5-yl]amino}piperidine-1-carboxylate

To a solution of 3-(6-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (WO2017197056 A1) (0.103 g, 0.356 mmol) and tert-butyl 4-oxo-1-piperidinecarboxylate (CAS Registry Number: 79099-07-3) (0.108 g, 0.542 mmol) in DMF (3 mL)-acetic acid (1 mL) was added 10% palladium carbon (0.100 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2.5 hr, and stirred with heating at 50°C for 3 hr. The reaction mixture was filtered through celite, the filtrate was neutralized with saturated aqueous sodium hydrogen carbonate solution and extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was washed with diethyl ether to give the title compound (0.096 g, 0.22 mmol, yield 61%).

[0795]

<Example BS2> 3-[1-Oxo-6-(piperidin-4-ylamino)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example BS1>, the title
5 compound was obtained by the same method as in <Example A05>.

[0796]

<Example BS3> 3-{6-[(1-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
10 2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-1-oxo-1,3-dihydro-2H-isoindol-2-yl}piperidine-2,6-dione

Using the compounds obtained in <Example B01> and
<Example BS2>, the title compound was obtained by the same
15 method as in <Example BM9>.

[0797]

<Example BT1> 5-Fluoro-6-iodo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one

5-Fluoro-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (ACS
20 Med. Chem. Lett., 2014, 5, 11, 1190.) (1.2 g, 7.2 mmol) was dissolved in acetic acid (15 mL), N-iodosuccinimide (1.8 g, 7.9 mmol) was added at room temperature, and the mixture was stirred for 18 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration and
25 dried under reduced pressure to give the title compound (1.5 g, 5.1 mmol, yield 71%).

[0798]

<Example BT2> 3-(6-Fluoro-5-iodo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione
30

Using the compound obtained in <Example BT1>, the title compound was obtained by the same method as in <Example Z5>.

[0799]

<Example BT3> tert-Butyl [1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-6-fluoro-3-
35

methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]carbamate

To 3-(6-fluoro-5-iodo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (50 mg, 0.094 mmol) were added tert-butyl carbamate (CAS Registry Number: 4248-19-5) (22 mg, 0.187 mmol), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (CAS Registry Number: 84030-20-6) (43 mg, 0.28 mmol), [(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (CAS Registry Number: 1447963-75-8) (7.5 mg, 0.0094 mmol), and DMSO (0.7 mL) at room temperature, and the mixture was stirred for 6 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (20 mg, 0.038 mmol, yield 41%).

[0800]

<Example BT4> 3-(5-Amino-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-(hydroxymethyl)piperidine-2,6-dione

To a solution of tert-butyl [1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]carbamate (20 mg, 0.038 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.5 mL) at room temperature, and the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (5.5 mg, 0.038 mmol, yield 50%).

[0801]

<Example BT5> tert-Butyl 4-{[1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}piperidine-1-carboxylate

Using the compound obtained in <Example BT4>, the title compound was obtained by the same method as in <Example BR1>.
[0802]

<Example BT6> 3-{6-Fluoro-5-[(1-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

10 Using the compounds obtained in <Example BT5> and <Example B01>, the title compound was obtained by the same method as in <Example CD2>.

[0803]

<Example BU1> 4,5-Dihydroimidazo[1,5,4-de][1,4]benzoxazin-2(1H)-one

Under ice-cooling, to a solution of 3,4-dihydro-2H-1,4-benzoxazin-5-amine (CAS Registry Number: 137469-91-1) (2.3 g, 15 mmol) in DCM (50 mL) was added dropwise a solution of triphosgene (2.3 g, 7.7 mmol) in DCM (5 mL), and pyridine (3.7 mL, 46 mmol) was gradually added. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with chloroform. The organic layer was washed successively with 1 mol/L hydrochloric acid and saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure, and dried under reduced pressure to give the title compound (2.1 g, 12 mmol, yield 78%).

[0804]

30 <Example BU2> 7-Iodo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-2(1H)-one

Using the compound obtained in <Example BU1>, the title compound was obtained by the same method as in <Example AW1>.

[0805]

35 <Example BU3> 3-(7-Iodo-2-oxo-4,5-dihydroimidazo[1,5,4-

de][1,4]benzoxazin-1(2H)-yl)-1-{[2-

(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compound obtained in <Example BU2>, the title compound was obtained by the same method as in <Example Z5>.

5 [0806]

<Example BU4> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-2-oxo-1,2,4,5-tetrahydroimidazo[1,5,4-de][1,4]benzoxazine-7-carboxylate

Using the compound obtained in <Example BU3>, the title
10 compound was obtained by the same method as in <Example BY5>.

[0807]

<Example BU5> 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
15 2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compounds obtained in <Example BU4> and
20 <Example A05>, the title compound was obtained by the same method as in <Example BI1>.

[0808]

<Example BU6> 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-
25 2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-4,5-dihydroimidazo[1,5,4-de][1,4]benzoxazin-1(2H)-yl}piperidine-2,6-dione

Using the compound obtained in <Example BU5>, the title
30 compound was obtained by the same method as in <Example BK9>.

[0809]

<Example BV1> tert-Butyl [(3S*,4S*)-4-(2-fluoro-3-nitrophenoxy)THF-3-yl]carbamate

Using tert-butyl [(3R*,4S*)-4-hydroxytetrahydrofuran-3-yl]carbamate (WO2020012334 A1) and 2-fluoro-3-nitrophenol (CAS
35

Registry Number: 179816-26-3), the title compound was obtained by the same method as in <Example AY4>.

[0810]

<Example BV2> (3S*,4S*)-4-(2-Fluoro-3-

5 nitrophenoxy)tetrahydrofuran-3-amine monohydrochloride

Using the compound obtained in <Example BV1>, the title compound was obtained by the same method as in <Example AO5>.

[0811]

<Example BV3> (3aS*,9aS*)-8-Nitro-3,3a,9,9a-tetrahydro-1H-

10 furo[3,4-b][1,4]benzoxazine

At room temperature, to a solution of (3S*,4S*)-4-(2-fluoro-3-nitrophenoxy)tetrahydrofuran-3-amine monohydrochloride (554 mg, 1.99 mmol) in DMF (15 mL) was added potassium carbonate (550 mg, 3.98 mmol), and the mixture was stirred at
15 60°C for 2 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give
20 the title compound (460 mg, 2.07 mmol, yield: quantitative).

[0812]

<Example BV4> (3aS*,9aS*)-3,3a,9,9a-Tetrahydro-1H-furo[3,4-b][1,4]benzoxazin-8-amine

Using the compound obtained in <Example BV3>, the title
25 compound was obtained by the same method as in <Example BK5>.

[0813]

<Example BV5> (6aS*,9aS*)-6a,7,9,9a-Tetrahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazin-1(2H)-one

Using the compound obtained in <Example BV4>, the title
30 compound was obtained by the same method as in <Example BU1>.

[0814]

<Example BV6> (6aS*,9aS*)-5-Iodo-6a,7,9,9a-tetrahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazin-1(2H)-one

Using the compound obtained in <Example BV5>, the title
35 compound was obtained by the same method as in <Example AW1>.

[0815]

<Example BV7> 3-[(6aS*,9aS*)-5-Iodo-1-oxo-6a,7,9,9a-tetrahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazin-2(1H)-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

5 Using the compound obtained in <Example BV6>, the title compound was obtained by the same method as in <Example Z5>.

[0816]

<Example BV8> 2,4,6-Trichlorophenyl (6aS*,9aS*)-2-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-1-oxo-

10 1,2,6a,7,9,9a-hexahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazine-5-carboxylate

 Using the compound obtained in <Example BV7>, the title compound was obtained by the same method as in <Example BY5>.

[0817]

15 <Example BV9> 3-[(6aS*,9aS*)-5-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-1-oxo-6a,7,9,9a-tetrahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazin-2(1H)-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

 Using the compounds obtained in <Example BV8> and <Example A05>, the title compound was obtained by the same method as in <Example BI1>.

25 [0818]

<Example BV10> 3-[(6aS*,9aS*)-5-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-

30 yl)carbonyl]-1-oxo-6a,7,9,9a-tetrahydrofuro[3,4-b]imidazo[1,5,4-de][1,4]benzoxazin-2(1H)-yl]piperidine-2,6-dione

 Using the compound obtained in <Example BV9>, the title compound was obtained by the same method as in <Example BK9>.

35 [0819]

<Example BW1> tert-Butyl 3-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino}azetidine-1-carboxylate

5 Using the compound obtained in <Example BK5> and tert-butyl 3-oxoazetidine-1-carboxylate (CAS Registry Number: 398489-26-4), the title compound was obtained by the same method as in <Example AS2>.

[0820]

10 <Example BW2> 3-[7-(Azetidin-3-ylamino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]-1-(hydroxymethyl)piperidine-2,6-dione dihydrochloride

 Using the compound obtained in <Example BW1>, the title compound was obtained by the same method as in <Example AO5>.

15 [0821]

<Example BW3> 3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}azetidin-3-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione

 3-[7-(Azetidin-3-ylamino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]-1-(hydroxymethyl)piperidine-2,6-dione dihydrochloride (0.138 g, 25 0.301 mmol), (4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride (0.110 g, 0.168 mmol), and HATU (0.083 g, 0.22 mmol) were dissolved in DMF (2 mL), DIPEA 30 (0.142 mL, 0.830 mmol) was added, and the mixture was stirred at room temperature for 19 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the 35 filtrate was concentrated under reduced pressure. The residue

was dissolved in ethyl acetate (1 mL), and N,N'-dimethylethylenediamine (0.020 mL, 0.19 mmol) was added. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title
5 compound (0.061 g, 0.064 mmol, yield 38%).

[0822]

<Example BX1> 7-Fluoro-6-iodo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one

7-Fluoro-1-methyl-1,3-dihydro-2H-benzimidazol-2-one
10 (WO2016097749 A1) (0.40 g, 2.4 mmol) was dissolved in acetic acid (10 mL), N-iodosuccinimide (0.61 g, 2.7 mmol) was added at room temperature, and the mixture was stirred for 18 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration, and dried under reduced pressure
15 to give the title compound (0.66 g, 2.3 mmol, yield 96%).

[0823]

<Example BX2> 3-(4-Fluoro-5-iodo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

20 Using the compound obtained in <Example BX1>, the title compound was obtained by the same method as in <Example Z5>.

[0824]

<Example BX3> tert-Butyl [1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-4-fluoro-3-
25 methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]carbamate

Using the compound obtained in <Example BX2>, the title compound was obtained by the same method as in <Example BT3>.

[0825]

<Example BX4> tert-Butyl 4-[[1-(2,6-dioxopiperidin-3-yl)-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-
30 yl]amino]piperidine-1-carboxylate

To a solution of tert-butyl [1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-4-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]carbamate (62 mg,
35 0.12 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL)

at room temperature, and the mixture was stirred for 1 hr and concentrated under reduced pressure. A solution of the residue and tert-butyl 4-oxo-1-piperidinecarboxylate (CAS Registry Number: 79099-07-3) in DCM (0.8 mL)-acetic acid (0.3 mL) was cooled to 0°C, borane-THF complex (0.89 mol/mL THF solution, 0.27 mL, 0.24 mmol) was added dropwise, and the mixture was stirred at said temperature for 5 min. To the reaction mixture were added ice and saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate (2 mL), N,N'-dimethylethylenediamine (0.014 mL, 0.13 mmol) was added and the mixture was stirred at room temperature for 30 min, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (51 mg, 0.11 mmol, yield 89%).

[0826]

<Example BX5> 3-[4-Fluoro-3-methyl-2-oxo-5-(piperidin-4-ylamino)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione dihydrochloride

Using the compound obtained in <Example BX4>, the title compound was obtained by the same method as in <Example A05>.

[0827]

<Example BX6> 3-{4-Fluoro-5-[(1-{[(4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

Using the compounds obtained in <Example BX5> and <Example V5>, the title compound was obtained by the same method as in <Example BM9>.

[0828]

<Example BY1> 5,8-dibromo-1,2,3,4-tetrahydroquinoxaline

To a suspension of 5,8-dibromoquinoxaline (CAS Registry Number: 148231-12-3) (4.47 g, 15.5 mmol) in ethanol (75 mL) was added sodium borohydride (4.67 g, 123 mmol), and the mixture
5 was stirred at 50°C for 1 hr. The reaction mixture was cooled to room temperature, water was added, and the mixture was concentrated under reduced pressure, and extracted with DCM. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. To
10 the residue was added IPA, and the mixture was dissolved at 60°C and stirred at room temperature. The precipitated solid was collected by filtration, washed with hexane, and dried under reduced pressure at 60°C to give the title compound (2.64 g, 9.04 mmol, yield 58%).

15 [0829]

<Example BY2> 5,8-Dibromo-N-(2,6-dioxopiperidin-3-yl)-3,4-dihydroquinoxaline-1(2H)-carboxamide

A solution of 5,8-dibromo-1,2,3,4-tetrahydroquinoxaline (6.31 g, 21.6 mmol) in DCM (40 mL) was ice-cooled, and a
20 solution of triphosgene (2.69 g, 9.08 mmol) in DCM (40 mL) was added dropwise. After stirring at said temperature for 5 min, triethylamine (6.00 mL, 43.3 mmol) was added dropwise, and the mixture was stirred at said temperature for 45 min. Water was added to the reaction mixture, and the mixture was extracted
25 with DCM. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. To a solution of the residue in acetonitrile (110 mL) were added 3-aminopiperidine-2,6-dione monohydrochloride (CAS Registry Number: 24666-56-6) (3.91 g, 23.8 mmol) and
30 triethylamine (15 mL, 108 mmol), and the mixture was stirred at 50°C for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with DCM. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was slurry
35 washed with IPA/diethyl ether to give the title compound (6.77

g, 15.2 mmol, yield 70%).

[0830]

<Example BY3> 5,8-Dibromo-N-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3,4-

5 dihydroquinoxaline-1(2H)-carboxamide

To a solution of 5,8-dibromo-N-(2,6-dioxopiperidin-3-yl)-3,4-dihydroquinoxaline-1(2H)-carboxamide (6.77 g, 15.2 mmol) in DMF (60 mL) were added, under ice-cooling, 1,8-diazabicyclo[5.4.0]-7-undecene (4.53 mL, 30.4 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (4.0 mL, 23 mmol), and the mixture was stirred at room temperature for 2 hr, and then heated to 40°C and stirred for 30 min. The reaction mixture cooled to room temperature, 2-(trimethylsilyl)ethoxymethyl chloride (0.53 mL, 3.0 mmol) was added. The mixture was stirred at room temperature for 2 hr and left standing overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the title compound (7.54 g, 13.1 mmol, yield 86%).

[0831]

<Example BY4> 3-(7-Bromo-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl)-1-{[2-

25 (trimethylsilyl)ethoxy]methyl}piperidine-2,6-dione

A suspension of 5,8-dibromo-N-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-3,4-dihydroquinoxaline-1(2H)-carboxamide (7.54 g, 13.1 mmol), copper(I) iodide (250 mg, 1.31 mmol), trans-4-hydroxy-L-proline (345 mg, 2.63 mmol), and tripotassium phosphate (5.55 g, 26.2 mmol) in DMSO (52 mL) was stirred at 80°C for 2 hr. The reaction mixture was cooled to room temperature, filtered through celite, and insoluble material was filtered off. The filtrate was diluted with ethyl acetate and washed successively with water and saturated brine. The organic layer was dried

over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (4.51 g, 9.10 mmol, yield 70%).

5 [0832]

<Example BY5> 2,4,6-Trichlorophenyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[1,5,4-de]quinoxaline-7-carboxylate

A solution of 3-(7-bromo-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl)-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (1.00 g, 2.02 mmol), palladium(II) acetate (22 mg, 0.098 mmol), XantPhos (117 mg, 0.202 mmol), and 2,4,6-trichlorophenyl formate (CAS Registry Number: 4525-65-9) (680 mg, 3.02 mmol) in toluene (10 mL) was deaerated, and purged with nitrogen. Then, triethylamine (0.560 mL, 4.04 mmol) was added, and the mixture was stirred under a carbon monoxide atmosphere at 110°C for 4 hr. To the reaction mixture were added palladium(II) acetate (22 mg, 0.098 mmol) and XantPhos (117 mg, 0.202 mmol), and the mixture was stirred again at 110°C for 4 hr. The reaction mixture was cooled to room temperature, filtered through celite, washed with ethyl acetate, and insoluble material was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (814 mg, 1.27 mmol, yield 63%).

[0833]

<Example BY6> 3-{7-[(4-[(4R)-4'-([2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl)-1-([2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione

35 To a suspension of 2,4,6-trichlorophenyl 1-(2,6-dioxo-1-

{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[1,5,4-de]quinoxaline-7-carboxylate (14.0 g, 21.9 mmol) and 3,3,3-trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-{[(4'R)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl]methyl}propan-1-amine dihydrochloride (15.5 g, 21.3 mmol) in acetonitrile (150 mL) were added DIPEA (19 mL, 109 mmol) and 4-dimethylaminopyridine (800 mg, 6.55 mmol), and the mixture was stirred at room
10 temperature for 4 days. The reaction mixture was diluted with ethyl acetate, washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified
15 by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (19.1 g, 17.4 mmol, yield 80%).

[0834]

<Example BY7> 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})-(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl})-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione

To a solution of 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl})-(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl})-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidine-2,6-
30 dione (23.1 g, 21.0 mmol) in DCM (42 mL) was added trifluoroacetic acid (42 mL), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, saturated aqueous sodium hydrogen carbonate solution
35 was added and the mixture was stirred. Two layers were

separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. To a solution of the
5 residue in ethyl acetate (105 mL) was added N,N'-dimethylethylenediamine (2.49 mL, 23.2 mmol), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with ethyl acetate, and washed successively with saturated aqueous sodium hydrogen carbonate solution and
10 saturated brine. The organic layer was dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol). The obtained solid was slurry washed with hexane/ethyl acetate, and dried
15 under reduced pressure at 60°C to give the title compound (14.0 g, 14.5 mmol, yield 69%).

[0835]

<Example BZ1> tert-Butyl (4S)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
20 2,3,4,5-tetrahydro[biphenyl]-4-carboxylate

Using the compounds obtained in <Example M3> and <Example W3>, the title compound was obtained by the same method as in <Example W4>.

25 [0836]

<Example BZ2> [(4S)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methanol

30 Using the compound obtained in <Example BZ1>, the title compound was obtained by the same method as in <Example W5>.

[0837]

<Example BZ3> [(4S)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
35

yl)methyl methanesulfonate

Using the compound obtained in <Example BZ2>, the title compound was obtained by the same method as in <Example X1>.

[0838]

5 <Example BZ4> tert-Butyl 4-{{[(4S)-4'-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazine-1-carboxylate

10 Using the compound obtained in <Example BZ3>, the title compound was obtained by the same method as in <Example X2>.

[0839]

<Example BZ5> 3,3,3-Trifluoro-N-{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}-2,2-dimethyl-N-
15 {{[(4'S)-4'-(piperazin-1-ylmethyl)-2',3',4',5'-tetrahydro[biphenyl]-4-yl)methyl}propan-1-amine dihydrochloride

Using the compound obtained in <Example BZ4>, the title compound was obtained by the same method as in <Example A05>.

[0840]

20 <Example BZ6> 3-{7-[(4-{{[(4S)-4'-{{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-
25 1(2H)-yl}-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidine-2,6-dione

Using the compounds obtained in <Example BZ5> and <Example BY5>, the title compound was obtained by the same method as in <Example BI1>.

30 [0841]

<Example BZ7> 3-{7-[(4-{{[(4S)-4'-{{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl}piperazin-1-
35 yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-

1(2H)-yl}piperidine-2,6-dione

Using the compound obtained in <Example BZ6>, the title compound was obtained by the same method as in <Example BK9>. [0842]

5 <Example CA1> 4-{[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]amino}-N-[4-(trans-4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}cyclohexyl)phenyl]piperidine-1-
10 carboxamide

To a solution of triphosgene (14.2 mg, 0.0479 mmol) in DCM (1 mL) were successively added, under ice-cooling, 4-(trans-4-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}cyclohexyl)aniline dihydrochloride
15 (50.5 mg, 0.0826 mmol) and triethylamine (0.0576 mL, 0.413 mmol), and the mixture was stirred at said temperature for 1 hr. The reaction mixture was warmed to room temperature, and stirred for 1 hr. To the reaction mixture were added 3-[3-methyl-2-oxo-5-(piperidin-4-ylamino)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione dihydrochloride (35.9
20 mg, 0.0834 mmol) and triethylamine (0.0576 mL, 0.413 mmol), and the mixture was stirred for 15 min. To the reaction mixture was added 3-[3-methyl-2-oxo-5-(piperidin-4-ylamino)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione
25 dihydrochloride (33.4 mg, 0.0776 mmol), and the mixture was further stirred for 45 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with DCM. The organic layer was dried
30 over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/methanol). The obtained solid was washed with hexane/ethyl acetate and dried under reduced pressure to give the title compound (26.1 mg,
35 0.0272 mmol, yield 33%).

[0843]

<Example CB1> 9-Nitro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine
-5-one

Methyl 2-fluoro-3-nitrobenzoate (CAS Registry Number:
5 946126-94-9) (5.00 g, 25.1 mmol) was dissolved in DMF (50 mL),
potassium carbonate (4.86 g, 35.2 mmol) and N-(tert-
butoxycarbonyl)-1,2-diaminoethane (CAS Registry Number: 57260-
73-8) (4.0 mL, 25 mmol) were added, and the mixture was stirred
at room temperature for 3 hr. To the reaction mixture was
10 added N-(tert-butoxycarbonyl)-1,2-diaminoethane (1.0 mL, 6.3
mmol), and the mixture was stirred at room temperature for 15
hr. Water was added to the reaction mixture, and the mixture
was extracted with ethyl acetate. The organic layer was washed
with saturated aqueous ammonium chloride solution, dried over
15 sodium sulfate and filtered, and the filtrate was concentrated
under reduced pressure. The residue was dissolved in DCM (40
mL), 4 mol/L hydrogen chloride/1,4-dioxane solution (65 mL, 260
mmol) was added, and the mixture was stirred at room
temperature for 2 hr and concentrated under reduced pressure.
20 The residue was suspended in ethanol (100 mL), sodium carbonate
(27.1 g, 256 mmol) was added, and the mixture was stirred with
heating at 90°C for 5 hr. The reaction mixture was
concentrated under reduced pressure, water was added and the
mixture was stirred. The resulting solid was collected by
25 filtration while washing with water and dried under reduced
pressure to give the title compound (5.42 g, 26.2 mmol, yield:
quantitative).

[0844]

<Example CB2> tert-Butyl 9-nitro-1,2,3,5-tetrahydro-4H-1,4-
30 benzodiazepine-4-carboxylate

9-Nitro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one
(5.20 g, 25.1 mmol) was suspended in DCM (50 mL), DIPEA (9.0
mL, 53 mmol) and di-tert-butyl dicarbonate (7.57 g, 34.7 mmol)
were added, and the mixture was stirred at room temperature for
35 30 min. To the reaction mixture were added DCM (200 mL) and 4-

dimethylaminopyridine (0.68 g, 5.6 mmol), and the mixture was stirred with heating at 40°C for 2.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with
5 saturated aqueous ammonium chloride solution and saturated brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (100 mL), borane-THF complex (0.89 mol/L THF solution, 56 mL, 50 mmol) was added
10 dropwise thereto, and the mixture was stirred with heating at 60°C for 30 min. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and filtered, and
15 the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (5.58 g, 19.0 mmol, yield 76%).

[0845]

20 <Example CB3> tert-Butyl 2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

tert-Butyl 9-nitro-1,2,3,5-tetrahydro-4H-1,4-benzodiazepine-4-carboxylate (5.58 g, 19.0 mmol) was dissolved in THF (100 mL), 10% palladium carbon (5.28 g) was added, and
25 the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hr, and then stirred with heating at 40°C for 1.5 hr. To the reaction mixture was added ethanol (50 mL), and the mixture was stirred with heating at 80°C for 2 hr. The reaction mixture was filtered through celite and the filtrate
30 was concentrated under reduced pressure. The residue was dissolved in THF (100 mL), 1,1'-carbonyldiimidazole (4.63 g, 28.6 mmol) was added, and the mixture was stirred with heating at 60°C for 1 hr. To the reaction mixture was added 1 mol/L aqueous sodium hydroxide solution, and the mixture was
35 extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (4.57 g, 15.8 mmol, yield 83%).

[0846]

<Example CB4> tert-Butyl 8-iodo-2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

10 Using the compound obtained in <Example CB3>, the title compound was obtained by the same method as in <Example AW1>.

[0847]

<Example CB5> tert-Butyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-8-iodo-2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

Using the compound obtained in <Example CB4>, the title compound was obtained by the same method as in <Example Z5>.

[0848]

20 <Example CB6> tert-Butyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-8-formyl-2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

tert-Butyl 1-(2,6-dioxo-1-([2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-8-iodo-2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate (0.502 g, 0.765 mmol), saccharin (CAS Registry Number: 81-07-2) (0.209 g, 1.14 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride DCM adduct (0.062 g, 0.076 mmol), sodium carbonate (0.121 g, 1.14 mmol), and triethylsilane (0.182 mL, 1.14 mmol) were dissolved in DMF (6 mL), and the mixture was stirred with heating at 85°C for 3 hr under a carbon monoxide atmosphere. The reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic

layer was washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
5 compound (0.432 g, 0.773 mmol, yield: quantitative).

[0849]

<Example CB7> tert-Butyl 8-({4-[(benzyloxy)carbonyl]piperazin-1-yl)methyl)-1-(2,6-dioxo-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-2-oxo-1,2,4,5-
10 tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

Using the compound obtained in <Example CB6>, the title compound was obtained by the same method as in <Example AS2>.

[0850]

15 <Example CB8> tert-Butyl 1-(2,6-dioxo-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-2-oxo-8-(piperazin-1-ylmethyl)-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

Using the compound obtained in <Example CB7>, the title
20 compound was obtained by the same method as in <Example AS4>.

[0851]

<Example CB9> tert-Butyl 1-(2,6-dioxo-1-{{2-(trimethylsilyl)ethoxy)methyl}piperidin-3-yl)-8-[(4-{{(4R)-2'-fluoro-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-
25 dimethyltetrahydro-2H-pyran-4-yl}ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl}carbonyl}piperazin-1-yl)methyl]-2-oxo-1,2,4,5-tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-carboxylate

30 Using the compounds obtained in <Example CB8> and <Example V5>, the title compound was obtained by the same method as in <Example BM9>.

[0852]

<Example CB10> 3-{8-[(4-{{(4R)-2'-Fluoro-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-
35 methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
 2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperazin-1-
 yl)methyl]-6-methyl-2-oxo-4,5,6,7-tetrahydroimidazo[4,5,1-
 jk][1,4]benzodiazepin-1(2H)-yl}piperidine-2,6-dione

5 tert-Butyl 1-(2,6-dioxo-1-{[2-
 (trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-8-[(4-{[(4R)-2'-
 fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-
 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-
 dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-
 10 yl]carbonyl}piperazin-1-yl)methyl]-2-oxo-1,2,4,5-
 tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-6(7H)-
 carboxylate (0.256 g, 0.208 mmol) was dissolved in acetonitrile
 (2 mL), para-toluenesulfonic acid monohydrate (0.258 g, 1.36
 mmol) was added, and the mixture was stirred at room
 15 temperature for 5 hr. To the reaction mixture was added para-
 toluenesulfonic acid monohydrate (0.045 g, 0.24 mmol), and the
 mixture was stirred at room temperature for 18 hr. To the
 reaction mixture was added para-toluenesulfonic acid
 monohydrate (0.083 g, 0.44 mmol), and the mixture was stirred
 20 at room temperature for 23 hr. To the reaction mixture was
 added saturated aqueous sodium hydrogen carbonate solution, and
 the mixture was extracted with ethyl acetate. The organic
 layer was dried over sodium sulfate and filtered, and the
 filtrate was concentrated under reduced pressure. The residue
 25 was dissolved in DCM (2 mL), acetic acid (0.120 mL, 2.10 mmol),
 sodium triacetoxyborohydride (0.240 g, 1.13 mmol), and 37%
 aqueous formaldehyde solution (0.100 mL, 1.34 mmol) were added,
 and the mixture was stirred at room temperature for 3.5 hr. To
 the reaction mixture was added saturated aqueous sodium
 30 hydrogen carbonate solution, and the mixture was extracted with
 DCM. The organic layer was dried over sodium sulfate and
 filtered, and the filtrate was concentrated under reduced
 pressure. The residue was dissolved in DCM (1 mL),
 trifluoroacetic acid (1.0 mL) was added, and the mixture was
 35 stirred at room temperature for 1.5 hr. To the reaction

mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The
5 residue was dissolved in ethyl acetate (1 mL), N,N'-dimethylethylenediamine (0.023 mL, 0.21 mmol) was added, and the mixture was left standing at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography (DCM/methanol) to give the title compound (0.106
10 g, 0.105 mmol, yield 50%).

[0853]

<Example CC1> N-[1-(2,6-Dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]-2-nitrobenzenesulfonamide
15 3-(7-Amino-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl)-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidine-2,6-dione (0.200 g, 0.464 mmol) was dissolved in pyridine (2 mL), 2-nitrobenzenesulfonyl chloride (CAS Registry Number: 1694-92-4)
20 (0.134 g, 0.605 mmol) was added, and the mixture was stirred at room temperature for 4 hr. To the reaction mixture was added 20% aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with
25 saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (0.301 g, 0.489 mmol, yield: quantitative).

30 [0854]

<Example CC2> tert-Butyl (7-exo)-7-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy)methyl]piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino}-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

35 Using the compound obtained in <Example CC1> and tert-

butyl (7-endo)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (CAS Registry Number: 1148006-31-8), the title compound was obtained by sequentially performing the same operations as in <Example AY4> and <Example AY5>.

5 [0855]

<Example CC3> 3-[7-{[(7-Exo)-9-{[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}-3-oxa-9-

10 azabicyclo[3.3.1]nonan-7-yl]amino}-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione

tert-Butyl (7-exo)-7-{[1-(2,6-dioxo-1-{[2-(trimethylsilyl)ethoxy]methyl}piperidin-3-yl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinolin-7-yl]amino}-3-oxa-9-

15 azabicyclo[3.3.1]nonane-9-carboxylate (0.103 g, 0.157 mmol) was dissolved in DCM (1 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, (4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-

20 dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride (0.085 g, 0.13 mmol), HATU (0.073 g, 0.19 mmol), DMF (2 mL), and DIPEA (0.22 mL, 1.3 mmol) were added to the residue, and the mixture was stirred at room

25 temperature for 16 hr. To the reaction mixture was added DIPEA (0.22 mL, 1.3 mmol), and the mixture was left standing at room temperature for 10 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer

30 was washed successively with water and saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (1 mL), N,N'-dimethylethylenediamine (0.015 mL, 0.14 mmol) was added, and the mixture was left standing at
35 room temperature for 1 hr. The reaction mixture was purified

by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (0.081 g, 0.079 mmol, yield 61%).

[0856]

<Example CD1> tert-Butyl 4-{{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]amino}piperidine-1-carboxylate

Using 3-(4-amino-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (WO2021170109 A1), the title compound was obtained by the same method as in <Example BR1>.

[0857]

<Example CD2> 3-{4-[(1-{{(4R)-2'-Fluoro-4'-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl]amino]-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione

To a solution of tert-butyl 4-{{[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]amino}piperidine-1-carboxylate (143 mg, 0.312 mmol) in DCM (1 mL) was added trifluoroacetic acid (1 mL) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with DMF (3 mL). DIPEA (0.55 mL, 3.21 mmol), (4R)-2'-fluoro-4'-{{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid monohydrochloride (200 mg, 0.312 mmol), and HATU (145 mg, 0.381 mmol) were added thereto, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The obtained organic layers were combined, washed with saturated brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography (ethyl acetate/methanol) to give the title compound (242 mg, 0.252 mmol, yield 81%).

[0858]

5 <Example CE1> (3S)-3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione

10 <Example CF1> (3R)-3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione

The diastereomeric mixture of 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione (1.04 g, 1.07 mmol) was optically resolved by chiral HPLC [column: CHIRALPAK IF (registered trademark, Daicel Corporation), mobile phase: ethyl acetate/THF = 90/10 (V/V)] to obtain S form as the component eluted first and R form as the component eluted later. The obtained solids were respectively washed with hexane/ethyl acetate and dried under reduced pressure at 60°C to obtain S form <Example CE1> (306 mg, 0.316 mmol, yield 29%) and R form <Example CF1> (304 mg, 0.314 mmol, yield 29%).

Analysis conditions column: CHIRALPAK IF (registered trademark, Daicel Corporation), size: 0.46 cm×15 cm, flow rate: 1.0 mL/min, temperature: 40°C, mobile phase: ethyl acetate/THF=90/10 (V/V), retention time: S form <Example CE1> 6.2 min, R form <Example CF1> 8.5 min

[0859]

<Example CG1> <Example CH1> (3S) or (3R)-{7-[(1-[(4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione

The diastereomeric mixture of 3-{7-[(1-[(4R)-2'-fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl]piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione (0.103 g, 0.105 mmol) was optically resolved by chiral HPLC [column: CHIRALPAK IF (registered trademark, Daicel Corporation), mobile phase: ethyl acetate/THF = 90/10 (V/V)] to obtain <Example CG1> (0.0400 g, 0.0406 mmol, yield: 39%) as the component eluted first and <Example CH1> (0.0407 g, 0.0413 mmol, yield: 40%) as the component eluted later.

Analysis conditions column: CHIRALPAK IF (registered trademark, Daicel Corporation), size: 0.46 cm×15 cm, flow rate: 1.0 mL/min, temperature: 40°C, mobile phase: ethyl acetate/THF=90/10 (V/V), retention time: <Example CG1> 6.7 min, <Example CH1> 10 min

[0860]

<Example CI1> 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione monobenzenesulfonate

The compound (300 mg) obtained in Example AW5 was dissolved in acetonitrile (3.0 mL), benzenesulfonic acid monohydrate (54.7 mg) was added at room temperature, and the mixture was stirred for 27 hr. The precipitated solid was

collected by filtration, and dried at room temperature for 15 hr to give the title compound (278 mg) as crystals (elemental analysis Found; C: 63.54%, H: 6.90%, N: 7.25%, F: 4.83%, S: 2.68%).

5 ¹H-NMR (DMSO-D₆) δ: 11.12 (1H, s), 9.32 (1H, br s), 7.61-7.57 (2H, m), 7.34-7.26 (5H, m), 7.19 (2H, d, J = 9.2 Hz), 7.07 (2H, d, J = 8.1 Hz), 7.02 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 8.0 Hz), 6.81 (2H, d, J = 8.8 Hz), 6.12 (1H, s), 5.40-5.35 (1H, m), 4.89-4.82 (0.4H, m), 4.57 (1H, br s), 3.84-3.75 (2H, m), 3.73-
10 3.60 (5H, m), 3.59-3.52 (2.5H, m), 3.48-3.41 (3.5H, m), 3.21-2.97 (5H, m), 2.96-2.87 (1.5H, m), 2.81-2.60 (5.5H, m), 2.47-2.30 (7H, m), 2.27-2.19 (2H, m), 2.14-2.00 (7H, m), 2.00-1.92 (4H, m), 1.86-1.78 (2H, m), 1.77-1.70 (1.7H, m), 1.59-1.49 (3H, m), 1.47-1.34 (3.5H, m), 1.17 (3H, d, J = 6.3 Hz), 1.15 (0.4H, s),
15 s), 1.06 (3.7H, s), 0.86 (7H, s), 0.56 (4.3H, s);
MS (m/z): 968 (M+H)⁺.

[0861]

The obtained crystals were measured using a powder X-ray diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 1. In Fig. 1 showing the diffraction pattern of powder X-ray diffraction (CuKα, λ=1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 1.

[0862]

25 [Table 1]

Peak No.	2θ	d value	relative intensity	Peak No.	2θ	d value	relative intensity
1	2.15	41.00	100	6	20.00	4.44	27
2	8.30	10.64	15	7	21.34	4.16	32
3	10.29	8.59	17	8	22.68	3.92	26
4	14.75	6.00	35	9	23.77	3.74	25
5	17.19	5.15	36	10	25.23	3.53	16

[0863]

<Example CJ1> 3-{7-[(4-{ [(4R)-4'-{ [{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-
2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl)piperazin-1-
yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-
1(2H)-yl}piperidine-2,6-dione monoethanesulfonate

5 The compound (300 mg) obtained in Example AW5 was
dissolved in acetonitrile (1.5 mL), ethanesulfonic acid (25.5
μL) was added at room temperature, and the mixture was stirred
for 30 min. Successively, isopropyl acetate (0.60 mL) was
added 5 times every 10 min at room temperature, and the mixture
10 was stirred for 24 hr. The precipitated solid was collected by
filtration and dried at room temperature for 15 hr to give the
title compound (264 mg) as crystals (elemental analysis Found;
C: 61.93%, H: 7.29%, N: 7.43%, F: 4.98%, S: 2.75%).

¹H-NMR (DMSO-D₆) δ: 11.12 (1H, s), 9.35 (1H, br s), 7.28 (2H,
15 d, J = 8.1 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.1
Hz), 7.02 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 8.0 Hz), 6.81
(2H, d, J = 8.9 Hz), 6.12 (1H, s), 5.41-5.35 (1H, m), 4.90-4.82
(0.4H, m), 4.57 (1H, br s), 3.84-3.75 (2.2H, m), 3.73-3.60 (5H,
m), 3.59-3.52 (2.2H, m), 3.48-3.40 (3H, m), 3.20-3.11 (3H, m),
20 2.97-2.88 (1.5H, m), 2.78 (2H, s), 2.75-2.66 (1.5H, m), 2.66-
2.63 (0.6H, m), 2.63-2.60 (1H, m), 2.47-2.44 (1.6H, m), 2.44-
2.30 (9H, m), 2.26-2.20 (2H, m), 2.14-2.00 (8H, m), 2.00-1.93
(4H, m), 1.86-1.78 (2H, m), 1.77-1.70 (2H, m), 1.58-1.50 (3H,
m), 1.47-1.33 (4H, m), 1.17 (3H, d, J = 6.3 Hz), 1.15-1.13
25 (0.6H, m), 1.08-1.03 (7H, m), 0.86 (7H, s), 0.56 (4H, s);
MS (m/z): 968 (M+H)⁺.

[0864]

The obtained crystals were measured using a powder X-ray
diffractometer (MiniFlex600-C, manufactured by Rigaku
30 Corporation), and the results are shown in Fig. 2. In Fig. 2
showing the diffraction pattern of powder X-ray diffraction
(CuKα, λ=1.54 angstroms, scanning speed=10°/min), the peaks
characteristic of the present crystals are shown in Table 2.

[0865]

35 [Table 2]

Peak No.	2 θ	d value	relative intensity	Peak No.	2 θ	d value	relative intensity
1	2.21	39.88	100	6	20.41	4.35	31
2	12.04	7.35	26	7	22.42	3.96	28
3	14.87	5.95	40	8	23.19	3.83	30
4	17.69	5.01	35	9	24.13	3.69	21
5	18.93	4.68	32	10	27.98	3.19	13

[0866]

<Example CK1> 3-{7-[(1-{[(4R)-2'-Fluoro-4'-{[2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-

5 yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]carbonyl}piperidin-4-yl)amino]-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl}piperidine-2,6-dione mono-10-camphorsulfonate

The compound (300 mg) obtained in Example BK9 was
10 dissolved in acetonitrile (6.0 mL), 10-camphorsulfonic acid solution (72.1 mg) was added at room temperature, and the mixture was stirred for 27 hr. The precipitated solid was collected by filtration, and dried at room temperature for 15 hr to give the title compound (352 mg) as crystals (elemental
15 analysis Found; C: 62.46%, H: 7.15%, N: 7.15%, F: 6.19%, S: 2.68%).

¹H-NMR (DMSO-D₆) δ : 11.09 (1H, s), 10.51 (1H, br s), 7.35-7.26 (0.3H, m), 7.21-7.13 (3H, m), 6.93-6.87 (2.2H, m), 6.80 (2H, d, J = 8.8 Hz), 5.94 (1H, s), 5.33 (1H, br s), 4.46 (1H, br s),
20 4.07 (1H, br s), 3.80-3.72 (1.5H, m), 3.70 (3H, s), 3.59-3.52 (2.5H, m), 3.46 (2H, s), 3.11 (1H, s), 2.97-2.87 (2.5H, m), 2.86 (0.6H, s), 2.84 (0.7H, s), 2.75-2.58 (4.7H, m), 2.41-2.28 (6H, m), 2.27-2.18 (3.2H, m), 2.13-2.03 (4.4H, m), 2.03-1.96 (2.3H, m), 1.95-1.90 (1.8H, m), 1.89-1.82 (2.3H, m), 1.82-1.80
25 (1H, m), 1.80-1.77 (1H, m), 1.77-1.70 (1H, m), 1.70-1.59 (1.2H, m), 1.57-1.49 (2.3H, m), 1.42-1.35 (1.5H, m), 1.30-1.22 (2.3H, m), 1.16-1.14 (0.4H, m), 1.05 (5.8H, d, J = 6.5 Hz), 0.92-0.87 (5.4H, m), 0.74 (3H, s), 0.56 (3H, s);

MS (m/z): 986 (M+H)⁺.

[0867]

The obtained crystals were measured using a powder X-ray diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 3. In Fig. 3 showing the diffraction pattern of powder X-ray diffraction (CuK α , λ =1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 3.

[0868]

[Table 3]

Peak No.	2 θ	d value	relative intensity	Peak No.	2 θ	d value	relative intensity
1	3.89	22.69	100	6	13.15	6.73	24
2	6.81	12.96	16	7	15.97	5.55	46
3	7.68	11.51	47	8	16.81	5.27	45
4	8.20	10.78	25	9	18.58	4.77	46
5	10.28	8.60	18	10	23.56	3.77	24

10

[0869]

<Example CL1> 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione monoethanesulfonate

The compound (3.0 g) obtained in Example BY7 was dissolved in acetonitrile (45.0 mL), a solution of ethanesulfonic acid in acetonitrile (0.21 mol/L; 15.0 mL) was added at 40°C over 3 hr, and the mixture was stirred at 40°C for 1 hr. Successively, and the mixture was stirred at room temperature for 20 hr. The precipitated solid was collected by filtration and dried at 40°C for 18 hr to give the title compound (3.0 g) as crystals (elemental analysis Found; C: 61.97%, H: 7.00%, N: 9.02%, F: 5.34%, S: 2.89%).

¹H-NMR (DMSO-D₆) δ : 11.10 (1H, br s), 9.33 (1H, br s), 7.28 (2.5H, d, J = 8.2 Hz), 7.19 (2.5H, d, J = 8.8 Hz), 7.07 (2.5H, d, J = 8.2 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.82 (2.5H, d, J =

8.9 Hz), 6.52 (1H, d, J = 8.3 Hz), 6.12 (1.1H, s), 6.05 (1H, s), 5.33-5.30 (1.1H, m), 4.15 (1.6H, br s), 3.90-3.79 (1.7H, m), 3.71 (3.1H, s), 3.62-3.49 (4H, m), 3.45 (4.1H, s), 3.41-3.36 (1.5H, m), 3.17-3.10 (4.1H, m), 2.94-2.88 (1.1H, m), 2.71-2.59 (2.3H, m), 2.48-2.44 (0.7H, m), 2.44-2.40 (1H, m), 2.40-2.30 (5H, m), 2.26-2.19 (0.5H, m), 2.15-2.07 (2.1H, m), 2.05-1.93 (2H, m), 1.86-1.78 (0.5H, m), 1.77-1.70 (0.5H, m), 1.57-1.50 (2H, m), 1.47-1.33 (2H, m), 1.15-1.14 (0.5H, m), 1.08-1.03 (6.5H, m), 0.86 (6.5H, s), 0.56 (6.5H, s);

10 MS (m/z): 969 (M+H)⁺.

[0870]

The obtained crystals were measured using a powder X-ray diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 4. In Fig. 4 showing the diffraction pattern of powder X-ray diffraction (CuK α , λ =1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 4.

[0871]

[Table 4]

Peak No.	2 θ	d value	relative intensity	Peak No.	2 θ	d value	relative intensity
1	2.27	38.85	44	6	15.80	5.60	74
2	8.18	10.80	70	7	16.91	5.24	94
3	9.88	8.94	74	8	17.77	4.99	72
4	13.09	6.76	59	9	18.87	4.70	73
5	14.57	6.08	100	10	20.14	4.41	80

20

[0872]

<Example CM1> 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl)piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione monosalicylate

The compound (50 mg) obtained in Example BY7 was dissolved in acetonitrile (1.5 mL), and a solution of salicylic

acid in acetonitrile (0.10 mol/L; 0.050 mL) was added, and the mixture was stirred at room temperature for 19 hr.

Successively, a solution of salicylic acid in acetonitrile (0.10 mol/L; 0.45 mL) was added over 8 hr, and the mixture was stirred at room temperature for 14 hr. The precipitated solid was collected by filtration and dried at 40°C to give the title compound (55 mg) as crystals (elemental analysis Found; C: 65.12%, H: 6.92%, N: 8.80%, F: 5.18%, S: 0.00%).

¹H-NMR (DMSO-D₆) δ: 11.09 (1H, s), 7.76-7.44 (1H, m), 7.44-7.37 (1H, m), 7.26 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.9 Hz), 7.05 (2H, d, J = 8.2 Hz), 6.89-6.79 (5H, m), 6.48 (1H, d, J = 8.2 Hz), 6.11 (1H, br s), 5.94 (1H, br s), 5.33-5.28 (1H, m), 3.86-3.79 (2.4H, m), 3.70 (3.3H, s), 3.62-3.50 (5H, m), 3.46-3.40 (5H, m), 2.95-2.86 (1.3H, m), 2.71-2.59 (4.2H, m), 2.45-2.29 (7.4H, m), 2.26-2.19 (1.4H, m), 2.13-2.07 (2.2H, m), 2.06-1.99 (1.3H, m), 1.96-1.78 (4.5H, m), 1.77-1.70 (1.2H, m), 1.58-1.50 (2.2H, m), 1.41-1.30 (2.2H, m), 1.15 (0.4H, s), 1.06 (3H, s), 0.86 (6H, s), 0.56 (3H, s);

MS (m/z): 969 (M+H)⁺.

[0873]

The obtained crystals were measured using a powder X-ray diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 5. In Fig. 5 showing the diffraction pattern of powder X-ray diffraction (CuKα, λ=1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 5.

[0874]

[Table 5]

Peak No.	2θ	d value	relative intensity	Peak No.	2θ	d value	relative intensity
1	2.20	40.15	100	6	16.98	5.22	79
2	4.34	20.37	53	7	18.09	4.90	75
3	9.45	9.35	45	8	20.20	4.39	70
4	10.97	8.06	45	9	21.32	4.16	67
5	13.23	6.69	39	10	25.19	3.53	44

[0875]

<Example CN1> 3-{7-[(4-{[(4R)-4'-{[2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl)methyl]piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl}piperidine-2,6-dione monobenzenesulfonate

The compound (50 mg) obtained in Example BY7 was dissolved in acetonitrile (1.5 mL), and a solution of
10 benzenesulfonic acid monohydrate in acetonitrile (0.10 mol/L; 0.10 mL) was added, and the mixture was stirred at room temperature for 15 hr. Successively, a solution of benzenesulfonic acid monohydrate in acetonitrile (0.10 mol/L; 0.15 mL) was added over 4 hr, and the mixture was stirred at
15 room temperature for 3 hr. Furthermore, a solution of benzenesulfonic acid monohydrate in acetonitrile (0.10 mol/L; 0.25 mL) was added at 40°C over 2 hr, and the mixture was stirred at room temperature for 15 hr. The precipitated solid was collected by filtration and dried at 40°C to give the title
20 compound (51 mg) as crystals (elemental analysis Found; C: 62.46%, H: 6.75%, N: 8.53%, F: 4.99%, S: 2.74%).

¹H-NMR (DMSO-D₆) δ: 11.10 (1H, s), 9.31 (1H, br s), 7.62-7.57 (2H, m), 7.34-7.25 (5H, m), 7.19 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.2 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.82 (2H, d, J = 8.9
25 Hz), 6.52 (1H, d, J = 8.3 Hz), 6.12 (1H, s), 6.05 (1H, s), 5.35-5.28 (1H, m), 4.15 (2H, br s), 3.89-3.80 (2H, m), 3.71 (3H, s), 3.60-3.50 (4H, m), 3.49-3.41 (4H, m), 3.19-3.06 (4H, m), 2.96-2.86 (1H, m), 2.71-2.58 (3H, m), 2.46 (1H, s), 2.44-2.29 (6H, m), 2.27-2.19 (1H, m), 2.15-2.07 (3H, m), 2.06-1.93
30 (3H, m), 1.86-1.78 (1H, m), 1.77-1.70 (1H, m), 1.58-1.50 (2H, m), 1.47-1.34 (2H, m), 1.06 (3H, s), 0.86 (6H, s), 0.56 (3H, s);

MS (m/z): 969 (M+H)⁺.

[0876]

35 The obtained crystals were measured using a powder X-ray

diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 6. In Fig. 6 showing the diffraction pattern of powder X-ray diffraction (CuK α , λ =1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 6. [0877]

[Table 6]

Peak No.	2 θ	d value	relative intensity	Peak No.	2 θ	d value	relative intensity
1	2.19	40.35	100	6	14.99	5.91	13
2	8.87	9.97	10	7	17.84	4.97	21
3	10.86	8.14	17	8	20.62	4.30	12
4	12.55	7.05	13	9	21.43	4.14	13
5	13.05	6.78	13	10	25.27	3.52	10

[0878]
 10 <Example CO1> 3-{7-[(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazin-1-yl)carbonyl]-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-15 1(2H)-yl}piperidine-2,6-dione mono-10-camphorsulfonate

The compound (50 mg) obtained in Example BY7 was dissolved in acetonitrile (1.5 mL), and a solution of 10-camphorsulfonic acid in acetonitrile (0.10 mol/L; 0.10 mL) was added, and the mixture was stirred at room temperature for 18
 20 hr. Successively, a solution of 10-camphorsulfonic acid in acetonitrile (0.10 mol/L; 0.40 mL) was added at 40°C over 8 hr, and the mixture was stirred at room temperature for 17 hr. The precipitated solid was collected by filtration, and dried at 40°C to give the title compound (59 mg) as crystals (elemental
 25 analysis Found; C: 63.38%, H: 7.06%, N: 8.09%, F: 4.78%, S: 2.62%).

¹H-NMR (DMSO-D₆) δ : 11.10 (1H, s), 9.31 (1H, br s), 7.28 (2H, d, J = 8.2 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.2 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.82 (2H, d, J = 8.9 Hz), 6.52

(1H, d, J = 8.2 Hz), 6.12 (1H, s), 6.05 (0.5H, s), 5.35-5.30 (1H, m), 4.15 (2H, br s), 3.88-3.80 (2H, m), 3.71 (3H, s), 3.61-3.51 (4H, m), 3.48-3.41 (4H, m), 3.18-3.07 (4.7H, m), 2.95-2.87 (1.5H, m), 2.86 (0.5H, s), 2.83 (0.5H, s), 2.74-2.59 (4.5H, m), 2.44-2.30 (9H, m), 2.26-2.20 (3H, m), 2.14-2.08 (4H, m), 2.05-2.00 (2H, m), 2.00-1.94 (3H, m), 1.93 (1.5H, d, J = 4.6 Hz), 1.88-1.78 (4.5H, m), 1.77 (0.8H, s), 1.77-1.70 (2.3H, m), 1.58-1.50 (3.7H, m), 1.47-1.34 (5H, m), 1.29-1.23 (3.6H, m), 1.16-1.13 (1H, m), 1.06 (7H, d, J = 7.4 Hz), 0.86 (7H, s), 0.74 (4H, s), 0.56 (3H, s);
 MS (m/z): 969 (M+H)⁺.

[0879]

The obtained crystals were measured using a powder X-ray diffractometer (MiniFlex600-C, manufactured by Rigaku Corporation), and the results are shown in Fig. 7. In Fig. 7 showing the diffraction pattern of powder X-ray diffraction (CuK α , λ =1.54 angstroms, scanning speed=10°/min), the peaks characteristic of the present crystals are shown in Table 7.

[0880]

[Table 7]

Peak No.	2 θ	d value	relative intensity	Peak No.	2 θ	d value	relative intensity
1	2.20	40.08	71	6	15.23	5.81	77
2	7.82	11.29	43	7	16.49	5.37	100
3	11.05	8.00	45	8	17.86	4.96	55
4	12.42	7.12	89	9	20.15	4.40	57
5	13.34	6.63	61	10	24.36	3.65	44

[0881]

The physicochemical data of the compounds described in the Examples are shown below in Table 8 to Table 57.

In the Tables, Ex indicates the Example number, and Data indicates the physicochemical data.

Other abbreviations used in the text have the following meanings:

Boc: tert-butoxycarbonyl group

tBu: tert-butyl group

[0882]

[Table 8]

Ex	Data
A1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (3H, s), 1.27 (3H, s), 1.32–1.38 (3H, m), 2.66 (1H, s), 2.72 (1H, t, $J = 5.8$ Hz), 3.05 (1H, s), 3.12 (1H, t, $J = 5.8$ Hz), 3.83 (1H, t, $J = 5.8$ Hz), 3.91 (1H, t, $J = 5.8$ Hz), 4.24–4.32 (2H, m). MS m/z : 224 ($\text{M}+\text{H}$) $^+$.
A2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (1.5H, s), 0.71 (1.5H, s), 1.00–1.05 (3H, m), 1.25 (1.5H, s), 1.27 (1.5H, s), 1.87 (0.5H, d, $J = 14.0$ Hz), 1.92–2.00 (0.5H, m), 2.03–2.12 (1H, m), 2.38–2.43 (0.5H, m), 2.54–2.60 (0.5H, m), 2.61–2.73 (1H, m), 3.51 (0.5H, s), 3.52 (0.5H, s), 3.64–3.74 (1H, m), 3.76–3.86 (1H, m), 3.89–4.00 (2H, m), 7.26–7.32 (1H, m), 7.34–7.41 (3H, m). MS m/z : 336 ($\text{M}+\text{H}$) $^+$.
A3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.19 (3H, s), 1.53–1.76 (4H, m), 2.10–2.18 (2H, m), 2.25–2.32 (1H, m), 2.45–2.54 (1H, m), 3.74–3.79 (2H, m), 7.21–7.25 (2H, m), 7.28–7.32 (2H, m). MS m/z : 268 ($\text{M}+\text{H}$) $^+$.
A4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J = 7.0$ Hz), 1.47–1.70 (4H, m), 2.06–2.15 (2H, m), 2.16–2.24 (2H, m), 2.33–2.42 (1H, m), 4.12–4.19 (2H, m), 4.30–4.38 (1H, m), 6.95–7.01 (2H, m), 7.80–7.85 (2H, m), 9.87 (1H, s).
A5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.19 (3H, s), 1.26 (3H, t, $J = 7.3$ Hz), 1.39–1.71 (7H, m), 1.74–1.84 (1H, m), 2.02–2.21 (6H, m), 2.24–2.47 (3H, m), 3.50 (2H, s), 3.73–3.77 (2H, m), 4.10–4.21 (3H, m), 6.79 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz), 7.29 (2H, d, $J = 8.5$ Hz). MS m/z : 528 ($\text{M}+\text{H}$) $^+$.
A6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 1.17–1.21 (9H, m), 1.17 (3H, s), 1.43–1.78 (8H, m), 2.04–2.24 (6H, m), 2.38–2.47 (1H, m), 2.47–2.60 (1H, m), 3.02–3.17 (1H, m), 3.64–3.73 (2H, m), 4.15–4.26 (2H, m), 4.45 (1H, d, $J = 14.6$ Hz), 6.77 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 584 ($\text{M}+\text{H}$) $^+$.
B1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65–0.73 (3H, m), 0.93–1.00 (3H, m), 1.26–1.29 (3H, m), 1.93–2.18 (2H, m), 2.39–2.75 (2H, m), 3.51–3.55 (1H, m), 3.65–3.96 (4H, m), 7.21–7.27 (2H, m), 7.39 (1H, d, $J = 8.5$ Hz), 7.49 (1H, d, $J = 8.5$ Hz).
B2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.20 (3H, s), 1.47–1.79 (4H, m), 2.08–2.18 (2H, m), 2.27–2.34 (1H, m), 2.46–2.55 (1H, m), 3.75–3.80 (2H, m), 7.15–7.20 (2H, m), 7.31 (2H, d, $J = 8.5$ Hz). MS m/z : 318 ($\text{M}+\text{H}$) $^+$.
B3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.19 (3H, s), 1.26 (3H, t, $J = 7.3$ Hz), 1.40–1.73 (7H, m), 1.75–1.84 (1H, m), 2.03–2.21 (6H, m), 2.26–2.47 (3H, m), 3.51 (2H, s), 3.74–3.78 (2H, m), 4.10–4.20 (3H, m), 6.79 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.16 (2H, d, $J = 8.5$ Hz), 7.30 (2H, d, $J = 8.5$ Hz). MS m/z : 578 ($\text{M}+\text{H}$) $^+$.

[0883]

[Table 9]

Ex	Data
B4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.63 (3H, s), 1.12–1.19 (9H, m), 1.17 (3H, s), 1.27 (3H, t, $J = 7.3$ Hz), 1.40–1.81 (8H, m), 2.02–2.22 (6H, m), 2.30–2.40 (1H, m), 2.47–2.65 (1H, m), 3.02–3.13 (1H, m), 3.67–3.73 (2H, m), 4.09–4.21 (3H, m), 4.29 (1H, d, $J = 15.3$ Hz), 4.40 (1H, d, $J = 15.3$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.11–7.15 (2H, m), 7.21–7.25 (2H, m). MS m/z : 662 ($\text{M}+\text{H}$) $^+$.
B5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 1.12–1.20 (9H, m), 1.17 (3H, s), 1.43–1.83 (8H, m), 2.03–2.23 (6H, m), 2.38–2.47 (1H, m), 2.48–2.64 (1H, m), 3.02–3.15 (1H, m), 3.66–3.75 (2H, m), 4.13–4.22 (1H, m), 4.29 (1H, d, $J = 15.3$ Hz), 4.40 (1H, d, $J = 15.3$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.11–7.16 (2H, m), 7.21–7.26 (2H, m). MS m/z : 634 ($\text{M}+\text{H}$) $^+$.
C1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.23–1.30 (4H, m), 1.37–1.65 (5H, m), 1.67–1.77 (2H, m), 1.82–1.94 (1H, m), 2.24 (2H, d, $J = 6.7$ Hz), 3.95–4.02 (1H, m), 4.13 (2H, q, $J = 7.1$ Hz).
C2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.10–1.23 (2H, m), 1.27 (3H, t, $J = 7.0$ Hz), 1.53–1.69 (2H, m), 1.85–1.98 (3H, m), 2.14–2.22 (2H, m), 2.25 (2H, d, $J = 6.7$ Hz), 4.15 (2H, q, $J = 7.3$ Hz), 4.28–4.38 (1H, m), 7.03 (1H, d, $J = 8.5$ Hz), 7.73 (1H, dd, $J = 8.5$, 1.8 Hz), 7.90 (1H, d, $J = 1.8$ Hz), 9.84 (1H, s). MS m/z : 325 ($\text{M}+\text{H}$) $^+$.
C3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65–0.72 (3H, m), 1.02 (3H, t, $J = 7.3$ Hz), 1.24–1.27 (3H, m), 1.80–2.10 (2H, m), 2.37–2.74 (2H, m), 3.48–3.52 (1H, m), 3.67–3.85 (2H, m), 3.81 (3H, s), 3.89–3.98 (2H, m), 6.87–6.92 (2H, m), 7.24 (1H, d, $J = 8.5$ Hz), 7.34 (1H, d, $J = 8.5$ Hz). MS m/z : 332 ($\text{M}+\text{H}$) $^+$.
C4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.72 (3H, s), 1.23 (3H, s), 1.73–1.84 (2H, m), 2.27–2.32 (1H, m), 2.38–2.53 (3H, m), 3.76–3.84 (5H, m), 6.89–6.94 (2H, m), 7.27–7.31 (2H, m). MS m/z : 260 ($\text{M}+\text{H}$) $^+$.
C5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.19 (3H, s), 1.49–1.76 (4H, m), 2.10–2.22 (2H, m), 2.27–2.34 (1H, m), 2.46–2.55 (1H, m), 3.72–3.84 (2H, m), 3.81 (3H, s), 6.86 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz). MS m/z : 264 ($\text{M}+\text{H}$) $^+$.
C6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.01–1.22 (5H, m), 1.26 (3H, t, $J = 7.0$ Hz), 1.40–2.50 (17H, m), 3.46 (2H, s), 3.74–3.80 (2H, m), 3.81 (3H, s), 4.03–4.18 (3H, m), 6.82–6.88 (3H, m), 6.92–6.98 (1H, m), 7.15–7.21 (3H, m). MS m/z : 572 ($\text{M}+\text{H}$) $^+$.
C7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.05–1.21 (14H, m), 1.27 (3H, t, $J = 7.3$ Hz), 1.48–2.25 (14H, m), 2.54–2.70 (1H, m), 3.11–3.22 (1H, m), 3.67–3.77 (2H, m), 3.81 (3H, s), 4.05–4.21 (4H, m), 4.36–4.43 (1H, m), 4.58–4.62 (1H, m), 6.74–6.86 (4H, m), 6.91–6.96 (1H, m), 7.09–7.20 (2H, m). MS m/z : 656 ($\text{M}+\text{H}$) $^+$.

[0884]

[Table 10]

Ex	Data
C8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.07–1.22 (14H, m), 1.42–2.23 (13H, m), 2.29 (2H, d, J = 6.7 Hz), 2.56–2.69 (1H, m), 3.11–3.21 (1H, m), 3.70–3.77 (2H, m), 3.81 (3H, s), 4.06–4.13 (1H, m), 4.17 (1H, d, J = 15.2 Hz), 4.39 (1H, d, J = 15.8 Hz), 6.76–6.86 (4H, m), 6.92–6.94 (1H, m), 7.10–7.16 (2H, m). MS m/z : 628 ($\text{M}+\text{H}$) $^+$.
D1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.18 (3H, s), 1.26 (3H, t, J = 7.3 Hz), 1.40–1.68 (7H, m), 1.74–1.83 (1H, m), 2.02–2.20 (6H, m), 2.27–2.37 (2H, m), 2.41–2.49 (1H, m), 3.49 (2H, s), 3.71–3.80 (2H, m), 3.81 (3H, s), 4.09–4.19 (3H, m), 6.79 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz). MS m/z : 524 ($\text{M}+\text{H}$) $^+$.
D2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.12–1.18 (12H, m), 1.23–1.30 (3H, m), 1.41–1.80 (12H, m), 2.02–2.23 (5H, m), 2.29–2.39 (1H, m), 2.53–2.71 (1H, m), 3.03–3.17 (1H, m), 3.67–3.78 (2H, m), 3.81 (3H, s), 4.27 (1H, d, J = 15.9 Hz), 4.40 (1H, d, J = 15.9 Hz), 6.75 (2H, d, J = 8.5 Hz), 6.80–6.88 (4H, m), 7.12 (2H, d, J = 8.5 Hz). MS m/z : 608 ($\text{M}+\text{H}$) $^+$.
D3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.10–1.19 (12H, m), 1.42–1.80 (8H, m), 2.04–2.23 (6H, m), 2.37–2.47 (1H, m), 2.52–2.74 (1H, m), 3.03–3.16 (1H, m), 3.67–3.78 (2H, m), 3.81 (3H, s), 4.13–4.22 (1H, m), 4.27 (1H, d, J = 15.3 Hz), 4.40 (1H, d, J = 15.3 Hz), 6.75 (2H, d, J = 8.5 Hz), 6.80–6.88 (4H, m), 7.12 (2H, d, J = 8.5 Hz). MS m/z : 580 ($\text{M}+\text{H}$) $^+$.
E1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.15 (9H, br s), 1.16 (3H, s), 1.27 (3H, t, J = 7.3 Hz), 1.41–1.80 (8H, m), 2.02–2.23 (6H, m), 2.34 (1H, tt, J = 11.3, 3.8 Hz), 2.53–2.74 (1H, m), 3.03–3.16 (1H, m), 3.65–3.78 (2H, m), 3.81 (3H, s), 4.11–4.20 (1H, m), 4.14 (2H, q, J = 7.3 Hz), 4.27 (1H, d, J = 15.3 Hz), 4.40 (1H, d, J = 15.3 Hz), 6.75 (2H, d, J = 8.5 Hz), 6.82 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 7.12 (2H, d, J = 8.5 Hz). MS m/z : 608 ($\text{M}+\text{H}$) $^+$.
E2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.08–1.20 (12H, m), 1.40–1.79 (8H, m), 2.03–2.24 (6H, m), 2.38–2.47 (1H, m), 2.56–2.69 (1H, m), 3.05–3.15 (1H, m), 3.68–3.77 (2H, m), 3.81 (3H, s), 4.11–4.21 (1H, m), 4.27 (1H, d, J = 15.3 Hz), 4.40 (1H, d, J = 15.3 Hz), 6.75 (2H, d, J = 8.5 Hz), 6.80–6.88 (4H, m), 7.12 (2H, d, J = 8.5 Hz). MS m/z : 580 ($\text{M}+\text{H}$) $^+$.
F1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.06–1.27 (12H, m), 1.42–2.23 (14H, m), 2.37–2.48 (1H, m), 2.58–2.73 (1H, m), 3.02–3.15 (1H, m), 3.66–3.77 (2H, m), 4.13–4.22 (1H, m), 4.30 (1H, d, J = 15.3 Hz), 4.42 (1H, d, J = 15.3 Hz), 6.73–6.80 (4H, m), 6.87 (2H, d, J = 8.5 Hz), 7.07 (2H, d, J = 8.5 Hz). MS m/z : 566 ($\text{M}+\text{H}$) $^+$.

[0885]

[Table 11]

Ex	Data
F2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.13–1.18 (12H, m), 1.27 (3H, t, $J = 7.3$ Hz), 1.40–1.68 (7H, m), 1.69–1.80 (1H, m), 2.02–2.21 (6H, m), 2.30–2.39 (1H, m), 2.58–2.73 (1H, m), 3.01–3.14 (1H, m), 3.67–3.77 (2H, m), 4.09–4.21 (3H, m), 4.30 (1H, d, $J = 15.3$ Hz), 4.41 (1H, d, $J = 15.3$ Hz), 5.08 (1H, s), 6.73–6.79 (4H, m), 6.87 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz). MS m/z : 594 ($\text{M}+\text{H}$) $^+$.
F3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.07–1.18 (9H, m), 1.16 (3H, s), 1.26 (3H, t, $J = 7.3$ Hz), 1.32–1.36 (6H, m), 1.40–1.79 (8H, m), 2.04–2.22 (6H, m), 2.29–2.40 (1H, m), 2.57–2.75 (1H, m), 3.03–3.16 (1H, m), 3.66–3.79 (2H, m), 4.10–4.20 (3H, m), 4.28 (1H, d, $J = 15.3$ Hz), 4.38 (1H, d, $J = 15.3$ Hz), 4.48–4.58 (1H, m), 6.75 (2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). MS m/z : 636 ($\text{M}+\text{H}$) $^+$.
F4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.07–1.18 (9H, m), 1.16 (3H, s), 1.34 (6H, d, $J = 6.1$ Hz), 1.42–1.82 (8H, m), 2.04–2.23 (6H, m), 2.37–2.46 (1H, m), 2.58–2.76 (1H, m), 3.05–3.16 (1H, m), 3.67–3.78 (2H, m), 4.12–4.21 (1H, m), 4.28 (1H, d, $J = 15.3$ Hz), 4.39 (1H, d, $J = 15.3$ Hz), 4.47–4.58 (1H, m), 6.76 (2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). MS m/z : 608 ($\text{M}+\text{H}$) $^+$.
G1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.62 (3H, s), 1.13–1.20 (12H, m), 1.27 (3H, t, $J = 7.3$ Hz), 1.41–1.80 (8H, m), 2.00–2.21 (6H, m), 2.30–2.40 (1H, m), 2.49–2.61 (1H, m), 3.00–3.12 (1H, m), 3.63–3.77 (2H, m), 4.09–4.22 (3H, m), 4.36 (2H, s), 6.78 (2H, d, $J = 8.5$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.29 (2H, d, $J = 8.5$ Hz). MS m/z : 726 ($\text{M}+\text{H}$) $^+$.
G2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.70 (3H, s), 1.11–1.20 (12H, m), 1.27 (3H, t, $J = 7.3$ Hz), 1.40–1.80 (8H, m), 1.99–2.21 (10H, m), 2.30–2.39 (1H, m), 2.64–2.78 (1H, m), 3.07–3.19 (1H, m), 3.24–3.31 (4H, m), 3.65–3.81 (2H, m), 4.09–4.18 (3H, m), 4.21 (1H, d, $J = 15.3$ Hz), 4.41 (1H, d, $J = 15.3$ Hz), 6.49 (2H, d, $J = 8.5$ Hz), 6.72 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.04 (2H, d, $J = 8.5$ Hz). MS m/z : 647 ($\text{M}+\text{H}$) $^+$.
G3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.70 (3H, s), 1.10–1.20 (12H, m), 1.42–1.81 (8H, m), 1.99–2.22 (10H, m), 2.36–2.45 (1H, m), 2.62–2.80 (1H, m), 3.06–3.20 (1H, m), 3.25–3.32 (4H, m), 3.65–3.81 (2H, m), 4.11–4.26 (2H, m), 4.41 (1H, d, $J = 15.3$ Hz), 6.49 (2H, d, $J = 8.5$ Hz), 6.72 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.04 (2H, d, $J = 8.5$ Hz). MS m/z : 619 ($\text{M}+\text{H}$) $^+$.

[0886]

[Table 12]

Ex	Data
H1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.08–1.26 (12H, m), 1.42–1.80 (8H, m), 2.00–2.28 (7H, m), 2.57–2.69 (1H, m), 2.96 (6H, s), 3.05–3.16 (1H, m), 3.68–3.75 (2H, m), 3.81 (3H, s), 4.13–4.20 (1H, m), 4.23–4.30 (1H, m), 4.37–4.44 (1H, m), 6.72–6.76 (2H, m), 6.80–6.89 (4H, m), 7.10–7.15 (2H, m), 7.98–8.03 (1H, m). MS m/z : 686 ($\text{M}+\text{H}$) ⁺ .
I1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.16 (3H, s), 1.26 (3H, t, $J = 7.0$ Hz), 1.39–1.81 (8H, m), 2.00–2.11 (3H, m), 2.12–2.20 (2H, m), 2.24–2.37 (2H, m), 2.71–2.81 (1H, m), 3.20–3.31 (1H, m), 3.70–3.85 (2H, m), 3.84 (3H, s), 4.09–4.18 (1H, m), 4.13 (2H, q, $J = 7.0$ Hz), 4.48 (2H, s), 5.98 (1H, d, $J = 8.5$ Hz), 6.46 (1H, dd, $J = 6.7, 4.9$ Hz), 6.75 (2H, d, $J = 8.5$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 6.97 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.24–7.29 (1H, m), 8.08 (1H, dd, $J = 4.9, 1.8$ Hz). MS m/z : 601 ($\text{M}+\text{H}$) ⁺ .
I2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.16 (3H, s), 1.39–1.81 (8H, m), 2.02–2.22 (5H, m), 2.22–2.33 (1H, m), 2.34–2.44 (1H, m), 2.70–2.82 (1H, m), 3.19–3.30 (1H, m), 3.72–3.87 (5H, m), 4.10–4.20 (1H, m), 4.49 (2H, s), 5.98 (1H, d, $J = 8.5$ Hz), 6.42–6.50 (1H, m), 6.75 (2H, d, $J = 7.9$ Hz), 6.89 (2H, d, $J = 7.9$ Hz), 6.97 (2H, d, $J = 7.9$ Hz), 7.18–7.31 (3H, m), 8.07–8.11 (1H, m). MS m/z : 573 ($\text{M}+\text{H}$) ⁺ .
J1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, s), 2.87 (2H, s), 3.68 (3H, s), 6.98 (2H, d, $J = 8.6$ Hz), 7.04 (2H, d, $J = 8.6$ Hz), 7.14 (2H, d, $J = 8.6$ Hz), 7.84 (2H, d, $J = 8.6$ Hz), 9.92 (1H, s).
J2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.68 (3H, s), 1.18 (9H, s), 1.58–1.67 (3H, m), 1.78–1.81 (1H, m), 2.13–2.16 (2H, m), 2.29–2.32 (1H, m), 2.45–2.47 (1H, m), 2.82 (2H, s), 3.54 (2H, s), 3.66 (3H, s), 3.73–3.83 (5H, m), 6.84–6.91 (6H, m), 7.04 (2H, d, $J = 8.6$ Hz), 7.11 (2H, d, $J = 8.6$ Hz), 7.20 (2H, d, $J = 8.6$ Hz).
J3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.11–1.21 (18H, m), 1.53–1.79 (4H, m), 2.07–2.23 (2H, m), 2.57–2.70 (1H, m), 2.84 (2H, s), 3.09–3.22 (1H, m), 3.67 (3H, s), 3.69–3.76 (2H, m), 3.77 (3H, s), 4.28 (1H, d, $J = 15.3$ Hz), 4.46 (1H, d, $J = 15.3$ Hz), 6.80–6.92 (8H, m), 7.06 (2H, d, $J = 8.6$ Hz), 7.13 (2H, d, $J = 8.6$ Hz).
J4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.10–1.33 (18H, m), 1.51–1.67 (3H, m), 1.71–1.80 (1H, m), 2.06–2.21 (2H, m), 2.58–2.72 (1H, m), 2.87 (2H, s), 3.06–3.15 (1H, m), 3.70–3.75 (2H, m), 3.77 (3H, s), 4.27 (1H, d, $J = 15.3$ Hz), 4.48 (1H, d, $J = 15.3$ Hz), 6.79–6.94 (8H, m), 7.11–7.15 (4H, m). MS m/z : 630 ($\text{M}+\text{H}$) ⁺ .
K1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.20–1.25 (1H, m), 1.37–1.63 (5H, m), 1.66–1.75 (2H, m), 1.83–1.97 (1H, m), 2.31 (2H, d, $J = 7.3$ Hz), 3.94–4.02 (1H, m), 5.12 (2H, s), 7.29–7.41 (5H, m).

[0887]

[Table 13]

Ex	Data
K2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.09–1.23 (2H, m), 1.44–1.57 (2H, m), 1.82–1.97 (3H, m), 2.10–2.20 (2H, m), 2.31 (2H, d, $J = 6.7$ Hz), 4.22–4.32 (1H, m), 5.13 (2H, s), 6.93–6.99 (2H, m), 7.31–7.41 (5H, m), 7.78–7.84 (2H, m), 9.87 (1H, s). MS m/z : 353 ($\text{M}+\text{H}$) $^+$.
K3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.04–1.20 (5H, m), 1.36–1.91 (9H, m), 2.07–2.17 (4H, m), 2.25–2.33 (3H, m), 2.39–2.49 (1H, m), 3.48 (2H, s), 3.70–3.83 (5H, m), 4.03–4.14 (1H, m), 5.12 (2H, s), 6.75–6.80 (2H, m), 6.82–6.87 (2H, m), 7.02–7.07 (2H, m), 7.16–7.21 (2H, m), 7.31–7.40 (5H, m). MS m/z : 600 ($\text{M}+\text{H}$) $^+$.
K4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.06–1.18 (5H, m), 1.39–1.66 (5H, m), 1.68–1.77 (1H, m), 1.82–2.02 (6H, m), 2.06–2.31 (7H, m), 2.45–2.54 (2H, m), 3.29 (1H, d, $J = 14.0$ Hz), 3.36 (1H, d, $J = 14.0$ Hz), 3.68–3.78 (2H, m), 3.80 (3H, s), 4.05–4.14 (1H, m), 5.12 (2H, s), 6.76 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz), 7.29–7.40 (5H, m). MS m/z : 696 ($\text{M}+\text{H}$) $^+$.
K5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.07–1.26 (5H, m), 1.42–2.31 (19H, m), 2.47–2.56 (2H, m), 3.28–3.41 (2H, m), 3.69–3.79 (2H, m), 3.81 (3H, s), 4.07–4.17 (1H, m), 6.74–6.80 (2H, m), 6.81–6.87 (2H, m), 6.99–7.05 (2H, m), 7.11–7.16 (2H, m). MS m/z : 606 ($\text{M}+\text{H}$) $^+$.
L1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.10–1.18 (12H, m), 1.26 (3H, t, $J = 7.3$ Hz), 1.40–1.79 (8H, m), 2.02–2.22 (6H, m), 2.30–2.39 (1H, m), 2.64–2.77 (1H, m), 2.84 (3H, s), 3.04–3.18 (1H, m), 3.62–3.79 (3H, m), 4.09–4.20 (3H, m), 4.25 (1H, d, $J = 15.3$ Hz), 4.40 (1H, d, $J = 15.3$ Hz), 6.55 (2H, d, $J = 8.5$ Hz), 6.75 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz). MS m/z : 607 ($\text{M}+\text{H}$) $^+$.
L2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.09–1.20 (12H, m), 1.43–1.79 (8H, m), 2.05–2.23 (6H, m), 2.37–2.46 (1H, m), 2.64–2.79 (1H, m), 2.84 (3H, s), 3.04–3.18 (1H, m), 3.65–3.80 (2H, m), 4.12–4.22 (1H, m), 4.26 (1H, d, $J = 15.3$ Hz), 4.40 (1H, d, $J = 15.3$ Hz), 6.56 (2H, d, $J = 8.5$ Hz), 6.75 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz). MS m/z : 579 ($\text{M}+\text{H}$) $^+$.
M1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.19 (3H, s), 1.49–1.76 (4H, m), 2.10–2.22 (2H, m), 2.27–2.34 (1H, m), 2.46–2.55 (1H, m), 3.72–3.84 (2H, m), 3.81 (3H, s), 6.86 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz).
M2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.18 (3H, s), 1.25 (3H, s), 1.25 (3H, s), 1.57–1.70 (3H, m), 1.72–1.81 (1H, m), 2.16 (1H, dd, $J = 14.0, 2.4$ Hz), 2.35 (1H, dd, $J = 14.0, 2.4$ Hz), 2.71–2.82 (1H, m), 3.17–3.27 (1H, m), 3.75–3.83 (5H, m), 5.39 (1H, br s), 6.89 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz). MS m/z : 402 ($\text{M}+\text{H}$) $^+$.

[0888]

[Table 14]

Ex	Data
M3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.01 (3H, s), 1.02 (3H, s), 1.19 (3H, s), 1.51–1.79 (4H, m), 2.04–2.18 (2H, m), 2.29–2.43 (4H, m), 3.72–3.84 (5H, m), 6.86 (2H, d, $J = 9.2$ Hz), 7.20 (2H, d, $J = 9.2$ Hz). MS m/z : 388 ($\text{M}+\text{H}$) $^+$.
M4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.26 (3H, t, $J = 7.1$ Hz), 1.40–1.65 (7H, m), 1.67–1.77 (1H, m), 1.81–1.91 (1H, m), 2.02–2.39 (10H, m), 3.39 (1H, d, $J = 13.4$ Hz), 3.43 (1H, d, $J = 13.4$ Hz), 3.65–3.80 (2H, m), 3.79 (3H, s), 4.09–4.21 (1H, m), 4.14 (2H, q, $J = 7.1$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 9.2$ Hz), 7.04 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 9.2$ Hz). MS m/z : 648 ($\text{M}+\text{H}$) $^+$.
M5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.41–1.78 (8H, m), 1.82–1.93 (1H, m), 2.04–2.37 (9H, m), 2.43 (1H, tt, $J = 11.3, 3.6$ Hz), 3.39 (1H, d, $J = 13.5$ Hz), 3.43 (1H, d, $J = 13.5$ Hz), 3.65–3.82 (2H, m), 3.80 (3H, s), 4.13–4.22 (1H, m), 6.77 (2H, d, $J = 8.6$ Hz), 6.81 (2H, d, $J = 8.6$ Hz), 7.04 (2H, d, $J = 8.6$ Hz), 7.10 (2H, d, $J = 8.6$ Hz). MS m/z : 620 ($\text{M}+\text{H}$) $^+$.
N1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.07–1.34 (12H, m), 1.53–1.80 (4H, m), 2.07–2.23 (2H, m), 2.58–2.70 (1H, m), 3.11–3.22 (1H, m), 3.69–3.80 (5H, m), 4.26 (1H, d, $J = 15.8$ Hz), 4.48 (1H, d, $J = 15.8$ Hz), 6.78–6.95 (8H, m), 7.14 (2H, d, $J = 8.5$ Hz), 7.44 (2H, d, $J = 8.5$ Hz). MS m/z : 608 [$\text{M}(79\text{Br})+\text{H}$] $^+$, 610 [$\text{M}(81\text{Br})+\text{H}$] $^+$.
N2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.06–1.34 (13H, m), 1.51–1.80 (3H, m), 1.98–2.24 (2H, m), 2.53–2.75 (1H, m), 3.08–3.20 (7H, m), 3.68–3.82 (5H, m), 4.27 (1H, d, $J = 15.2$ Hz), 4.44 (1H, d, $J = 15.2$ Hz), 6.79–6.93 (8H, m), 7.04–7.08 (2H, m), 7.10–7.16 (2H, m). MS m/z : 621 ($\text{M}+\text{H}$) $^+$.
O1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.17 (3H, s), 1.26 (3H, t, $J = 7.1$ Hz), 1.37–1.81 (8H, m), 2.02–2.11 (3H, m), 2.12–2.21 (2H, m), 2.23–2.38 (2H, m), 2.73–2.85 (1H, m), 3.37–3.49 (1H, m), 3.71–3.86 (2H, m), 3.84 (3H, s), 4.09–4.19 (1H, m), 4.14 (2H, q, $J = 7.1$ Hz), 4.32 (1H, d, $J = 15.3$ Hz), 4.58 (1H, d, $J = 15.3$ Hz), 6.72 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz), 8.12 (2H, s). MS m/z : 620 ($\text{M}+\text{H}$) $^+$.
O2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 1.17 (3H, s), 1.38–1.82 (8H, m), 2.01–2.21 (5H, m), 2.23–2.31 (1H, m), 2.41 (1H, tt, $J = 11.0, 3.7$ Hz), 2.73–2.85 (1H, m), 3.37–3.48 (1H, m), 3.71–3.86 (2H, m), 3.83 (3H, s), 4.10–4.20 (1H, m), 4.32 (1H, d, $J = 15.0$ Hz), 4.58 (1H, d, $J = 15.0$ Hz), 6.72 (2H, d, $J = 8.5$ Hz), 6.83–6.91 (4H, m), 7.18 (2H, d, $J = 8.5$ Hz), 8.12 (2H, s). MS m/z : 592 ($\text{M}+\text{H}$) $^+$.
P1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.53 (3H, d, $J = 7.4$ Hz), 3.70 (3H, s), 3.76 (1H, q, $J = 7.4$ Hz), 7.05–7.07 (4H, m), 7.35 (2H, d, $J = 8.6$ Hz), 7.85 (2H, d, $J = 8.6$ Hz), 9.93 (1H, s).

[0889]

[Table 15]

Ex	Data
P2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.47–1.65 (6H, m), 1.69–1.77 (1H, m), 1.84–1.93 (1H, m), 2.05–2.16 (2H, m), 2.25–2.34 (1H, m), 2.35–2.41 (2H, m), 3.46 (2H, s), 3.67–3.79 (9H, m), 6.81 (2H, d, $J = 8.6$ Hz), 6.88 (2H, d, $J = 8.6$ Hz), 6.92 (2H, d, $J = 8.6$ Hz), 7.08–7.13 (4H, m), 7.26 (2H, d, $J = 8.6$ Hz).
P3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.47–1.64 (6H, m), 1.71–1.74 (1H, m), 1.87–1.90 (1H, m), 2.08–2.13 (2H, m), 2.28–2.31 (1H, m), 2.37 (2H, s), 3.44–3.48 (2H, m), 3.68–3.79 (6H, m), 6.80 (2H, d, $J = 8.6$ Hz), 6.88 (2H, d, $J = 8.6$ Hz), 6.93 (2H, d, $J = 8.6$ Hz), 7.10–7.12 (4H, m), 7.28 (2H, d, $J = 8.6$ Hz). MS m/z : 642 (M+H) $^+$.
Q1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.18 (3H, s), 1.57–1.68 (3H, m), 1.75–1.84 (1H, m), 2.10–2.19 (2H, m), 2.25–2.32 (1H, m), 2.40–2.48 (1H, m), 2.55 (3H, s), 3.57 (2H, s), 3.72–3.83 (5H, m), 3.87 (3H, s), 6.85 (2H, d, $J = 9.2$ Hz), 7.00–7.05 (2H, m), 7.19 (2H, d, $J = 8.6$ Hz), 7.82 (1H, d, $J = 8.0$ Hz).
Q2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 1.16 (3H, s), 1.33–1.36 (6H, m), 1.54–1.80 (4H, m), 2.10–2.21 (2H, m), 2.54 (3H, s), 2.70 (1H, br s), 3.18–3.23 (1H, m), 3.74–3.79 (5H, m), 3.89 (3H, s), 4.30 (1H, d, $J = 15.9$ Hz), 4.48 (1H, d, $J = 15.9$ Hz), 6.81–6.83 (4H, m), 7.11–7.13 (2H, m), 7.80 (1H, d, $J = 8.0$ Hz).
Q3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.17 (3H, s), 1.34 (6H, br s), 1.54–1.80 (4H, m), 2.13–2.19 (2H, m), 2.59 (3H, s), 2.70 (1H, br s), 3.22–3.26 (1H, m), 3.70–3.77 (2H, m), 3.80 (3H, s), 4.31 (1H, d, $J = 15.9$ Hz), 4.51 (1H, d, $J = 15.9$ Hz), 6.83–6.86 (4H, m), 7.12–7.14 (2H, m), 7.94 (1H, d, $J = 8.0$ Hz).
Q4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.18 (3H, s), 1.35 (6H, br s), 1.56–1.82 (4H, m), 2.14–2.21 (2H, m), 2.27 (3H, s), 2.72–2.74 (3H, m), 3.04 (2H, t, $J = 7.4$ Hz), 3.20–3.25 (1H, m), 3.73–3.79 (5H, m), 4.34 (1H, d, $J = 15.9$ Hz), 4.53 (1H, d, $J = 15.9$ Hz), 6.83–6.85 (4H, m), 7.15–7.19 (3H, m), 7.31 (2H, d, $J = 8.0$ Hz), 7.71 (2H, d, $J = 8.0$ Hz). MS m/z : 682 (M+H) $^+$.
R1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.19 (3H, t, $J = 7.1$ Hz), 1.26 (3H, t, $J = 7.4$ Hz), 2.99–3.07 (2H, m), 3.36–3.40 (1H, m), 3.63–3.67 (1H, m), 4.02–4.04 (1H, m), 4.18–4.21 (2H, m), 7.01–7.04 (4H, m), 7.29 (2H, d, $J = 8.6$ Hz), 7.84 (2H, d, $J = 8.6$ Hz), 9.92 (1H, s).

[0890]

[Table 16]

Ex	Data
R2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.17–1.19 (6H, m), 1.25 (3H, q, $J = 7.2$ Hz), 1.47–1.64 (3H, m), 1.71–1.75 (1H, m), 1.87–1.90 (1H, m), 2.07–2.13 (2H, m), 2.28–2.31 (1H, m), 2.37 (2H, s), 2.99–3.00 (2H, m), 3.35–3.39 (1H, m), 3.43–3.47 (2H, m), 3.61–3.64 (1H, m), 3.71–3.74 (2H, m), 3.78 (3H, s), 3.99–4.01 (1H, m), 4.19 (2H, q, $J = 7.2$ Hz), 6.81 (2H, d, $J = 9.2$ Hz), 6.87 (2H, d, $J = 8.6$ Hz), 6.90 (2H, d, $J = 8.6$ Hz), 7.09–7.11 (4H, m), 7.21 (2H, d, $J = 8.6$ Hz).
R3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.92 (6H, s), 1.16 (3H, s), 1.21 (3H, t, $J = 7.1$ Hz), 1.44–1.57 (2H, m), 1.60–1.63 (1H, m), 1.70–1.73 (1H, m), 1.85–1.88 (1H, m), 2.07–2.10 (2H, m), 2.27–2.30 (1H, m), 2.37 (2H, s), 2.99–3.02 (1H, m), 3.11–3.15 (1H, m), 3.47–3.51 (3H, m), 3.60–3.63 (1H, m), 3.69–3.75 (2H, m), 3.78 (3H, s), 4.08–4.10 (1H, m), 6.81 (2H, d, $J = 8.6$ Hz), 6.87 (2H, d, $J = 8.6$ Hz), 6.90 (2H, d, $J = 8.6$ Hz), 7.09–7.12 (4H, m), 7.20 (2H, d, $J = 8.6$ Hz). MS m/z : 686 ($\text{M}+\text{H}$) ⁺ .
S1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.31 (4H, m), 1.37–1.65 (5H, m), 1.66–1.76 (2H, m), 1.81–1.94 (1H, m), 2.24 (2H, d, $J = 6.7$ Hz), 3.95–4.02 (1H, m), 4.13 (2H, q, $J = 7.1$ Hz).
S2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.13–1.31 (5H, m), 1.45–1.58 (2H, m), 1.78–1.92 (3H, m), 2.13–2.21 (2H, m), 2.24 (2H, d, $J = 6.7$ Hz), 4.14 (2H, q, $J = 7.1$ Hz), 5.04–5.15 (1H, m), 6.77 (1H, d, $J = 8.5$ Hz), 8.04 (1H, dd, $J = 8.5, 2.4$ Hz), 8.59 (1H, d, $J = 2.4$ Hz), 9.93 (1H, s). MS m/z : 292 ($\text{M}+\text{H}$) ⁺ .
S3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.15–1.28 (2H, m), 1.16 (3H, s), 1.27 (3H, t, $J = 7.3$ Hz), 1.39–2.39 (19H, m), 3.34–3.44 (2H, m), 3.66–3.78 (2H, m), 3.79 (3H, s), 4.14 (2H, q, $J = 7.3$ Hz), 4.87–4.97 (1H, m), 6.56 (1H, d, $J = 8.5$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.33 (1H, dd, $J = 8.5, 2.4$ Hz), 7.89 (1H, d, $J = 2.4$ Hz). MS m/z : 663 ($\text{M}+\text{H}$) ⁺ .
S4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.17–2.39 (21H, m), 3.34–3.44 (2H, m), 3.67–3.77 (2H, m), 3.79 (3H, s), 4.87–4.97 (1H, m), 6.56 (1H, d, $J = 8.5$ Hz), 6.78–6.82 (2H, m), 7.10 (2H, d, $J = 8.5$ Hz), 7.33 (1H, dd, $J = 8.5, 2.4$ Hz), 7.90 (1H, d, $J = 2.4$ Hz). MS m/z : 635 ($\text{M}+\text{H}$) ⁺ .
T1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.88 (6H, s), 1.06–1.19 (2H, m), 1.16 (3H, s), 1.38–2.36 (19H, m), 3.35–3.46 (2H, m), 3.66–3.78 (2H, m), 3.79 (3H, s), 4.04–4.14 (1H, m), 5.13 (2H, s), 6.75 (2H, d, $J = 8.5$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.31–7.40 (5H, m). MS m/z : 724 ($\text{M}+\text{H}$) ⁺ .
T2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.08–1.22 (2H, m), 1.16 (3H, s), 1.40–2.39 (19H, m), 3.35–3.46 (2H, m), 3.66–3.77 (2H, m), 3.79 (3H, s), 4.07–4.16 (1H, m), 6.76 (2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 7.04 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). MS m/z : 634 ($\text{M}+\text{H}$) ⁺ .

[0891]

[Table 17]

Ex	Data
U1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.18 (3H, s), 1.55–1.68 (3H, m), 1.73–1.83 (1H, m), 2.08–2.16 (2H, m), 2.26–2.32 (1H, m), 2.40–2.48 (1H, m), 3.50 (2H, s), 3.71–3.84 (5H, m), 5.03 (2H, s), 6.83–6.89 (4H, m), 7.07 (2H, d, $J = 8.8$ Hz), 7.18 (2H, d, $J = 8.8$ Hz), 7.25–7.45 (5H, m). MS m/z : 460 ($\text{M}+\text{H}$) $^+$.
U2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.96–1.37 (6H, m), 1.50–1.81 (7H, m), 2.01–2.24 (2H, m), 2.49–2.81 (1H, m), 3.00–3.15 (1H, m), 3.64–3.77 (2H, m), 3.80 (3H, s), 4.21–4.44 (2H, m), 5.04 (2H, s), 6.11 (1H, t, $J = 56.7$ Hz), 6.77–6.94 (6H, m), 7.04–7.18 (2H, m), 7.30–7.47 (5H, m). MS m/z : 580 ($\text{M}+\text{H}$) $^+$.
U3	MS m/z : 490 ($\text{M}+\text{H}$) $^+$.
U4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.05 (9H, s), 1.18–1.33 (2H, m), 1.40–1.76 (7H, m), 2.46 (3H, s), 3.90 (2H, d, $J = 6.7$ Hz), 3.98 (1H, brs), 7.99–7.47 (8H, m), 7.63 (4H, d, $J = 6.7$ Hz), 7.82 (2H, d, $J = 7.9$ Hz).
U5	NMR (CDCl_3) δ : 1.05 (9H, s), 1.21–1.41 (2H, m), 1.48–1.74 (7H, m), 2.12 (3H, s), 2.49 (2H, d, $J = 6.7$ Hz), 4.01 (1H, brs), 7.34–7.47 (6H, m), 7.68 (4H, d, $J = 6.3$ Hz).
U6	NMR (CDCl_3) δ : 1.09 (9H, s), 1.34–1.47 (2H, m), 1.52–1.85 (6H, m), 1.96 (1H, m), 2.55 (1H, dd, $J = 12.7, 9.6$ Hz), 2.61 (3H, s), 2.79 (1H, dd, $J = 12.7, 4.7$ Hz), 4.04 (1H, brs), 7.34–7.49 (6H, m), 7.67 (4H, d, $J = 6.3$ Hz).
U7	$^1\text{H-NMR}$ (CDCl_3) δ : 1.09 (9H, s), 1.34–1.46 (2H, m), 1.62–1.81 (6H, m), 2.12 (1H, m), 3.22 (1H, dd, $J = 14.1, 6.3$ Hz), 3.28 (3H, s), 3.45 (1H, dd, $J = 14.1, 6.3$ Hz), 4.00 (1H, brs), 5.15 (2H, s), 7.30–7.53 (11H, m), 7.62–7.69 (4H, m).
U8	$^1\text{H-NMR}$ (CDCl_3) δ : 1.57–1.82 (8H, m), 2.21 (1H, m), 3.20 (1H, dd, $J = 14.3, 6.5$ Hz), 3.28 (3H, s), 3.43 (1H, dd, $J = 14.1, 5.9$ Hz), 4.02 (1H, brs), 5.15 (2H, s), 7.30–7.44 (5H, m).
U9	$^1\text{H-NMR}$ (CDCl_3) δ : 1.33–1.36 (1H, m), 1.55–1.78 (8H, m), 2.14–2.24 (1H, m), 3.18 (1H, dd, $J = 14.3, 6.5$ Hz), 3.25 (3H, s), 3.41 (1H, dd, $J = 14.3, 6.5$ Hz), 3.97–4.02 (1H, m), 5.13 (2H, s), 7.27–7.42 (5H, m).
U10	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.93–1.36 (11H, m), 1.39–1.82 (6H, m), 2.02–2.25 (7H, m), 2.65 (1H, brs), 3.07 (1H, m), 3.16 (1H, dd, $J = 14.1, 6.3$ Hz), 3.26 (3H, s), 3.43 (1H, dd, $J = 14.1, 5.9$ Hz), 3.63–3.78 (2H, m), 3.80 (3H, s), 4.10 (1H, m), 4.21–4.40 (2H, m), 5.13 (2H, s), 6.10 (1H, t, $J = 56.5$ Hz), 6.74 (2H, d, $J = 8.2$ Hz), 6.79–6.90 (4H, m), 7.13 (2H, d, $J = 7.8$ Hz), 7.27–7.43 (5H, m). MS m/z : 819 ($\text{M}+\text{Na}$) $^+$.

[0892]

[Table 18]

Ex	Data
U11	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.93–1.37 (11H, m), 1.44–1.81 (6H, m), 1.99–2.25 (7H, m), 2.49–2.78 (2H, m), 2.93–3.14 (6H, m), 3.61–3.78 (2H, m), 3.81 (3H, s), 4.12 (1H, m), 4.22–4.42 (2H, m), 6.10 (1H, t, $J = 56.5$ Hz), 6.76 (2H, d, $J = 8.6$ Hz), 6.79–6.91 (4H, m), 7.06–7.19 (2H, m). MS m/z : 663 ($\text{M}+\text{H}$) $^+$.
V1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.73–1.90 (1H, m), 2.06–2.17 (1H, m), 2.46–2.61 (5H, m), 6.02–6.11 (1H, m), 7.40 (1H, dd, $J = 7.7$ Hz, 7.9 Hz), 7.53 (1H, dd, $J = 10.4$ Hz, 1.5 Hz), 7.61 (1H, dd, $J = 7.9$, 1.5 Hz), 9.95 (1H, d, $J = 1.8$ Hz).
V2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.73–1.90 (1H, m), 2.06–2.17 (1H, m), 2.46–2.61 (5H, m), 6.02–6.11 (1H, m), 7.40 (1H, dd, $J = 7.7$ Hz, 7.9 Hz), 7.53 (1H, dd, $J = 10.4$ Hz, 1.5 Hz), 7.61 (1H, dd, $J = 7.9$, 1.5 Hz), 9.95 (1H, d, $J = 1.8$ Hz).
V3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.73–1.90 (1H, m), 2.06–2.17 (1H, m), 2.46–2.61 (5H, m), 6.02–6.11 (1H, m), 7.40 (1H, dd, $J = 7.7$ Hz, 7.9 Hz), 7.53 (1H, dd, $J = 10.4$ Hz, 1.5 Hz), 7.61 (1H, dd, $J = 7.9$, 1.5 Hz), 9.95 (1H, d, $J = 1.8$ Hz).
V4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.44–1.66 (3H, m), 1.48 (9H, s), 1.66–1.93 (3H, m), 2.02–2.16 (3H, m), 2.23–2.34 (1H, m), 2.34–2.50 (6H, m), 2.50–2.60 (1H, m), 3.46 (2H, dd, $J = 16.4$, 14.6 Hz), 3.64–3.80 (2H, m), 3.78 (3H, s), 5.88–5.94 (1H, m), 6.75–6.87 (4H, m), 7.03–7.13 (3H, m).
V5	MS m/z : 620 ($\text{M}+\text{H}$) $^+$.
W1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.77–1.88 (1H, m), 2.13–2.21 (1H, m), 2.43–2.59 (5H, m), 6.27–6.31 (1H, m), 7.53 (2H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz), 9.98 (1H, s). MS m/z : 287 ($\text{M}+\text{H}$) $^+$.
W2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.77–1.88 (1H, m), 2.13–2.21 (1H, m), 2.43–2.59 (5H, m), 6.27–6.31 (1H, m), 7.53 (2H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz), 9.98 (1H, s).
W3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.77–1.88 (1H, m), 2.13–2.21 (1H, m), 2.43–2.59 (5H, m), 6.27–6.31 (1H, m), 7.53 (2H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz), 9.98 (1H, s).
W4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.16 (3H, s), 1.44–1.64 (11H, m), 1.69–1.92 (3H, m), 2.04–2.18 (3H, m), 2.24–2.56 (9H, m), 3.43–3.51 (2H, m), 3.65–3.75 (2H, m), 3.78 (3H, s), 6.08–6.11 (1H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.06–7.11 (4H, m), 7.24 (2H, d, $J = 8.5$ Hz). MS m/z : 658 ($\text{M}+\text{H}$) $^+$.
W5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.35 (1H, t, $J = 5.5$ Hz), 1.40–1.64 (3H, m), 1.69–1.77 (1H, m), 1.83–1.93 (3H, m), 1.94–2.14 (4H, m), 2.25–2.40 (4H, m), 2.45–2.51 (2H, m), 3.42–3.52 (2H, m), 3.57–3.79 (7H, m), 6.09–6.13 (1H, m), 6.80 (2H, d, $J = 8.0$ Hz), 7.07–7.12 (4H, m), 7.26 (2H, d, $J = 8.0$ Hz). MS m/z : 588 ($\text{M}+\text{H}$) $^+$.

[0893]

[Table 19]

Ex	Data
X1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.44–1.66 (4H, m), 1.67–1.79 (1H, m), 1.81–1.93 (1H, m), 1.94–2.22 (5H, m), 2.22–2.57 (6H, m), 3.04 (3H, s), 3.45 (1H, d, $J = 14.0$ Hz), 3.50 (1H, d, $J = 14.0$ Hz), 3.64–3.80 (2H, m), 3.78 (3H, s), 4.19 (2H, d, $J = 6.1$ Hz), 6.04–6.11 (1H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.06–7.13 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 666 ($\text{M}+\text{H}$) $^+$.
X2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.32–1.66 (4H, m), 1.56 (9H, s), 1.66–1.79 (1H, m), 1.79–1.93 (3H, m), 1.93–2.03 (1H, m), 2.03–2.14 (2H, m), 2.21–2.51 (12H, m), 3.38–3.54 (6H, m), 3.64–3.80 (2H, m), 3.78 (3H, s), 6.07–6.12 (1H, m), 6.80 (2H, d, $J = 8.8$ Hz), 7.08 (2H, d, $J = 7.9$ Hz), 7.10 (2H, d, $J = 8.8$ Hz), 7.26 (2H, d, $J = 7.9$ Hz). MS m/z : 756 ($\text{M}+\text{H}$) $^+$.
Y1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (9H, s), 2.19–2.26 (1H, m), 2.62–2.74 (1H, m), 2.76–2.86 (1H, m), 2.89–2.97 (1H, m), 3.25 (2H, t, $J = 5.8$ Hz), 3.35–3.43 (5H, m), 3.98 (1H, br s), 4.81 (1H, br s), 5.17 (1H, dd, $J = 12.8, 5.5$ Hz), 6.32–6.36 (2H, m), 6.60 (1H, d, $J = 9.1$ Hz), 8.04 (1H, s). MS m/z : 362 ($\text{M-tBu}+\text{H}$) $^+$.
Y2	$^1\text{H-NMR}$ ($\text{DMSO-}D_6$) δ : 1.92–2.02 (1H, m), 2.54–2.73 (2H, m), 2.83–3.05 (3H, m), 3.26–3.37 (5H, m), 5.28 (1H, dd, $J = 12.8, 5.5$ Hz), 6.40–6.46 (1H, m), 6.55–6.59 (1H, m), 6.91 (1H, d, $J = 8.5$ Hz), 7.87–8.03 (3H, m), 11.08 (1H, s). MS m/z : 318 ($\text{M}+\text{H}$) $^+$.
Y3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.44–1.54 (1H, m), 1.91–2.02 (2H, m), 2.13–2.24 (1H, m), 2.36 (2H, d, $J = 7.3$ Hz), 2.39–2.48 (1H, m), 2.48–2.56 (2H, m), 3.71 (3H, s), 6.24–6.27 (1H, m), 7.53 (2H, d, $J = 8.5$ Hz), 7.82 (2H, d, $J = 8.5$ Hz), 9.98 (1H, s). MS m/z : 259 ($\text{M}+\text{H}$) $^+$.
Y4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.16 (3H, s), 1.42–1.65 (5H, m), 1.68–1.78 (1H, m), 1.82–1.99 (3H, m), 2.04–2.23 (3H, m), 2.25–2.42 (6H, m), 2.45–2.50 (2H, m), 3.43–3.52 (2H, m), 3.67–3.76 (4H, m), 3.78 (3H, s), 6.04–6.08 (1H, m), 6.80 (2H, d, $J = 9.7$ Hz), 7.08 (2H, d, $J = 6.7$ Hz), 7.10 (2H, d, $J = 6.7$ Hz), 7.25 (2H, d, $J = 9.7$ Hz). MS m/z : 630 ($\text{M}+\text{H}$) $^+$.
Y5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.16 (3H, s), 1.43–1.77 (3H, m), 1.82–2.24 (4H, m), 2.25–2.51 (7H, m), 3.43–3.51 (2H, m), 3.64–3.76 (2H, m), 3.78 (3H, s), 6.05–6.09 (1H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.08 (2H, d, $J = 5.2$ Hz), 7.10 (2H, d, $J = 5.2$ Hz), 7.25 (7H, d, $J = 9.1$ Hz). MS m/z : 616 ($\text{M}+\text{H}$) $^+$.

[0894]

[Table 20]

Ex	Data
Y6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.39–1.80 (4H, m), 1.80–1.99 (4H, m), 2.04–2.14 (3H, m), 2.14–2.49 (10H, m), 2.63–2.74 (1H, m), 2.75–2.86 (1H, m), 2.88–2.98 (1H, m), 3.26–3.32 (2H, m), 3.37 (3H, s), 3.40–3.62 (4H, m), 3.64–3.76 (2H, m), 3.78 (3H, s), 5.16 (1H, dd, $J = 12.5, 5.2$ Hz), 5.82–5.87 (1H, m), 6.03–6.07 (1H, m), 6.32–6.38 (2H, m), 6.61 (1H, d, $J = 8.5$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.07–7.14 (4H, m), 7.24 (2H, d, $J = 8.5$ Hz), 8.14 (1H, s). MS m/z : 915 ($\text{M}+\text{H}$) $^+$.
Z1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.87–1.96 (2H, m), 2.03–2.10 (2H, m), 2.52–2.59 (2H, m), 2.78–2.85 (2H, m), 3.16 (2H, s), 4.44–4.52 (1H, m), 6.99 (2H, d, $J = 8.5$ Hz), 7.82 (2H, d, $J = 8.5$ Hz), 9.87 (1H, s). MS m/z : 320 ($\text{M}+\text{H}$) $^+$.
Z2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.45–1.65 (12H, m), 1.67–1.77 (1H, m), 1.81–1.90 (3H, m), 1.97–2.15 (4H, m), 2.23–2.37 (3H, m), 2.46–2.55 (2H, m), 2.78–2.85 (2H, m), 3.15 (2H, s), 3.36–3.45 (2H, m), 3.66–3.82 (5H, m), 4.26–4.33 (1H, m), 6.77 (2H, d, $J = 8.5$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.04 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). MS m/z : 691 ($\text{M}+\text{H}$) $^+$.
Z3	MS m/z : 635 ($\text{M}+\text{H}$) $^+$.
Z4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–0.97 (2H, m), 2.23–2.31 (1H, m), 2.37–2.48 (1H, m), 2.72–2.82 (1H, m), 3.03–3.13 (1H, m), 3.59–3.64 (2H, m), 4.63–4.75 (1H, m), 5.20–5.29 (2H, m).
Z5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.98 (2H, m), 2.20–2.29 (1H, m), 2.67–2.80 (1H, m), 2.85–2.94 (1H, m), 3.05–3.12 (1H, m), 3.55 (3H, s), 3.60–3.69 (2H, m), 5.21–5.32 (3H, m), 6.99 (1H, d, $J = 7.9$ Hz), 7.12 (1H, t, $J = 8.2$ Hz), 7.66 (1H, d, $J = 8.5$ Hz). MS m/z : 407 ($\text{M}-\text{C}_2\text{H}_4+\text{H}$) $^+$.
Z6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93–0.99 (2H, m), 2.15–2.22 (1H, m), 2.67–2.79 (1H, m), 2.80–2.91 (1H, m), 3.00–3.07 (1H, m), 3.61–3.68 (2H, m), 3.71–3.76 (5H, m), 5.18 (1H, dd, $J = 12.8, 5.5$ Hz), 5.27 (1H, d, $J = 9.2$ Hz), 5.31 (1H, d, $J = 9.2$ Hz), 6.29 (1H, d, $J = 8.2$ Hz), 6.46 (1H, d, $J = 8.2$ Hz), 6.85 (1H, t, $J = 8.2$ Hz). MS m/z : 427 ($\text{M}+\text{Na}$) $^+$.
Z7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.66 (3H, s), 0.89 (6H, s), 0.96 (2H, t, $J = 8.5$ Hz), 1.16 (3H, s), 1.47–1.64 (3H, m), 1.68–1.78 (1H, m), 1.82–1.95 (3H, m), 2.00–2.15 (4H, m), 2.18–2.36 (4H, m), 2.58–2.80 (3H, m), 2.82–2.99 (3H, m), 3.02–3.10 (1H, m), 3.26 (2H, s), 3.37–3.47 (2H, m), 3.62–3.77 (7H, m), 3.80 (3H, s), 4.35–4.41 (1H, m), 5.21 (1H, dd, $J = 13.1, 5.2$ Hz), 5.27 (1H, d, $J = 9.1$ Hz), 5.31 (1H, d, $J = 9.1$ Hz), 6.67 (1H, d, $J = 7.9$ Hz), 6.79 (2H, d, $J = 6.1$ Hz), 6.81 (2H, d, $J = 6.1$ Hz), 7.01–7.13 (5H, m), 7.30 (1H, d, $J = 7.9$ Hz), 9.29 (1H, s).

[0895]

[Table 21]

Ex	Data
Z8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.43–1.66 (3H, m), 1.68–1.78 (1H, m), 1.82–1.96 (3H, m), 1.99–2.16 (4H, m), 2.19–2.38 (4H, m), 2.56–3.00 (7H, m), 3.26 (2H, s), 3.37–3.47 (2H, m), 3.62–3.84 (8H, m), 4.34–4.43 (1H, m), 5.20 (1H, dd, $J = 12.5, 5.2$ Hz), 6.70 (1H, d, $J = 7.9$ Hz), 6.79 (2H, d, $J = 6.7$ Hz), 6.81 (2H, d, $J = 6.7$ Hz), 7.03–7.14 (5H, m), 7.31 (1H, d, $J = 7.9$ Hz), 8.12 (1H, s), 9.29 (1H, s). MS m/z : 891 (M+H) ⁺ .
AA1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, t, $J = 7.3$ Hz), 3.70 (2H, s), 4.18 (2H, q, $J = 7.1$ Hz), 7.33–7.37 (1H, m), 7.42–7.47 (1H, m), 7.52–7.58 (2H, m), 7.73–7.78 (2H, m), 7.94–7.98 (2H, m), 10.06 (1H, s). MS m/z : 269 (M+H) ⁺ .
AA2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.93–0.96 (6H, m), 1.16 (3H, s), 1.27 (3H, t, $J = 7.1$ Hz), 1.48–1.66 (3H, m), 1.71–1.79 (1H, m), 1.86–1.95 (1H, m), 2.06–2.15 (2H, m), 2.28–2.44 (3H, m), 3.54 (2H, dd, $J = 17.3, 13.7$ Hz), 3.67–3.77 (7H, m), 4.18 (2H, q, $J = 7.1$ Hz), 6.77–6.81 (2H, m), 7.09–7.12 (2H, m), 7.19–7.23 (2H, m), 7.27 (1H, d, $J = 8.5$ Hz), 7.38–7.42 (1H, m), 7.45–7.52 (4H, m). MS m/z : 640 (M+H) ⁺ .
AA3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.93–0.96 (6H, m), 1.17 (3H, s), 1.48–1.66 (3H, m), 1.71–1.79 (1H, m), 1.86–1.94 (1H, m), 2.06–2.14 (2H, m), 2.28–2.43 (3H, m), 3.53 (2H, dd, $J = 17.0, 14.6$ Hz), 3.68–3.77 (7H, m), 6.79 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 9.1$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.27 (1H, d, $J = 6.1$ Hz), 7.38–7.47 (3H, m), 7.49–7.52 (2H, m). MS m/z : 612 (M+H) ⁺ .
AA4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.95 (6H, s), 1.16 (3H, s), 1.46–1.93 (6H, m), 2.07–2.44 (6H, m), 2.60–2.93 (3H, m), 3.20–3.35 (5H, m), 3.47–3.59 (4H, m), 3.65–3.77 (7H, m), 5.12–5.18 (1H, m), 5.87–5.93 (1H, m), 6.25–6.30 (2H, m), 6.57 (1H, d, $J = 8.5$ Hz), 6.78 (2H, d, $J = 6.7$ Hz), 7.08–7.23 (5H, m), 7.39–7.54 (5H, m), 8.31 (1H, s). MS m/z : 911 (M+H) ⁺ .
AB1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (3H, t, $J = 7.5$ Hz), 2.05–2.24 (4H, m), 2.89 (2H, t, $J = 7.0$ Hz), 3.22 (2H, t, $J = 7.0$ Hz), 4.30 (2H, q, $J = 7.5$ Hz). MS m/z : 228 (M+H) ⁺ .
AB2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.02 (6H, s), 1.65–1.82 (6H, m), 1.89–2.00 (2H, m), 2.25–2.33 (4H, m), 2.43 (2H, s), 3.81 (3H, s), 6.89 (2H, d, $J = 9.1$ Hz), 7.22 (2H, d, $J = 9.1$ Hz). MS m/z : 394 (M+H) ⁺ .
AB3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.95 (2H, tt, $J = 12.5, 4.2$ Hz), 2.10 (2H, tt, $J = 10.0, 3.0$ Hz), 2.56–2.61 (2H, m), 2.81–2.86 (2H, m), 3.30 (2H, s), 3.77 (3H, s), 4.49–4.54 (1H, m), 7.02 (2H, d, $J = 8.5$ Hz), 7.85 (2H, d, $J = 8.5$ Hz), 9.90 (1H, s). MS m/z : 278 (M+H) ⁺ .

[0896]

[Table 22]

Ex	Data
AB4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (6H, s), 1.62–1.72 (6H, m), 1.82–1.92 (4H, m), 1.99–2.07 (2H, m), 2.10–2.17 (4H, m), 2.36 (2H, s), 2.48–2.55 (2H, m), 2.78–2.84 (2H, m), 3.27 (2H, s), 3.42 (2H, s), 3.74 (3H, s), 3.80 (3H, s), 4.28–4.34 (1H, m), 6.78 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz). MS m/z : 655 (M+H) ⁺ .
AB5	MS m/z : 641 (M+H) ⁺ .
AB6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (6H, s), 1.60–1.82 (6H, m), 1.82–1.98 (4H, m), 1.98–2.39 (9H, m), 2.55–3.04 (7H, m), 3.26 (2H, s), 3.43 (2H, s), 3.66 (3H, s), 3.80 (3H, s), 4.34–4.44 (1H, m), 5.19 (1H, dd, $J = 12.5, 5.2$ Hz), 6.70 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 6.84 (2H, d, $J = 8.5$ Hz), 7.03–7.09 (3H, m), 7.13 (2H, d, $J = 8.5$ Hz), 7.31 (1H, d, $J = 7.9$ Hz), 8.02 (1H, s), 9.29 (1H, s). MS m/z : 897 (M+H) ⁺ .
AC1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (3H, t, $J = 7.0$ Hz), 2.80 (2H, t, $J = 5.5$ Hz), 3.19 (2H, t, $J = 5.5$ Hz), 3.80 (2H, t, $J = 5.5$ Hz), 3.88 (2H, t, $J = 5.5$ Hz), 4.29 (2H, q, $J = 7.1$ Hz).
AC2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.03 (6H, s), 1.73–1.87 (4H, m), 2.09–2.16 (2H, m), 2.25–2.31 (2H, m), 2.43 (2H, s), 3.51–3.59 (2H, m), 3.74–3.83 (5H, m), 6.89 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz). MS m/z : 360 (M+H) ⁺ .
AC3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (6H, s), 1.68–1.79 (4H, m), 1.82–1.94 (2H, m), 1.96–2.14 (6H, m), 2.37 (2H, s), 2.48–2.54 (2H, m), 2.77–2.84 (2H, m), 3.27 (2H, s), 3.43 (2H, s), 3.48–3.56 (2H, m), 3.67–3.76 (5H, m), 3.80 (3H, s), 4.28–4.34 (1H, m), 6.78 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz). MS m/z : 621 (M+H) ⁺ .
AC4	MS m/z : 607 (M+H) ⁺ .
AC5	MS m/z : 993 (M+H) ⁺ .
AC6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (6H, s), 1.68–1.80 (4H, m), 1.84–1.95 (2H, m), 1.96–2.15 (6H, m), 2.20–2.28 (1H, m), 2.38 (2H, s), 2.56–2.66 (2H, m), 2.69–2.89 (2H, m), 2.89–3.01 (3H, m), 3.26 (2H, s), 3.45 (2H, s), 3.47–3.57 (2H, m), 3.64–3.74 (5H, m), 3.80 (3H, s), 4.35–4.43 (1H, m), 5.19 (1H, dd, $J = 12.8, 5.5$ Hz), 6.70 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 7.04–7.12 (5H, m), 7.31 (1H, d, $J = 7.9$ Hz), 8.04 (1H, s), 9.29 (1H, s). MS m/z : 863 (M+H) ⁺ .

[0897]

[Table 23]

Ex	Data
AD1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.46–1.65 (2H, m), 1.67–1.78 (5H, m), 1.81–1.91 (1H, m), 1.93–2.01 (2H, m), 2.05–2.14 (2H, m), 2.20–2.35 (4H, m), 2.37–2.46 (2H, m), 2.52–2.69 (4H, m), 2.72–2.88 (2H, m), 2.93–3.00 (1H, m), 3.18 (2H, s), 3.36–3.46 (2H, m), 3.64–3.83 (9H, m), 4.63–4.68 (1H, m), 5.19 (1H, dd, $J = 12.1, 5.5$ Hz), 6.64–6.71 (3H, m), 6.81 (2H, d, $J = 8.5$ Hz), 7.02–7.13 (5H, m), 7.33 (1H, d, $J = 7.9$ Hz), 8.01 (1H, s), 9.32 (1H, s). MS m/z : 931 (M+H) $^+$.
AE1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.45–1.66 (3H, m), 1.67–2.01 (7H, m), 2.03–2.15 (2H, m), 2.20–2.64 (10H, m), 2.66–2.90 (2H, m), 2.91–3.01 (1H, m), 3.08–3.15 (2H, m), 3.37–3.48 (5H, m), 3.65–3.82 (6H, m), 4.61–4.70 (1H, m), 5.20 (1H, dd, $J = 13.1, 5.2$ Hz), 6.67 (2H, d, $J = 8.5$ Hz), 6.72 (1H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 6.90–6.98 (1H, m), 7.04 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.71 (1H, s), 8.02 (1H, s), 9.22 (1H, s). MS m/z : 931 (M+H) $^+$.
AF1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.43–1.65 (2H, m), 1.66–1.92 (5H, m), 1.92–2.03 (2H, m), 2.03–2.17 (2H, m), 2.18–2.67 (11H, m), 2.76–2.99 (2H, m), 3.07–3.17 (2H, m), 3.35–3.46 (3H, m), 3.63–3.81 (6H, m), 4.34 (1H, d, $J = 15.9$ Hz), 4.48 (1H, d, $J = 15.9$ Hz), 4.60–4.70 (1H, m), 5.21 (1H, dd, $J = 13.1, 5.2$ Hz), 6.67 (2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.24–7.35 (1H, m), 7.84 (1H, d, $J = 8.5$ Hz), 7.90 (1H, s), 8.18 (1H, s), 9.52 (1H, s). MS m/z : 916 (M+H) $^+$.
AG1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (3H, t, $J = 7.3$ Hz), 1.83–1.93 (1H, m), 2.18–2.25 (1H, m), 2.46–2.68 (5H, m), 4.18 (2H, q, $J = 7.3$ Hz), 6.28–6.32 (1H, m), 7.53 (2H, d, $J = 7.9$ Hz), 7.83 (2H, d, $J = 7.9$ Hz), 9.99 (1H, s). MS m/z : 259 (M+H) $^+$.
AG2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.28 (3H, t, $J = 7.0$ Hz), 1.46–1.65 (3H, m), 1.68–1.78 (1H, m), 1.80–1.91 (2H, m), 2.05–2.14 (2H, m), 2.16–2.23 (1H, m), 2.25–2.35 (1H, m), 2.36 (2H, s), 2.43–2.54 (4H, m), 2.56–2.65 (1H, m), 3.45 (1H, d, $J = 14.0$ Hz), 3.50 (1H, d, $J = 14.0$ Hz), 3.66–3.75 (2H, m), 3.78 (3H, s), 4.18 (2H, q, $J = 7.0$ Hz), 6.08–6.12 (1H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.09 (2H, d, $J = 9.1$ Hz), 7.10 (2H, d, $J = 9.1$ Hz), 7.25 (2H, d, $J = 9.1$ Hz). MS m/z : 630 (M+H) $^+$.
AG3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.35 (1H, t, $J = 5.5$ Hz), 1.39–1.65 (3H, m), 1.68–1.78 (1H, m), 1.82–2.14 (6H, m), 2.25–2.41 (4H, m), 2.43–2.53 (2H, m), 3.45 (1H, d, $J = 14.0$ Hz), 3.50 (1H, d, $J = 14.0$ Hz), 3.57–3.81 (8H, m), 6.09–6.13 (1H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.26 (2H, d, $J = 8.5$ Hz). MS m/z : 588 (M+H) $^+$.

[0898]

[Table 24]

Ex	Data
AG4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.46–1.64 (3H, m), 1.69–1.78 (1H, m), 1.83–1.93 (1H, m), 1.97–2.19 (6H, m), 2.24–2.45 (4H, m), 2.46–2.54 (2H, m), 3.04 (3H, s), 3.45 (1H, d, J = 14.0 Hz), 3.50 (1H, d, J = 14.0 Hz), 3.65–3.75 (2H, m), 3.78 (3H, s), 4.19 (2H, d, J = 6.7 Hz), 6.05–6.09 (1H, m), 6.80 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 7.10 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz). MS m/z : 666 (M+H) $^+$.
AG5	MS m/z : 656 (M+H) $^+$.
AG6	$^1\text{H-NMR}$ (DMSO-D_6) δ : 1.97–2.10 (1H, m), 2.36–2.50 (1H, m), 2.57–2.69 (1H, m), 2.86–2.99 (1H, m), 4.50 (1H, d, J = 18.0 Hz), 4.62 (1H, d, J = 18.0 Hz), 5.18 (1H, dd, J = 13.4, 5.5 Hz), 7.97 (2H, s), 7.99 (1H, d, J = 7.9 Hz), 8.32 (1H, dd, J = 7.9, 1.2 Hz), 8.48 (1H, d, J = 1.2 Hz), 11.06 (1H, s). MS m/z : 467 (M+H) $^+$.
AG7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.88–0.93 (6H, m), 1.16 (3H, s), 1.36–1.67 (3H, m), 1.68–2.15 (7H, m), 2.20–2.61 (14H, m), 2.81–3.00 (2H, m), 3.36–3.52 (4H, m), 3.64–3.93 (8H, m), 4.39 (1H, d, J = 16.4 Hz), 4.54 (1H, d, J = 16.4 Hz), 5.24 (1H, dd, J = 13.4, 4.9 Hz), 6.08–6.12 (1H, m), 6.80 (2H, d, J = 8.5 Hz), 7.07–7.12 (4H, m), 7.24–7.29 (2H, m), 7.51 (1H, d, J = 8.5 Hz), 7.54 (1H, s), 7.91–7.96 (2H, m). MS m/z : 926 (M+H) $^+$.
AH1	$^1\text{H-NMR}$ (CDCl_3) δ : -0.03 (9H, s), 0.93 (2H, t, J = 8.3 Hz), 2.13–2.21 (1H, m), 2.63–2.75 (1H, m), 2.81–2.88 (1H, m), 2.99–3.06 (1H, m), 3.58–3.66 (2H, m), 3.76 (3H, s), 5.18 (1H, dd, J = 12.7, 5.4 Hz), 5.25 (2H, q, J = 9.8 Hz), 6.68 (1H, d, J = 7.8 Hz), 6.87 (1H, t, J = 8.1 Hz), 7.20 (1H, d, J = 8.3 Hz). MS m/z : 440 $[\text{M}(^{79}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$, 442 $[\text{M}(^{81}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$.
AH2	MS m/z : 634 (M+Na) $^+$.
AH3	MS m/z : 1071 (M+H) $^+$.
AH4	$^1\text{H-NMR}$ (DMSO-D_6) δ : 0.55 (3H, s), 0.86 (6H, s), 1.06 (3H, s), 1.24–1.44 (2H, m), 1.46–1.61 (2H, m), 1.67–1.97 (5H, m), 2.00–2.16 (3H, m), 2.17–2.57 (12H, m), 2.58–2.80 (2H, m), 2.82–3.00 (1H, m), 3.27 (3H, s), 3.30–3.37 (2H, m), 3.44 (2H, s), 3.50–3.61 (2H, m), 3.65–3.84 (2H, m), 3.70 (3H, s), 5.43 (1H, dd, J = 12.2, 4.9 Hz), 6.08–6.14 (1H, m), 6.81 (2H, d, J = 8.5 Hz), 6.95 (1H, d, J = 7.3 Hz), 7.04 (2H, d, J = 8.5 Hz), 7.07–7.13 (1H, m), 7.16–7.22 (1H, m), 7.19 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz), 11.15 (1H, s). MS m/z : 941 (M+H) $^+$.
AI1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (3H, t, J = 7.0 Hz), 1.58–1.84 (6H, m), 2.23–2.33 (2H, m), 2.58–2.67 (1H, m), 2.69–2.75 (1H, m), 4.20 (2H, q, J = 7.0 Hz), 7.36 (2H, d, J = 7.9 Hz), 7.81 (2H, d, J = 7.9 Hz), 9.97 (1H, s). MS m/z : 261 (M+H) $^+$.

[0899]

[Table 25]

Ex	Data
AI2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, t, $J = 7.0$ Hz), 1.43–1.69 (4H, m), 1.95–2.03 (2H, m), 2.09–2.18 (2H, m), 2.31–2.42 (1H, m), 2.57–2.68 (1H, m), 4.15 (2H, q, $J = 7.0$ Hz), 7.37 (2H, d, $J = 7.9$ Hz), 7.82 (2H, t, $J = 3.9$ Hz), 9.98 (1H, s). MS m/z : 261 (M+H) $^+$.
AI3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.15 (3H, s), 1.29 (3H, t, $J = 7.0$ Hz), 1.44–1.80 (10H, m), 1.87 (1H, td, $J = 12.5, 3.6$ Hz), 2.03–2.14 (2H, m), 2.20–2.39 (5H, m), 2.47–2.55 (1H, m), 2.67–2.72 (1H, m), 3.43 (1H, d, $J = 14.0$ Hz), 3.48 (1H, d, $J = 14.0$ Hz), 3.65–3.81 (5H, m), 4.19 (2H, q, $J = 7.0$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 7.05–7.14 (6H, m). MS m/z : 632 (M+H) $^+$.
AI4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.24–1.33 (1H, m), 1.42–1.93 (13H, m), 2.03–2.15 (2H, m), 2.23–2.39 (3H, m), 2.54–2.66 (1H, m), 3.43 (1H, d, $J = 14.0$ Hz), 3.49 (1H, d, $J = 14.0$ Hz), 3.65–3.81 (8H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.05–7.13 (6H, m). MS m/z : 590 (M+H) $^+$.
AI5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.15 (3H, s), 1.36–1.94 (11H, m), 2.02–2.14 (2H, m), 2.23–2.59 (7H, m), 3.42 (1H, d, $J = 14.0$ Hz), 3.47 (1H, d, $J = 14.0$ Hz), 3.65–3.83 (5H, m), 6.80 (2H, d, $J = 8.5$ Hz), 6.99–7.12 (6H, m), 9.79 (1H, s). MS m/z : 588 (M+H) $^+$.
AI6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.48–1.78 (21H, m), 1.83–1.98 (2H, m), 2.02–2.13 (2H, m), 2.23–2.45 (9H, m), 2.50–2.60 (1H, m), 3.38–3.51 (6H, m), 3.65–3.82 (5H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.05–7.13 (6H, m). MS m/z : 758 (M+H) $^+$.
AI7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.42–1.79 (14H, m), 1.82–1.99 (2H, m), 2.03–2.14 (2H, m), 2.24–2.60 (10H, m), 2.84–2.94 (4H, m), 3.43 (1H, d, $J = 14.0$ Hz), 3.48 (1H, d, $J = 14.0$ Hz), 3.66–3.80 (4H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.04–7.14 (6H, m). MS m/z : 658 (M+H) $^+$.
AI8	$^1\text{H-NMR}$ (CDCl_3) δ : 1.65 (9H, s), 3.51 (3H, s), 7.14 (1H, d, $J = 7.9$ Hz), 7.67 (1H, s), 7.83 (1H, dd, $J = 8.2, 1.5$ Hz), 10.00 (1H, br s). MS m/z : 249 (M+H) $^+$.
AI9	$^1\text{H-NMR}$ (CDCl_3) δ : 1.65 (9H, s), 3.51 (3H, s), 7.14 (1H, d, $J = 7.9$ Hz), 7.67 (1H, s), 7.83 (1H, dd, $J = 8.2, 1.5$ Hz), 10.00 (1H, br s). MS m/z : 360 (M+H) $^+$.

[0900]

[Table 26]

Ex	Data
AI10	$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.00–2.04 (1H, m), 2.59–2.75 (2H, m), 2.85–2.90 (1H, m), 3.37 (3H, s), 5.42 (1H, dd, J = 12.5, 5.2 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.67–7.72 (2H, m), 11.14 (1H, s), 12.77 (1H, br s). MS m/z : 304 (M+H) $^+$.
AI11	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.89 (6H, s), 1.15 (3H, s), 1.41–1.78 (13H, m), 1.82–1.98 (2H, m), 2.03–2.14 (2H, m), 2.19–2.60 (11H, m), 2.66–2.90 (2H, m), 2.93–3.02 (1H, m), 3.40–3.55 (6H, m), 3.64–3.84 (7H, m), 5.24 (1H, dd, J = 12.8, 5.5 Hz), 6.76–6.85 (3H, m), 7.05–7.18 (8H, m), 8.11 (1H, s). MS m/z : 943 (M+H) $^+$.
AJ1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.27 (3H, t, J = 7.0 Hz), 1.40–1.66 (7H, m), 1.67–1.78 (1H, m), 1.82–1.191 (1H, m), 1.92–2.00 (2H, m), 2.03–2.15 (4H, m), 2.24–2.40 (4H, m), 2.44–2.53 (1H, m), 3.44 (1H, d, J = 14.0 Hz), 3.49 (1H, d, J = 14.0 Hz), 3.64–3.82 (5H, m), 4.15 (2H, q, J = 7.0 Hz), 6.80 (2H, d, J = 9.1 Hz), 7.04–7.12 (6H, m). MS m/z : 632 (M+H) $^+$.
AJ2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.32 (1H, t, J = 5.5 Hz), 1.41–1.78 (8H, m), 1.82–1.98 (6H, m), 2.03–2.14 (2H, m), 2.24–2.51 (4H, m), 3.42–3.55 (4H, m), 3.66–3.81 (5H, m), 6.81 (2H, d, J = 9.1 Hz), 7.08 (4H, s), 7.10 (2H, d, J = 9.1 Hz). MS m/z : 590 (M+H) $^+$.
AJ3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.37–1.93 (10H, m), 1.99–2.20 (6H, m), 2.24–2.38 (4H, m), 3.44 (1H, d, J = 14.0 Hz), 3.49 (1H, d, J = 14.0 Hz), 3.64–3.84 (5H, m), 6.80 (2H, d, J = 9.1 Hz), 7.00–7.14 (6H, m), 9.69 (1H, s). MS m/z : 588 (M+H) $^+$.
AJ4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 0.97–1.11 (2H, m), 1.15 (3H, s), 1.37–1.78 (17H, m), 1.82–1.98 (5H, m), 2.03–2.13 (2H, m), 2.15–2.21 (2H, m), 2.25–2.53 (7H, m), 3.38–3.52 (6H, m), 3.65–3.83 (5H, m), 6.80 (2H, d, J = 9.1 Hz), 7.04–7.15 (6H, m). MS m/z : 758 (M+H) $^+$.
AJ5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 0.98–1.11 (2H, m), 1.15 (3H, s), 1.36–1.78 (10H, m), 1.83–1.98 (4H, m), 2.03–2.13 (2H, m), 2.14–2.20 (2H, m), 2.24–2.54 (7H, m), 2.83–2.99 (4H, m), 3.43 (1H, d, J = 14.0 Hz), 3.48 (1H, d, J = 14.0 Hz), 3.65–3.82 (5H, m), 6.80 (2H, d, J = 9.1 Hz), 7.03–7.13 (6H, m). MS m/z : 658 (M+H) $^+$.
AJ6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 0.99–1.12 (2H, m), 1.15 (3H, s), 1.37–1.77 (10H, m), 1.82–1.98 (4H, m), 2.03–2.13 (2H, m), 2.17–2.61 (11H, m), 2.66–2.90 (2H, m), 2.93–3.02 (1H, m), 3.38–3.59 (6H, m), 3.64–3.88 (6H, m), 5.24 (1H, dd, J = 12.8, 5.5 Hz), 6.77–6.83 (3H, m), 7.06–7.18 (8H, m), 8.08 (1H, s). MS m/z : 943 (M+H) $^+$.

[0901]

[Table 27]

Ex	Data
AK1	MS m/z: 271 (M-tBu+H) ⁺ .
AK2	¹ H-NMR (CDCl ₃) δ : 1.53 (9H, s), 2.79–2.87 (2H, m), 2.91 (3H, d, J = 5.1 Hz), 3.59–3.69 (2H, m), 4.50–4.60 (2H, m), 4.70–4.80 (1H, m), 6.61–6.72 (1H, m), 7.06–7.16 (1H, m), 7.80–7.91 (1H, m). MS m/z: 328 (M-tBu+H) ⁺ .
AK3	¹ H-NMR (CDCl ₃) δ : 1.53 (9H, s), 2.86–2.97 (2H, m), 3.62–3.76 (2H, m), 3.71 (3H, s), 5.02–5.05 (2H, m), 6.83–6.96 (2H, m), 8.22–8.36 (1H, m). MS m/z: 304 (M+H) ⁺ .
AK4	¹ H-NMR (CDCl ₃) δ : 1.54 (9H, s), 2.88–2.97 (2H, m), 3.63–3.73 (2H, m), 3.73–3.82 (3H, m), 5.08 (2H, s), 5.29–5.52 (4H, m), 6.51–6.57 (2H, m), 6.77–6.85 (1H, m), 7.24–7.31 (6H, m), 7.36–7.46 (4H, m), 7.60 (1H, d, J = 8.2 Hz). MS m/z: 593 (M+H) ⁺ .
AK5	¹ H-NMR (CDCl ₃) δ : 1.53 (9H, s), 2.21–2.30 (1H, m), 2.69–3.02 (5H, m), 3.60–3.79 (5H, m), 4.99–5.07 (2H, m), 5.18–5.27 (1H, m), 6.67 (1H, d, J = 8.2 Hz), 6.88 (1H, d, J = 8.2 Hz), 8.03 (1H, s). MS m/z: 359 (M-tBu+H) ⁺ .
AK6	¹ H-NMR (CDCl ₃) δ : 1.46 (9H, s), 1.58–1.64 (4H, m), 1.96–2.01 (2H, m), 2.42–2.49 (2H, m), 3.30–3.35 (2H, m), 3.37–3.41 (2H, m), 4.73–4.81 (1H, m), 6.89 (2H, d, J = 8.5 Hz), 7.82 (2H, d, J = 8.5 Hz), 9.88 (1H, s). MS m/z: 290 (M-tBu+H) ⁺ .
AK7	¹ H-NMR (CDCl ₃) δ : 1.46 (9H, s), 1.69–1.74 (4H, m), 1.92–1.99 (2H, m), 2.39–2.57 (6H, m), 3.10 (2H, s), 4.70–4.78 (1H, m), 6.89 (2H, d, J = 8.5 Hz), 7.81 (2H, d, J = 8.5 Hz), 9.87 (1H, s). MS m/z: 360 (M+H) ⁺ .
AK8	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.42–1.64 (12H, m), 1.66–1.76 (5H, m), 1.80–1.95 (3H, m), 2.04–2.14 (2H, m), 2.22–2.57 (9H, m), 3.09 (2H, s), 3.38 (1H, d, J = 14.0 Hz), 3.43 (1H, d, J = 14.0 Hz), 3.66–3.82 (5H, m), 4.58–4.66 (1H, m), 6.66 (2H, d, J = 8.5 Hz), 6.81 (2H, d, J = 8.5 Hz), 7.02 (2H, d, J = 8.5 Hz), 7.10 (2H, d, J = 8.5 Hz). MS m/z: 731 (M+H) ⁺ .
AK9	MS m/z: 675 (M+H) ⁺ .
AK10	¹ H-NMR (CDCl ₃) δ : 0.67 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.43–1.77 (12H, m), 1.77–1.97 (3H, m), 2.04–2.16 (2H, m), 2.18–2.51 (7H, m), 2.69–3.00 (5H, m), 3.23–3.29 (2H, m), 3.41 (2H, d, J = 4.3 Hz), 3.68–3.85 (9H, m), 4.58–4.67 (1H, m), 5.07–5.26 (2H, m), 5.37–5.41 (1H, m), 6.63–6.69 (3H, m), 6.81 (2H, d, J = 9.0 Hz), 6.87 (1H, d, J = 7.8 Hz), 7.03 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.6 Hz), 8.01 (1H, s). MS m/z: 971 (M+H) ⁺ .
AL1	¹ H-NMR (CDCl ₃) δ : 1.51 (4.5H, s), 1.53 (4.5H, s), 4.52–4.68 (6H, m), 7.26 (1H, d, J = 26.6 Hz). MS m/z: 291 [M(⁷⁹ Br- ⁷⁹ Br)-Boc+H] ⁺ , 293 [M(⁷⁹ Br- ⁸¹ Br)-Boc+H] ⁺ , 295 [M(⁸¹ Br- ⁸¹ Br)-Boc+H] ⁺ .

[0902]

[Table 28]

Ex	Data
AL2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.51 (4.5H, s), 1.53 (4.5H, s), 4.07 (2H, s), 4.54–4.70 (4H, m), 6.69 (1H, dd, $J = 8.2, 5.5$ Hz), 6.94 (0.5H, d, $J = 8.2$ Hz), 6.99 (0.5H, d, $J = 7.8$ Hz). MS m/z : 257 $[\text{M}(^{79}\text{Br})-\text{tBu}+\text{H}]^+$, 259 $[\text{M}(^{81}\text{Br})-\text{tBu}+\text{H}]^+$.
AL3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.51–1.58 (9H, m), 2.20–2.30 (1H, m), 2.69–3.02 (3H, m), 3.53–3.59 (3H, m), 4.63–4.72 (2H, m), 4.92–5.05 (2H, m), 5.19–5.24 (1H, m), 6.73 (1H, dd, $J = 11.7, 4.7$ Hz), 6.90–7.02 (1H, m), 7.98–8.08 (1H, m). MS m/z : 401 (M+H) $^+$.
AL4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.44–1.98 (12H, m), 2.03–2.60 (12H, m), 2.69–3.02 (2H, m), 3.20–3.28 (2H, m), 3.41 (2H, d, $J = 3.9$ Hz), 3.58 (3H, s), 3.58–3.77 (3H, m), 3.80 (3H, s), 4.59–5.32 (5H, m), 6.67 (2H, d, $J = 8.6$ Hz), 6.73–6.79 (1H, m), 6.81 (2H, d, $J = 9.0$ Hz), 6.94–7.01 (1H, m), 7.04 (2H, d, $J = 8.2$ Hz), 7.11 (2H, d, $J = 9.0$ Hz), 8.00 (1H, s). MS m/z : 957 (M+H) $^+$.
AM1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.68 (3H, s), 1.04 (3H, s), 1.05 (3H, s), 1.18 (3H, s), 1.53–1.67 (4H, m), 1.72–1.81 (1H, m), 2.10–2.18 (2H, m), 2.26–2.33 (1H, m), 2.36–2.44 (1H, m), 2.46 (2H, s), 3.72–3.82 (2H, m), 6.69 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz). MS m/z : 374 (M+H) $^+$.
AM2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.93 (3H, s), 0.98 (3H, s), 1.19 (3H, s), 1.40 (9H, s), 1.54–1.75 (3H, m), 2.06–2.12 (1H, m), 2.22–2.29 (1H, m), 2.41–2.51 (1H, m), 2.80–2.97 (1H, m), 2.98–3.09 (1H, m), 3.16–3.25 (2H, m), 3.74–3.82 (2H, m), 4.71 (1H, s), 6.81 (2H, d, $J = 9.1$ Hz), 7.11–7.17 (2H, m). MS m/z : 374 (M-Boc+H) $^+$.
AM3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.93 (3H, s), 0.98 (3H, s), 1.20 (3H, s), 1.37–1.44 (9H, m), 1.57–1.77 (4H, m), 2.09–2.14 (1H, m), 2.24–2.31 (1H, m), 2.38–2.48 (1H, m), 2.76–3.25 (3H, m), 3.76–3.81 (2H, m), 6.49 (1H, t, $J = 73.8$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.26–7.31 (2H, m). MS m/z : 424 (M-Boc+H) $^+$.
AM4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.02 (6H, s), 1.20 (3H, s), 1.54–1.79 (4H, m), 2.03–2.11 (1H, m), 2.12–2.18 (1H, m), 2.30–2.44 (4H, m), 3.74–3.79 (2H, m), 6.52 (1H, t, $J = 74.1$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.29 (2H, d, $J = 8.5$ Hz). MS m/z : 424 (M+H) $^+$.
AM5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.92 (6H, s), 1.17 (3H, s), 1.29 (3H, t, $J = 7.3$ Hz), 1.51–1.69 (3H, m), 1.69–1.90 (3H, m), 2.04–2.16 (2H, m), 2.16–2.33 (2H, m), 2.33–2.41 (2H, m), 2.42–2.55 (4H, m), 2.56–2.65 (1H, m), 3.48 (2H, s), 3.70–3.73 (2H, m), 4.18 (2H, q, $J = 7.1$ Hz), 6.09–6.12 (1H, m), 6.44 (1H, t, $J = 74.1$ Hz), 7.00 (2H, d, $J = 9.1$ Hz), 7.08 (2H, d, $J = 9.1$ Hz), 7.18 (2H, d, $J = 9.1$ Hz), 7.25 (2H, d, $J = 9.1$ Hz).

[0903]

[Table 29]

Ex	Data
AM6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.93 (6H, s), 1.17 (3H, s), 1.34–1.60 (3H, m), 1.47 (9H, s), 1.60–1.93 (5H, m), 1.95–2.02 (1H, m), 2.04–2.14 (2H, m), 2.22–2.50 (12H, m), 3.41–3.49 (6H, m), 3.69–3.73 (2H, m), 6.09–6.12 (1H, m), 6.44 (1H, t, $J = 74.1$ Hz), 7.00 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.5$ Hz), 7.26 (2H, d, $J = 8.5$ Hz). MS m/z : 792 (M+H) $^+$.
AM7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.98 (2H, m), 2.18–2.26 (1H, m), 2.62–2.75 (1H, m), 2.82–2.92 (1H, m), 3.02–3.09 (1H, m), 3.42 (3H, s), 3.61–3.67 (2H, m), 5.19 (1H, dd, $J = 12.8, 5.5$ Hz), 5.25 (1H, d, $J = 9.7$ Hz), 5.30 (1H, d, $J = 9.7$ Hz), 6.65 (1H, d, $J = 9.1$ Hz), 7.16–7.20 (2H, m). MS m/z : 490 [$\text{M}^{(79}\text{Br})+\text{Na}$] $^+$, 492 [$\text{M}^{(81}\text{Br})+\text{Na}$] $^+$.
AM8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–1.00 (2H, m), 2.22–2.32 (1H, m), 2.68–2.83 (1H, m), 2.85–2.97 (1H, m), 3.05–3.14 (1H, m), 3.53 (3H, s), 3.60–3.71 (2H, m), 5.23–5.35 (3H, m), 6.91 (1H, d, $J = 8.5$ Hz), 7.44 (2H, s), 7.89 (1H, d, $J = 1.2$ Hz), 8.05 (1H, dd, $J = 8.5, 1.2$ Hz). MS m/z : 634 (M+Na) $^+$.
AM9	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.64 (3H, s), 0.86–1.00 (8H, m), 1.17 (3H, s), 1.37–1.68 (6H, m), 1.68–1.95 (2H, m), 1.95–2.15 (4H, m), 2.18–2.59 (14H, m), 2.62–3.11 (3H, m), 3.45–3.49 (6H, m), 3.62–3.74 (5H, m), 5.20–5.34 (3H, m), 6.09–6.13 (1H, m), 6.43 (1H, t, $J = 74.4$ Hz), 6.78 (1H, d, $J = 7.9$ Hz), 6.99 (2H, d, $J = 8.5$ Hz), 7.05–7.19 (5H, m), 7.21–7.31 (3H, m). MS m/z : 1107 (M+H) $^+$.
AM10	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.92 (6H, s), 1.17 (3H, s), 1.35–1.49 (1H, m), 1.49–1.93 (8H, m), 1.96–2.16 (3H, m), 2.20–2.57 (13H, m), 2.65–3.04 (3H, m), 3.32–3.91 (10H, m), 5.20–5.27 (1H, m), 6.08–6.13 (1H, m), 6.43 (1H, t, $J = 74.4$ Hz), 6.81 (1H, d, $J = 8.5$ Hz), 6.99 (2H, d, $J = 7.9$ Hz), 7.07 (2H, d, $J = 7.9$ Hz), 7.10–7.19 (4H, m), 7.25 (2H, d, $J = 7.9$ Hz), 8.05 (1H, s). MS m/z : 977 (M+H) $^+$.
AN1	MS m/z : 150 (M+H) $^+$.
AN2	$^1\text{H-NMR}$ (CDCl_3) δ : 3.52–3.55 (2H, m), 3.96 (1H, s), 4.00 (2H, dd, $J = 5.7, 4.5$ Hz), 6.41 (1H, t, $J = 4.1$ Hz), 6.54 (1H, d, $J = 7.8$ Hz), 6.86 (1H, t, $J = 8.0$ Hz), 8.24 (1H, s). MS m/z : 176 (M+H) $^+$.
AN3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.46–1.77 (9H, m), 1.83–2.00 (3H, m), 2.03–2.15 (2H, m), 2.23–2.62 (9H, m), 3.35–3.57 (4H, m), 3.65–3.78 (2H, m), 3.80 (3H, s), 3.93–4.05 (2H, m), 4.11–4.19 (2H, m), 4.60–4.68 (1H, m), 6.39–6.54 (1H, m), 6.66 (2H, d, $J = 8.6$ Hz), 6.81 (2H, d, $J = 9.0$ Hz), 6.83–6.89 (1H, m), 7.00–7.06 (3H, m), 7.11 (2H, d, $J = 9.0$ Hz). MS m/z : 832 (M+H) $^+$.
AN4	MS m/z : 1073 (M+H) $^+$.

[0904]

[Table 30]

Ex	Data
AN5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.45–2.15 (19H, m), 2.18–2.59 (5H, m), 2.66–3.03 (2H, m), 3.35–3.46 (4H, m), 3.66–3.78 (2H, m), 3.80 (3H, s), 3.99–4.23 (4H, m), 4.58–4.69 (1H, m), 5.16–5.25 (1H, m), 6.60–6.69 (3H, m), 6.81 (2H, d, $J = 9.0$ Hz), 7.00–7.07 (3H, m), 7.11 (2H, dd, $J = 6.7, 2.0$ Hz), 7.23–7.31 (1H, m), 8.00–8.08 (1H, m). MS m/z : 943 ($\text{M}+\text{H}$) $^+$.
A01	$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 2.15–2.35 (2H, m), 2.49 (2H, t, $J = 7.0$ Hz), 4.16–4.22 (1H, m), 5.36 (2H, s), 5.46 (1H, br s), 6.19 (1H, br s), 6.80 (1H, d, $J = 9.1$ Hz), 7.34–7.46 (5H, m), 8.11 (1H, dd, $J = 9.1, 2.1$ Hz), 8.63 (1H, d, $J = 6.1$ Hz), 8.93 (1H, d, $J = 2.1$ Hz). MS m/z : 402 ($\text{M}+\text{tBu}+\text{H}$) $^+$.
A02	$^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (9H, s), 2.22 (2H, t, $J = 7.3$ Hz), 2.34–2.45 (1H, m), 2.54–2.64 (1H, m), 5.10 (1H, dd, $J = 9.7, 5.5$ Hz), 5.35 (2H, s), 5.65 (1H, br s), 6.46 (1H, br s), 7.19 (1H, d, $J = 8.5$ Hz), 7.33–7.46 (5H, m), 7.75 (1H, d, $J = 1.8$ Hz), 7.87 (1H, dd, $J = 8.5, 1.8$ Hz), 9.24 (1H, s). MS m/z : 476 ($\text{M}+\text{Na}$) $^+$.
A03	$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (9H, s), 2.14–2.28 (2H, m), 2.35–2.45 (1H, m), 2.53–2.63 (1H, m), 3.47 (3H, s), 5.06 (1H, dd, $J = 9.7, 6.1$ Hz), 5.38 (2H, s), 5.48 (1H, br s), 6.42 (1H, br s), 7.19 (1H, d, $J = 8.5$ Hz), 7.32–7.48 (5H, m), 7.72 (1H, s), 7.90 (1H, d, $J = 8.5$ Hz). MS m/z : 490 ($\text{M}+\text{Na}$) $^+$.
A04	$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (9H, s), 2.19–2.28 (2H, m), 2.37–2.47 (1H, m), 2.54–2.66 (1H, m), 3.50 (3H, s), 5.07–5.12 (1H, m), 5.61 (1H, br s), 6.45 (1H, br s), 7.24 (1H, d, $J = 7.9$ Hz), 7.74 (1H, s), 7.92 (1H, d, $J = 7.9$ Hz). MS m/z : 400 ($\text{M}+\text{Na}$) $^+$.
A05	MS m/z : 656 ($\text{M}+\text{H}$) $^+$.
A06	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (6H, s), 1.16 (3H, s), 1.21–1.76 (8H, m), 1.41 (9H, s), 1.79–1.95 (3H, m), 1.95–2.67 (20H, m), 3.39–3.55 (2H, m), 3.46 (3H, s), 3.66–3.82 (2H, m), 3.78 (3H, s), 5.07 (1H, dd, $J = 9.7, 6.1$ Hz), 5.36 (1H, br s), 6.08–6.13 (1H, m), 6.39 (1H, br s), 6.80 (2H, d, $J = 9.1$ Hz), 7.04–7.20 (7H, m), 7.26 (2H, d, $J = 5.5$ Hz). MS m/z : 1015 ($\text{M}+\text{H}$) $^+$.
A07	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.35–1.67 (6H, m), 1.67–1.80 (1H, m), 1.80–1.95 (3H, m), 1.95–2.03 (1H, m), 2.03–2.16 (3H, m), 2.20–2.59 (13H, m), 2.65–2.79 (1H, m), 2.79–2.91 (1H, m), 2.92–3.02 (1H, m), 3.40–3.54 (5H, m), 3.63–3.85 (6H, m), 5.24 (1H, dd, $J = 12.5, 5.2$ Hz), 6.07–6.12 (1H, m), 6.77–6.83 (3H, m), 7.05–7.18 (6H, m), 7.23–7.29 (2H, m), 8.02–8.10 (1H, m). MS m/z : 941 ($\text{M}+\text{H}$) $^+$.
AP1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 2.15–2.35 (2H, m), 2.49 (2H, t, $J = 7.0$ Hz), 4.16–4.22 (1H, m), 5.36 (2H, s), 5.46 (1H, br s), 6.19 (1H, br s), 6.80 (1H, d, $J = 9.1$ Hz), 7.34–7.46 (5H, m), 8.11 (1H, dd, $J = 9.1, 2.1$ Hz), 8.63 (1H, d, $J = 6.1$ Hz), 8.93 (1H, d, $J = 2.1$ Hz). MS m/z : 402 ($\text{M}+\text{tBu}+\text{H}$) $^+$.

[0905]

[Table 31]

Ex	Data
AP2	¹ H-NMR (CDCl ₃) δ : 1.38 (9H, s), 2.22 (2H, t, J = 7.3 Hz), 2.34–2.45 (1H, m), 2.54–2.64 (1H, m), 5.10 (1H, dd, J = 9.7, 5.5 Hz), 5.35 (2H, s), 5.69 (1H, br s), 6.49 (1H, br s), 7.19 (1H, d, J = 8.5 Hz), 7.33–7.46 (5H, m), 7.75 (1H, d, J = 1.8 Hz), 7.87 (1H, dd, J = 8.5, 1.8 Hz), 9.37 (1H, s). MS m/z: 476 (M+Na) ⁺ .
AP3	¹ H-NMR (CDCl ₃) δ : 1.40 (9H, s), 2.14–2.28 (2H, m), 2.35–2.45 (1H, m), 2.53–2.63 (1H, m), 3.47 (3H, s), 5.06 (1H, dd, J = 9.7, 6.1 Hz), 5.38 (2H, s), 6.38 (1H, br s), 7.19 (1H, d, J = 8.5 Hz), 7.32–7.48 (5H, m), 7.72 (1H, s), 7.90 (1H, d, J = 8.5 Hz). MS m/z: 490 (M+Na) ⁺ .
AP4	¹ H-NMR (CDCl ₃) δ : 1.41 (9H, s), 2.19–2.28 (2H, m), 2.37–2.47 (1H, m), 2.54–2.66 (1H, m), 3.50 (3H, s), 5.07–5.12 (1H, m), 5.91 (1H, br s), 6.56 (1H, br s), 7.24 (1H, d, J = 7.9 Hz), 7.74 (1H, s), 7.92 (1H, d, J = 7.9 Hz). MS m/z: 400 (M+Na) ⁺ .
AP5	¹ H-NMR (CDCl ₃) δ : 0.65 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.15 (3H, s), 1.35–1.80 (8H, m), 1.41 (9H, s), 1.80–1.94 (3H, m), 1.94–2.64 (20H, m), 3.41–3.54 (2H, m), 3.46 (3H, s), 3.63–3.83 (2H, m), 3.78 (3H, s), 5.06 (1H, dd, J = 9.4, 5.8 Hz), 5.37 (1H, br s), 6.07–6.14 (1H, m), 6.39 (1H, br s), 6.80 (2H, d, J = 8.5 Hz), 7.05–7.19 (7H, m), 7.25 (2H, d, J = 5.5 Hz). MS m/z: 1015 (M+H) ⁺ .
AP6	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.33–1.66 (6H, m), 1.66–1.79 (1H, m), 1.78–1.95 (3H, m), 1.95–2.03 (1H, m), 2.05–2.16 (2H, m), 2.20–2.62 (13H, m), 2.66–2.79 (1H, m), 2.85 (1H, dt, J = 22.3, 7.6 Hz), 2.93–3.02 (1H, m), 3.39–3.57 (6H, m), 3.62–3.86 (6H, m), 5.24 (1H, dd, J = 12.5, 5.2 Hz), 6.07–6.13 (1H, m), 6.78–6.83 (3H, m), 7.05–7.18 (6H, m), 7.23–7.29 (2H, m), 8.07 (1H, br s). MS m/z: 941 (M+H) ⁺ .
AQ1	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.89 (6H, s), 1.16 (3H, s), 1.46–1.66 (5H, m), 1.69–1.91 (5H, m), 1.94–2.02 (2H, m), 2.02–2.21 (3H, m), 2.21–2.39 (3H, m), 2.39–2.48 (1H, m), 2.48–2.65 (3H, m), 2.69–2.96 (3H, m), 3.15 (2H, s), 3.36–3.46 (2H, m), 3.65–3.81 (6H, m), 4.61–4.70 (1H, m), 4.94–5.02 (1H, m), 6.67 (2H, d, J = 8.5 Hz), 6.81 (2H, d, J = 9.1 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.10 (2H, d, J = 8.5 Hz), 7.85 (1H, d, J = 8.5 Hz), 7.98 (1H, s), 8.03–8.07 (2H, m), 9.72 (1H, s). MS m/z: 930 (M+H) ⁺ .
AR1	¹ H-NMR (CDCl ₃) δ : 0.67 (3H, s), 1.19 (3H, s), 1.57–1.71 (3H, m), 1.73–2.04 (3H, m), 2.16 (1H, dd, J = 14.0, 2.4 Hz), 2.25–2.44 (5H, m), 2.74–2.84 (1H, m), 3.22–3.32 (1H, m), 3.74–3.85 (5H, m), 5.11 (1H, br s), 6.89 (2H, d, J = 8.5 Hz), 7.23 (2H, d, J = 8.5 Hz). MS m/z: 414 (M+H) ⁺ .

[0906]

[Table 32]

Ex	Data
AR2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.67 (3H, s), 1.19 (3H, s), 1.53–1.69 (3H, m), 1.73–1.96 (5H, m), 2.09–2.22 (4H, m), 2.30–2.37 (1H, m), 2.39–2.47 (1H, m), 2.61 (2H, s), 3.72–3.85 (5H, m), 6.86 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz). MS m/z : 400 ($\text{M}+\text{H}$) $^+$.
AR3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.16 (3H, s), 1.28 (3H, t, $J = 7.3$ Hz), 1.47–1.68 (3H, m), 1.68–1.95 (7H, m), 2.00–2.30 (6H, m), 2.40–2.54 (6H, m), 2.55–2.67 (1H, m), 3.38–3.49 (2H, m), 3.66–3.76 (2H, m), 3.78 (3H, s), 4.17 (2H, q, $J = 7.1$ Hz), 6.08–6.12 (1H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.12 (2H, d, $J = 8.5$ Hz), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 642 ($\text{M}+\text{H}$) $^+$.
AR4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 1.16 (3H, s), 1.44–1.66 (13H, m), 1.68–1.94 (8H, m), 1.95–2.17 (5H, m), 2.22–2.48 (12H, m), 3.39–3.49 (6H, m), 3.66–3.75 (2H, m), 3.79 (3H, s), 6.08–6.12 (1H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.10 (2H, d, $J = 9.1$ Hz), 7.11 (2H, d, $J = 7.9$ Hz), 7.26 (2H, d, $J = 7.9$ Hz). MS m/z : 768 ($\text{M}+\text{H}$) $^+$.
AR5	MS m/z : 668 ($\text{M}+\text{H}$) $^+$.
AR6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.93–0.99 (2H, m), 1.16 (3H, s), 1.36–1.66 (8H, m), 1.67–1.95 (6H, m), 1.95–2.55 (17H, m), 2.64–2.76 (1H, m), 2.83–2.96 (1H, m), 3.02–3.10 (1H, m), 3.39–3.49 (6H, m), 3.61–3.81 (9H, m), 5.20–5.33 (3H, m), 6.08–6.12 (1H, m), 6.76–6.82 (3H, m), 7.07–7.17 (6H, m), 7.24–7.29 (2H, m). MS m/z : 1083 ($\text{M}+\text{H}$) $^+$.
AR7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 1.16 (3H, s), 1.42–1.69 (4H, m), 1.69–2.19 (12H, m), 2.19–2.56 (13H, m), 2.64–3.03 (3H, m), 3.39–3.88 (15H, m), 5.24 (1H, dd, $J = 12.5, 5.2$ Hz), 6.08–6.14 (1H, m), 6.77–6.85 (3H, m), 7.06–7.19 (6H, m), 7.23–7.30 (2H, m), 8.07 (1H, s). MS m/z : 953 ($\text{M}+\text{H}$) $^+$.
AS1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.99 (2H, m), 2.22–2.29 (1H, m), 2.69–2.80 (1H, m), 2.85–2.95 (1H, m), 3.05–3.12 (1H, m), 3.50 (3H, s), 3.61–3.69 (2H, m), 5.22–5.34 (3H, m), 6.91 (1H, d, $J = 8.5$ Hz), 7.58–7.62 (2H, m), 9.95 (1H, s). MS m/z : 390 ($\text{M}-\text{C}_2\text{H}_4+\text{H}$) $^+$.
AS2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93–0.98 (2H, m), 2.18–2.25 (1H, m), 2.36–2.45 (4H, m), 2.64–2.77 (1H, m), 2.82–2.92 (1H, m), 3.01–3.10 (1H, m), 3.44 (3H, s), 3.49–3.54 (6H, m), 3.61–3.68 (2H, m), 5.13 (2H, s), 5.20–5.33 (3H, m), 6.70 (1H, d, $J = 7.9$ Hz), 6.97 (1H, d, $J = 7.9$ Hz), 7.03 (1H, s), 7.29–7.38 (5H, m). MS m/z : 622 ($\text{M}+\text{H}$) $^+$.
AS3	$^1\text{H-NMR}$ (CDCl_3) δ : 2.22–2.27 (1H, m), 2.41 (4H, s), 2.67–2.98 (3H, m), 3.44 (3H, s), 3.48–3.55 (6H, m), 5.13 (2H, s), 5.21 (1H, dd, $J = 12.5, 5.2$ Hz), 6.73 (1H, d, $J = 8.5$ Hz), 7.00 (1H, d, $J = 8.5$ Hz), 7.03 (1H, s), 7.29–7.39 (5H, m), 8.04 (1H, s). MS m/z : 492 ($\text{M}+\text{H}$) $^+$.

[0907]

[Table 33]

Ex	Data
AS4	MS m/z: 358 (M+H) ⁺ .
AS5	¹ H-NMR (CDCl ₃) δ : 1.29 (3H, t, J = 7.3 Hz), 1.82–1.96 (1H, m), 2.09–2.19 (1H, m), 2.22–2.36 (2H, m), 2.34 (3H, s), 2.40–2.49 (2H, m), 2.67 (1H, tt, J = 11.5, 3.8 Hz), 4.19 (2H, q, J = 7.3 Hz), 5.58–5.64 (1H, m), 7.22 (1H, d, J = 7.9 Hz), 7.65 (1H, d, J = 7.9 Hz), 7.68 (1H, s), 9.96 (1H, s).
AS6	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.29 (3H, t, J = 7.3 Hz), 1.45–1.66 (3H, m), 1.68–1.79 (1H, m), 1.80–1.93 (2H, m), 2.02–2.18 (3H, m), 2.21 (3H, s), 2.23–2.38 (5H, m), 2.39–2.46 (2H, m), 2.59–2.70 (1H, m), 3.45 (2H, dd, J = 19.4, 14.0 Hz), 3.65–3.81 (2H, m), 3.78 (3H, s), 4.18 (2H, q, J = 7.1 Hz), 5.50–5.56 (1H, m), 6.80 (2H, d, J = 8.5 Hz), 6.92 (1H, s), 6.93 (2H, d, J = 6.7 Hz), 7.10 (2H, d, J = 8.5 Hz).
AS7	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.16 (3H, s), 1.43–1.68 (5H, m), 1.68–1.82 (1H, m), 1.82–2.00 (3H, m), 2.00–2.16 (2H, m), 2.17–2.41 (10H, m), 2.41–2.63 (5H, m), 2.63–3.08 (4H, m), 3.34–3.52 (5H, m), 3.52–3.63 (3H, m), 3.63–3.87 (6H, m), 5.16–5.31 (1H, m), 5.50–5.62 (1H, m), 6.69–6.88 (3H, m), 6.88–7.17 (7H, m), 8.02–8.14 (1H, m). MS m/z: 955 (M+H) ⁺ .
AT1	¹ H-NMR (CDCl ₃) δ : 1.29 (3H, t, J = 7.0 Hz), 1.79–1.93 (1H, m), 2.15–2.26 (1H, m), 2.43–2.57 (4H, m), 2.58–2.69 (1H, m), 4.18 (2H, q, J = 7.1 Hz), 6.30–6.36 (1H, m), 7.15 (1H, d, J = 12.1 Hz), 7.29 (1H, d, J = 9.1 Hz), 7.81 (1H, t, J = 7.6 Hz), 10.31 (1H, s).
AT2	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.87 (3H, s), 0.88 (3H, s), 1.17 (3H, s), 1.29 (3H, t, J = 7.0 Hz), 1.49–1.69 (4H, m), 1.70–1.95 (3H, m), 2.06–2.25 (3H, m), 2.25–2.36 (1H, m), 2.36–2.40 (2H, m), 2.40–2.55 (4H, m), 2.55–2.66 (1H, m), 3.52 (2H, dd, J = 24.0, 14.3 Hz), 3.66–3.81 (2H, m), 3.78 (3H, s), 4.18 (1H, q, J = 7.1 Hz), 6.10–6.17 (1H, m), 6.80 (2H, d, J = 8.5 Hz), 6.98 (1H, d, J = 12.1 Hz), 7.03 (1H, d, J = 7.9 Hz), 7.08 (1H, d, J = 7.3 Hz), 7.12 (2H, d, J = 9.1 Hz).
AT3	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.86 (3H, s), 0.87 (3H, s), 1.17 (3H, s), 1.44–2.65 (20H, m), 2.65–3.04 (4H, m), 3.39–3.62 (10H, m), 3.62–3.83 (7H, m), 5.10–5.31 (1H, m), 6.10–6.20 (1H, m), 6.68–6.88 (3H, m), 6.88–7.18 (7H, m), 7.99–8.11 (1H, m). MS m/z: 959 (M+H) ⁺ .
AU1	¹ H-NMR (CDCl ₃) δ : 0.65 (3H, s), 0.97 (6H, s), 1.16 (3H, s), 1.29 (3H, t, J = 7.0 Hz), 1.40–1.65 (3H, m), 1.71 (1H, td, J = 12.1, 3.6 Hz), 1.79–1.94 (2H, m), 2.03–2.19 (3H, m), 2.21–2.51 (7H, m), 2.67 (1H, tt, J = 11.8, 3.9 Hz), 3.44 (2H, s), 3.63–3.80 (2H, m), 3.77 (3H, s), 4.18 (2H, q, J = 7.3 Hz), 5.74–5.82 (1H, m), 6.66 (2H, d, J = 8.5 Hz), 6.79 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz). MS m/z: 666 (M+H) ⁺ .

[0908]

[Table 34]

Ex	Data
AU2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.97 (6H, s), 1.16 (3H, s), 1.44–1.66 (3H, m), 1.48 (9H, s), 1.66–1.79 (1H, m), 1.79–2.00 (3H, m), 2.05–2.17 (2H, m), 2.17–2.35 (3H, m), 2.35–2.51 (3H, m), 2.51–2.64 (1H, m), 2.79–2.94 (1H, m), 3.33–3.77 (12H, m), 3.78 (3H, s), 5.78–5.85 (1H, m), 6.67 (2H, d, $J = 8.5$ Hz), 6.79 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz). MS m/z : 806 ($\text{M}+\text{H}$) $^+$.
AU3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.92–1.00 (2H, m), 0.97 (6H, s), 1.16 (3H, s), 1.36–1.99 (6H, m), 2.02–2.35 (8H, m), 2.34–2.64 (8H, m), 2.64–2.79 (1H, m), 2.79–2.95 (2H, m), 3.00–3.11 (1H, m), 3.40–3.48 (5H, m), 3.52–3.81 (9H, m), 3.77 (3H, s), 5.23 (1H, dd, $J = 13.7, 5.8$ Hz), 5.29 (2H, q, $J = 8.9$ Hz), 5.78–5.85 (1H, m), 6.67 (2H, d, $J = 7.9$ Hz), 6.72 (1H, d, $J = 7.9$ Hz), 6.79 (2H, d, $J = 9.1$ Hz), 6.99 (1H, d, $J = 7.9$ Hz), 7.02–7.12 (3H, m). MS m/z : 1107 ($\text{M}+\text{H}$) $^+$.
AU4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.97 (6H, s), 1.16 (3H, s), 1.40–1.79 (5H, m), 1.79–2.02 (3H, m), 2.02–2.19 (2H, m), 2.19–2.65 (12H, m), 2.65–2.91 (3H, m), 2.91–3.04 (1H, m), 3.37–3.83 (15H, m), 5.13–5.28 (1H, m), 5.77–5.86 (1H, m), 6.61–6.73 (2H, m), 6.73–6.84 (3H, m), 6.97–7.14 (4H, m), 8.07 (1H, br s). MS m/z : 977 ($\text{M}+\text{H}$) $^+$.
AV1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.17 (3H, s), 1.29 (3H, t, $J = 7.0$ Hz), 1.47–1.67 (3H, m), 1.75 (1H, td, $J = 12.1, 3.6$ Hz), 1.80–1.92 (2H, m), 2.06–2.20 (3H, m), 2.29 (1H, td, $J = 12.5, 4.9$ Hz), 2.35–2.57 (6H, m), 2.58–2.70 (1H, m), 3.53 (2H, s), 3.67–3.81 (2H, m), 3.78 (3H, s), 4.18 (2H, q, $J = 7.3$ Hz), 5.94–5.99 (1H, m), 6.80 (2H, d, $J = 9.1$ Hz), 6.83 (2H, t, $J = 4.3$ Hz), 7.11 (2H, d, $J = 9.1$ Hz). MS m/z : 666 ($\text{M}+\text{H}$) $^+$.
AV2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.90 (3H, s), 1.17 (3H, s), 1.45–2.01 (10H, m), 2.03–2.18 (2H, m), 2.18–2.35 (3H, m), 2.35–2.63 (9H, m), 2.63–2.92 (3H, m), 2.92–3.03 (1H, m), 3.40–3.85 (13H, m), 5.13–5.28 (1H, m), 5.92–6.04 (1H, m), 6.69–6.92 (5H, m), 6.97–7.07 (2H, m), 7.07–7.15 (2H, m), 8.08 (1H, br s). MS m/z : 977 ($\text{M}+\text{H}$) $^+$.
AW1	$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.00–2.06 (2H, m), 2.59–2.67 (2H, m), 3.63–3.69 (2H, m), 6.66 (1H, d, $J = 7.9$ Hz), 7.30 (1H, d, $J = 7.9$ Hz), 10.79 (1H, s). MS m/z : 301 ($\text{M}+\text{H}$) $^+$.
AW2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.98 (2H, m), 2.13–2.26 (2H, m), 2.59–2.71 (1H, m), 2.74–2.81 (1H, m), 2.84–2.93 (1H, m), 3.01–3.09 (1H, m), 3.60–3.67 (2H, m), 3.81–3.88 (1H, m), 5.18–5.31 (3H, m), 6.43 (1H, d, $J = 7.9$ Hz), 7.39 (1H, d, $J = 7.9$ Hz). MS m/z : 564 ($\text{M}+\text{Na}$) $^+$.

[0909]

[Table 35]

Ex	Data
AW3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93–1.00 (2H, m), 2.14–2.33 (3H, m), 2.63–2.78 (1H, m), 2.87–2.96 (1H, m), 3.04–3.13 (1H, m), 3.30–3.39 (2H, m), 3.59–3.70 (2H, m), 3.85–3.97 (2H, m), 5.15–5.37 (3H, m), 6.75 (1H, d, $J = 8.5$ Hz), 7.43 (2H, s), 8.05 (1H, d, $J = 8.5$ Hz).
AW4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.87–1.00 (8H, m), 1.16 (3H, s), 1.36–1.64 (6H, m), 1.67–1.79 (1H, m), 1.82–1.92 (3H, m), 1.95–2.01 (1H, m), 2.04–2.99 (20H, m), 3.02–3.12 (1H, m), 3.30–3.39 (2H, m), 3.41–3.53 (2H, m), 3.60–3.97 (10H, m), 5.12–5.43 (3H, m), 6.09 (1H, br s), 6.63 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 9.1$ Hz), 6.90 (1H, d, $J = 7.9$ Hz), 7.08–7.10 (4H, m), 7.25 (2H, d, $J = 6.1$ Hz). MS m/z : 1097 ($\text{M}+\text{H}$) $^+$.
AW5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.35–1.65 (7H, m), 1.68–1.78 (1H, m), 1.80–2.02 (4H, m), 2.04–2.19 (4H, m), 2.22–3.05 (16H, m), 3.30–3.40 (2H, m), 3.41–3.53 (2H, m), 3.63–3.98 (9H, m), 5.19–5.25 (1H, br m), 6.09 (1H, br s), 6.66 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 9.1$ Hz), 6.92 (1H, d, $J = 7.9$ Hz), 7.06–7.13 (4H, m), 7.25 (2H, d, $J = 7.3$ Hz), 8.16 (1H, s). MS m/z : 967 ($\text{M}+\text{H}$) $^+$.
AX1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.45–1.64 (3H, m), 1.68–1.77 (1H, m), 1.82–1.91 (1H, m), 1.99–2.14 (6H, m), 2.24–2.38 (3H, m), 2.39–2.54 (3H, m), 3.42–3.49 (4H, m), 3.68–3.75 (2H, m), 3.78 (3H, s), 6.05–6.09 (1H, m), 6.80 (2H, d, $J = 8.5$ Hz), 7.07–7.11 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 650 [$\text{M}(^{79}\text{Br})+\text{H}$] $^+$, 652 [$\text{M}(^{81}\text{Br})+\text{H}$] $^+$.
AX2	MS m/z : 770 ($\text{M}+\text{H}$) $^+$.
AX3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.39–1.78 (4H, m), 1.81–2.13 (6H, m), 2.20–2.56 (8H, m), 2.64–3.01 (5H, m), 3.20 (2H, s), 3.32–3.53 (9H, m), 3.60 (2H, s), 3.65–3.81 (5H, m), 5.23 (1H, dd, $J = 13.1, 5.2$ Hz), 6.05–6.09 (1H, m), 6.75 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 6.99–7.13 (6H, m), 7.24 (2H, d, $J = 8.5$ Hz), 8.20 (1H, s). MS m/z : 941 ($\text{M}+\text{H}$) $^+$.
AY1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–0.98 (2H, m), 2.23–2.30 (1H, m), 2.67–2.79 (1H, m), 2.85–2.95 (1H, m), 3.05–3.13 (1H, m), 3.52 (3H, s), 3.61–3.68 (2H, m), 5.21–5.32 (3H, m), 6.86 (1H, d, $J = 8.5$ Hz), 7.94 (1H, d, $J = 2.4$ Hz), 8.07 (1H, dd, $J = 8.5, 2.4$ Hz). MS m/z : 407 ($\text{M}-\text{C}_2\text{H}_4+\text{H}$) $^+$.
AY2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.99 (2H, m), 2.16–2.23 (1H, m), 2.61–2.73 (1H, m), 2.81–2.91 (1H, m), 2.99–3.07 (1H, m), 3.37 (3H, s), 3.54–3.68 (4H, m), 5.17 (1H, dd, $J = 13.1, 5.2$ Hz), 5.25–5.31 (2H, m), 6.37–6.41 (2H, m), 6.55 (1H, d, $J = 9.1$ Hz).

[0910]

[Table 36]

Ex	Data
AY3	$^1\text{H-NMR}$ (CDCl_3) δ : -0.02 (9H, s), 0.91-0.95 (2H, m), 2.14-2.21 (1H, m), 2.59-2.72 (1H, m), 2.81-2.90 (1H, m), 3.00-3.07 (1H, m), 3.40 (3H, s), 3.58-3.65 (2H, m), 5.14 (1H, dd, J = 13.1, 5.2 Hz), 5.22-5.29 (2H, m), 6.61 (1H, d, J = 7.9 Hz), 6.75 (1H, dd, J = 7.9, 1.8 Hz), 7.01 (1H, d, J = 1.8 Hz), 7.30 (1H, s), 7.60 (1H, t, J = 7.9 Hz), 7.72 (1H, t, J = 7.9 Hz), 7.82 (1H, d, J = 7.9 Hz), 7.88 (1H, d, J = 7.9 Hz). MS m/z : 612 ($\text{M}+\text{Na}$) $^+$.
AY4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92-1.00 (2H, m), 1.44 (9H, s), 1.70-1.88 (1H, m), 2.16-2.34 (4H, m), 2.60-2.82 (2H, m), 2.82-2.96 (1H, m), 3.01-3.12 (1H, m), 3.35-3.42 (2H, m), 3.58-3.74 (3H, m), 4.53-4.96 (1H, m), 4.96-5.23 (2H, m), 5.28 (2H, dd, J = 14.3, 9.4 Hz), 6.61-6.77 (2H, m), 6.78-6.86 (1H, m), 7.46-7.56 (1H, m), 7.56-7.61 (1H, m), 7.63-7.73 (2H, m). MS m/z : 781 ($\text{M}+\text{Na}$) $^+$.
AY5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92-0.99 (2H, m), 1.45 (9H, s), 2.12-2.40 (5H, m), 2.57-2.74 (1H, m), 2.79-2.92 (1H, m), 2.98-3.09 (1H, m), 3.37 (3H, s), 3.57-3.70 (2H, m), 3.70-3.89 (1H, m), 3.89-4.00 (1H, m), 4.20-4.36 (1H, m), 4.69-4.89 (1H, m), 5.17 (1H, dd, J = 13.1, 5.2 Hz), 5.28 (2H, dd, J = 17.0, 9.7 Hz), 6.16-6.26 (2H, m), 6.57 (1H, d, J = 7.9 Hz).
AY6	MS m/z : 374 ($\text{M}+\text{H}$) $^+$.
AY7	MS m/z : 602 ($\text{M}+\text{H}$) $^+$.
AY8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.39-1.67 (8H, m), 1.67-1.85 (1H, m), 1.82-1.97 (2H, m), 2.02-2.17 (3H, m), 2.17-2.62 (8H, m), 2.62-2.75 (1H, m), 2.75-2.89 (1H, m), 2.89-3.01 (1H, m), 3.31-3.40 (3H, m), 3.40-3.57 (2H, m), 3.61-3.83 (5H, m), 3.81-3.93 (1H, m), 3.93-4.04 (1H, m), 4.49-4.69 (1H, m), 5.11-5.23 (1H, m), 5.73-5.88 (1H, m), 6.09-6.16 (1H, m), 6.16-6.29 (2H, m), 6.55-6.65 (1H, m), 6.72-6.83 (2H, m), 7.05-7.16 (4H, m), 7.19-7.30 (2H, m), 8.09 (1H, s). MS m/z : 927 ($\text{M}+\text{H}$) $^+$.
AZ1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.69-1.77 (4H, m), 2.47-2.61 (4H, m), 3.33-3.39 (2H, m), 3.43-3.49 (2H, m), 3.95 (3H, s), 5.05-5.15 (1H, m), 7.41 (1H, d, J = 8.8 Hz), 8.04 (1H, dd, J = 8.8, 2.0 Hz), 8.14 (1H, s), 8.51 (1H, d, J = 2.0 Hz). MS m/z : 344 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
AZ2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.68-1.75 (4H, m), 2.51-2.62 (4H, m), 3.34-3.39 (2H, m), 3.42-3.47 (2H, m), 3.94 (3H, s), 5.03-5.13 (1H, m), 7.72 (1H, d, J = 9.1 Hz), 7.90 (1H, dd, J = 9.1, 1.8 Hz), 8.09 (1H, s), 8.49 (1H, s). MS m/z : 344 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
AZ3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.66-1.75 (4H, m), 2.48-2.59 (4H, m), 3.33-3.37 (2H, m), 3.41-3.47 (2H, m), 4.75 (2H, s), 5.01-5.09 (1H, m), 7.30 (1H, d, J = 8.5 Hz), 7.61 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 7.94 (1H, s). MS m/z : 372 ($\text{M}+\text{H}$) $^+$.

[0911]

[Table 37]

Ex	Data
AZ4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.69–1.75 (4H, m), 2.51–2.63 (4H, m), 3.34–3.39 (2H, m), 3.43–3.47 (2H, m), 5.03–5.16 (1H, m), 7.77 (1H, d, $J = 9.1$ Hz), 7.82 (1H, dd, $J = 9.1, 1.8$ Hz), 8.18 (1H, s), 8.21 (1H, d, $J = 1.8$ Hz), 10.00 (1H, s). MS m/z : 370 ($\text{M}+\text{H}$) $^+$.
AZ5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.89 (3H, s), 0.89 (3H, s), 1.15 (3H, s), 1.44–1.53 (10H, m), 1.59–1.67 (2H, m), 1.67–1.79 (5H, m), 1.86–1.95 (1H, m), 2.05–2.13 (2H, m), 2.29–2.44 (3H, m), 2.49–2.60 (4H, m), 3.34–3.38 (2H, m), 3.42–3.49 (2H, m), 3.48–3.55 (2H, m), 3.64–3.77 (5H, m), 5.03–5.07 (1H, m), 6.77 (2H, d, $J = 9.1$ Hz), 7.09 (2H, d, $J = 9.1$ Hz), 7.18 (1H, d, $J = 9.1$ Hz), 7.27 (1H, s), 7.61 (1H, d, $J = 9.1$ Hz), 7.87 (1H, s). MS m/z : 741 ($\text{M}+\text{H}$) $^+$.
AZ6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.88–0.90 (6H, m), 1.15 (3H, s), 1.45–1.66 (12H, m), 1.73–1.95 (6H, m), 2.04–2.13 (2H, m), 2.28–2.62 (11H, m), 3.12 (2H, s), 3.48–3.56 (2H, m), 3.64–3.77 (5H, m), 4.98–5.06 (1H, m), 6.76 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.17 (1H, d, $J = 8.5$ Hz), 7.26–7.28 (1H, m), 7.61 (1H, d, $J = 8.5$ Hz), 7.87 (1H, s). MS m/z : 755 ($\text{M}+\text{H}$) $^+$.
AZ7	MS m/z : 699 ($\text{M}+\text{H}$) $^+$.
AZ8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.89 (3H, s), 0.89 (3H, s), 1.15 (3H, s), 1.44–1.66 (3H, m), 1.72–1.83 (1H, m), 1.83–1.95 (4H, m), 2.04–2.15 (2H, m), 2.20–2.42 (4H, m), 2.51–3.01 (12H, m), 3.11–3.17 (2H, m), 3.45 (3H, s), 3.48–3.57 (2H, m), 3.64–3.79 (5H, m), 5.01–5.08 (1H, m), 5.20 (1H, dd, $J = 12.8, 5.5$ Hz), 6.72–6.79 (3H, m), 6.93–6.98 (1H, m), 7.10 (2H, d, $J = 9.1$ Hz), 7.19 (1H, d, $J = 9.1$ Hz), 7.26–7.29 (1H, m), 7.61 (1H, d, $J = 9.1$ Hz), 7.72 (1H, s), 7.88 (1H, s), 8.06 (1H, s), 9.22 (1H, s). MS m/z : 955 ($\text{M}+\text{H}$) $^+$.
BA1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.67–1.77 (4H, m), 2.45–2.59 (4H, m), 3.33–3.38 (2H, m), 3.43–3.47 (2H, m), 4.79 (2H, s), 5.03–5.13 (1H, m), 7.40–7.41 (2H, m), 7.70 (1H, s), 8.02 (1H, s). MS m/z : 316 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
BA2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 1.67–1.78 (4H, m), 2.47–2.62 (4H, m), 3.33–3.39 (2H, m), 3.43–3.48 (2H, m), 5.05–5.16 (1H, m), 7.49 (1H, d, $J = 8.5$ Hz), 7.93 (1H, d, $J = 8.5$ Hz), 8.21 (1H, s), 8.25 (1H, s), 10.04 (1H, s). MS m/z : 314 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
BA3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.15 (3H, s), 1.44–1.65 (11H, m), 1.68–1.81 (5H, m), 1.85–1.94 (1H, m), 2.03–2.13 (2H, m), 2.26–2.61 (8H, m), 3.33–3.39 (2H, m), 3.42–3.49 (2H, m), 3.53–3.61 (2H, m), 3.63–3.77 (5H, m), 5.02–5.10 (1H, m), 6.75 (2H, d, $J = 9.1$ Hz), 7.08 (2H, d, $J = 9.1$ Hz), 7.20–7.30 (2H, m), 7.39 (1H, s), 7.97 (1H, s). MS m/z : 741 ($\text{M}+\text{H}$) $^+$.

[0912]

[Table 38]

Ex	Data
BA4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.15 (3H, s), 1.45–1.64 (11H, m), 1.70–1.94 (5H, m), 2.04–2.13 (2H, m), 2.26–2.64 (11H, m), 3.12 (2H, s), 3.53–3.61 (2H, m), 3.64–3.77 (5H, m), 4.09–4.15 (2H, m), 4.98–5.06 (1H, m), 6.75 (2H, d, J = 9.1 Hz), 7.08 (2H, d, J = 9.1 Hz), 7.19–7.30 (2H, m), 7.39 (1H, s), 7.96 (1H, s).
BA5	MS m/z : 699 ($\text{M}+\text{H}$) $^+$.
BA6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.64 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.15 (3H, s), 1.46–1.66 (2H, m), 1.68–1.97 (6H, m), 2.02–2.13 (2H, m), 2.21–3.02 (16H, m), 3.11–3.17 (2H, m), 3.46 (3H, s), 3.52–3.78 (7H, m), 5.00–5.10 (1H, m), 5.20 (1H, dd, J = 12.8, 5.5 Hz), 6.71–6.78 (3H, m), 6.92–6.99 (1H, m), 7.08 (2H, d, J = 9.1 Hz), 7.21–7.31 (2H, m), 7.40 (1H, s), 7.73 (1H, d, J = 1.8 Hz), 7.98 (1H, s), 8.02 (1H, s), 9.25 (1H, s). MS m/z : 955 ($\text{M}+\text{H}$) $^+$.
BB1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.40–1.55 (9H, m), 1.71–3.03 (7H, m), 4.83–5.23 (1H, m).
BB2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.73–1.97 (1H, m), 2.05–2.25 (1H, m), 2.40–2.61 (3H, m), 2.61–2.82 (2H, m), 7.25–7.44 (2H, m), 7.85 (2H, d, J = 8.5 Hz), 9.99 (1H, s).
BB3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.92 (6H, s), 1.16 (3H, s), 1.39–1.67 (3H, m), 1.48 (9H, s), 1.67–1.95 (3H, m), 2.01–2.22 (4H, m), 2.22–2.77 (7H, m), 3.41–3.58 (2H, m), 3.63–3.83 (2H, m), 3.78 (3H, s), 6.80 (2H, d, J = 7.9 Hz), 7.10 (2H, d, J = 7.3 Hz), 7.12 (2H, d, J = 7.3 Hz), 7.27 (2H, d, J = 7.3 Hz). MS m/z : 676 ($\text{M}+\text{H}$) $^+$.
BB4	MS m/z : 620 ($\text{M}+\text{H}$) $^+$.
BB5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–1.00 (2H, m), 1.46 (9H, s), 2.07–2.27 (3H, m), 2.27–2.48 (4H, m), 2.60–2.74 (1H, m), 2.81–2.96 (3H, m), 3.00–3.11 (1H, m), 3.29–3.54 (6H, m), 3.57–3.71 (2H, m), 3.87 (2H, t, J = 5.8 Hz), 5.23 (1H, dd, J = 13.1, 5.2 Hz), 5.29 (2H, q, J = 9.7 Hz), 6.55 (1H, d, J = 8.5 Hz), 6.88 (1H, d, J = 7.9 Hz). MS m/z : 636 ($\text{M}+\text{Na}$) $^+$.
BB6	MS m/z : 414 ($\text{M}+\text{H}$) $^+$.
BB7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.92 (6H, s), 1.15 (3H, s), 1.41–1.68 (3H, m), 1.68–1.80 (1H, m), 1.80–1.99 (2H, m), 2.00–2.21 (4H, m), 2.21–2.60 (11H, m), 2.60–2.78 (1H, m), 2.78–3.05 (6H, m), 3.37–3.76 (11H, m), 3.78 (3H, s), 3.83–3.93 (2H, m), 5.15–5.29 (1H, m), 6.55–6.65 (1H, m), 6.73–6.87 (2H, m), 6.87–6.95 (1H, m), 7.03–7.19 (4H, m), 7.19–7.32 (2H, m), 8.07 (1H, s). MS m/z : 985 ($\text{M}+\text{H}$) $^+$.

[0913]

[Table 39]

Ex	Data
BC1	MS m/z: 202 [M(⁷⁹ Br)+H] ⁺ , 204 [M(⁸¹ Br)+H] ⁺ .
BC2	¹ H-NMR (CDCl ₃) δ: 3.49 (3H, s), 7.16 (1H, d, J = 7.9 Hz), 7.18 (1H, t, J = 5.2 Hz), 8.96 (1H, s). MS m/z: 228 [M(⁷⁹ Br)+H] ⁺ , 230 [M(⁸¹ Br)+H] ⁺ .
BC3	¹ H-NMR (CDCl ₃) δ: 0.01 (9H, s), 0.87–0.99 (2H, m), 2.21–2.31 (1H, m), 2.55–2.67 (1H, m), 2.84–2.93 (1H, m), 3.00–3.12 (1H, m), 3.51 (3H, s), 3.57–3.67 (2H, m), 5.16–5.32 (3H, m), 6.87 (1H, d, J = 7.9 Hz), 7.15 (1H, d, J = 7.9 Hz). MS m/z: 469 [M(⁷⁹ Br)+H] ⁺ , 471 [M(⁸¹ Br)+H] ⁺ .
BC4	¹ H-NMR (CDCl ₃) δ: 0.01 (9H, s), 0.95–0.99 (2H, m), 2.28–2.35 (1H, m), 2.63–2.75 (1H, m), 2.86–2.98 (1H, m), 3.06–3.15 (1H, m), 3.60–3.69 (5H, m), 5.24–5.34 (3H, m), 7.13 (1H, d, J = 7.9 Hz), 7.44 (2H, s), 8.14 (1H, d, J = 8.5 Hz).
BC5	¹ H-NMR (CDCl ₃) δ: 0.01 (9H, s), 0.66 (3H, s), 0.91 (6H, s), 0.93–0.98 (2H, m), 1.16 (3H, s), 1.37–1.79 (5H, m), 1.83–1.94 (3H, m), 1.97–2.14 (3H, m), 2.23–2.73 (13H, m), 2.86–2.95 (1H, m), 3.04–3.13 (1H, m), 3.42–3.54 (5H, m), 3.60–3.93 (11H, m), 5.21–5.35 (3H, m), 6.11 (1H, br s), 6.80 (2H, d, J = 8.5 Hz), 7.04–7.14 (5H, m), 7.27 (2H, d, J = 8.5 Hz), 7.40 (1H, d, J = 7.9 Hz). MS m/z: 1072 (M+H) ⁺ .
BC6	¹ H-NMR (CDCl ₃) δ: 0.66 (3H, s), 0.91 (6H, d, J = 3.1 Hz), 1.16 (3H, s), 1.37–1.66 (5H, m), 1.67–1.79 (1H, m), 1.83–2.15 (6H, m), 2.24–2.61 (13H, m), 2.62–2.75 (1H, m), 2.82–2.91 (1H, m), 2.95–3.04 (1H, m), 3.43–3.56 (5H, m), 3.63–3.95 (8H, m), 5.26 (1H, dd, J = 13.1, 5.2 Hz), 6.11 (1H, br s), 6.81 (2H, d, J = 8.5 Hz), 7.07–7.13 (5H, m), 7.27 (2H, d, J = 7.9 Hz), 7.43 (1H, d, J = 7.9 Hz), 8.08 (1H, br s). MS m/z: 942 (M+H) ⁺ .
BD1	¹ H-NMR (CDCl ₃) δ: 0.68 (3H, s), 0.76–0.94 (3H, m), 0.92 (3H, s), 0.93 (3H, s), 1.17–1.29 (2H, m), 1.18 (3H, s), 1.42–1.82 (8H, m), 1.89–2.41 (9H, m), 3.71–3.83 (2H, m), 3.77 (3H, s), 6.86 (2H, d, J = 9.0 Hz), 7.10 (2H, d, J = 8.6 Hz), 7.18 (2H, d, J = 9.0 Hz), 7.23 (2H, d, J = 8.2 Hz). MS m/z: 594 (M+H) ⁺ .
BD2	¹ H-NMR (CDCl ₃) δ: 0.68 (3H, s), 0.77–0.92 (3H, m), 0.92 (6H, s), 1.17 (3H, s), 1.19–1.28 (2H, m), 1.41–1.82 (8H, m), 1.50 (9H, s), 1.87–1.98 (1H, m), 2.04–2.38 (8H, m), 3.70–3.83 (5H, m), 6.37 (1H, s), 6.85 (2H, d, J = 9.0 Hz), 7.09 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 9.0 Hz), 7.25 (2H, d, J = 6.7 Hz). MS m/z: 675 (M+H) ⁺ .
BD3	MS m/z: 575 (M+H) ⁺ .
BD4	¹ H-NMR (CDCl ₃) δ: 1.44–1.50 (9H, m), 2.00–2.15 (2H, m), 2.17–2.27 (1H, m), 2.62–2.75 (3H, m), 2.76–2.87 (2H, m), 2.89–2.98 (1H, m), 3.38 (3H, s), 3.71–4.21 (2H, m), 5.17 (1H, dd, J = 12.5, 5.2 Hz), 6.20–6.32 (2H, m), 6.60 (1H, d, J = 7.9 Hz), 8.05 (1H, s). MS m/z: 429 (M+H) ⁺ .

[0914]

[Table 40]

Ex	Data
BD5	MS m/z: 373 (M+H) ⁺ .
BD6	¹ H-NMR (CDCl ₃) δ : 0.69 (3H, s), 0.81–0.97 (9H, m), 1.20 (3H, s), 1.23–1.31 (2H, m), 1.47–1.82 (11H, m), 1.94 (1H, t, J = 11.0 Hz), 2.11–2.37 (10H, m), 2.64–2.95 (5H, m), 3.38 (3H, d, J = 1.8 Hz), 3.74–3.82 (5H, m), 3.91–4.01 (1H, m), 5.17 (1H, dd, J = 12.6, 5.2 Hz), 6.26–6.33 (2H, m), 6.61 (1H, d, J = 8.0 Hz), 6.85–6.91 (2H, m), 7.22–7.06 (5H, m), 7.42–7.52 (2H, m), 8.04 (1H, s). MS m/z: 929 (M+H) ⁺ .
BE1	¹ H-NMR (CDCl ₃) δ : 1.26 (3H, t, J = 7.0 Hz), 1.51 (9H, s), 1.73–1.88 (1H, m), 2.11–2.19 (1H, m), 2.32–2.47 (4H, m), 2.52–2.61 (1H, m), 4.15 (2H, q, J = 7.0 Hz), 6.02–6.09 (1H, m), 6.65 (1H, s), 7.01–7.14 (2H, m), 7.97 (1H, s). MS m/z: 264 (M-BOC+H) ⁺ .
BE2	¹ H-NMR (CDCl ₃) δ : 1.34–1.49 (1H, m), 1.50 (9H, s), 1.82–2.02 (3H, m), 2.26–2.45 (3H, m), 3.51–3.64 (3H, m), 6.07 (1H, s), 6.64 (1H, s), 7.04–7.16 (2H, m), 7.88–8.04 (1H, m). MS m/z: 222 (M-BOC+H) ⁺ .
BE3	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.92 (6H, s), 1.17 (3H, s), 1.22–1.98 (9H, m), 1.51 (9H, s), 2.04–2.40 (10H, m), 3.68–3.83 (5H, m), 6.00 (1H, s), 6.64 (1H, s), 6.81 (2H, d, J = 8.6 Hz), 7.02–7.13 (2H, m), 7.15 (2H, d, J = 8.6 Hz), 7.97 (1H, s). MS m/z: 691 (M+H) ⁺ .
BE4	MS m/z: 591 (M+H) ⁺ .
BE5	¹ H-NMR (CDCl ₃) δ : 0.68 (3H, s), 0.93 (6H, s), 1.20 (3H, s), 1.23–1.80 (9H, m), 1.85–2.00 (2H, m), 2.00–2.42 (13H, m), 2.63–3.03 (6H, m), 3.38 (3H, d, J = 1.2 Hz), 3.70–3.86 (5H, m), 3.93 (1H, brs), 5.17 (1H, dd, J = 12.9, 5.5 Hz), 6.05 (1H, s), 6.23–6.36 (2H, m), 6.61 (1H, d, J = 8.0 Hz), 6.83 (2H, d, J = 8.6 Hz), 7.05–7.20 (4H, m), 7.99 (1H, s), 8.21–8.34 (1H, m). MS m/z: 945 (M+H) ⁺ .
BF1	¹ H-NMR (CDCl ₃) δ : 1.91–1.99 (2H, m), 2.78 (2H, t, J = 6.7 Hz), 3.32–3.38 (2H, m), 4.55 (1H, br s), 6.73 (1H, d, J = 7.9 Hz), 7.09 (1H, d, J = 7.9 Hz). MS m/z: 290 [M(⁷⁹ Br ⁷⁹ Br)+H] ⁺ , 292 [M(⁷⁹ Br ⁸¹ Br)+H] ⁺ , 294 [M(⁸¹ Br ⁸¹ Br)+H] ⁺ .
BF2	¹ H-NMR (CDCl ₃) δ : 1.40 (9H, s), 1.89–2.07 (4H, m), 2.28–2.36 (1H, m), 2.48–2.56 (1H, m), 2.74–2.84 (2H, m), 3.46–3.98 (2H, m), 4.34–4.40 (1H, m), 5.33 (1H, br s), 5.82 (1H, br s), 6.65 (1H, br s), 7.33 (1H, d, J = 8.5 Hz), 7.37 (1H, d, J = 8.5 Hz). MS m/z: 540 [M(⁷⁹ Br ⁷⁹ Br)+Na] ⁺ , 542 [M(⁷⁹ Br ⁸¹ Br)+Na] ⁺ , 544 [M(⁸¹ Br ⁸¹ Br)+Na] ⁺ .
BF3	¹ H-NMR (CDCl ₃) δ : 1.41 (9H, s), 2.13–2.29 (4H, m), 2.31–2.42 (1H, m), 2.50–2.60 (1H, m), 2.83–2.88 (2H, m), 3.82–3.87 (2H, m), 4.99 (1H, dd, J = 9.7, 6.1 Hz), 5.47 (1H, br s), 6.40 (1H, br s), 6.90 (1H, d, J = 7.9 Hz), 7.19 (1H, d, J = 7.9 Hz). MS m/z: 460 [M(⁷⁹ Br)+Na] ⁺ , 462 [M(⁸¹ Br)+Na] ⁺ .

[0915]

[Table 41]

Ex	Data
BF4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (9H, s), 2.15–2.33 (4H, m), 2.37–2.48 (1H, m), 2.54–2.65 (1H, m), 3.31–3.37 (2H, m), 3.85–3.95 (2H, m), 5.07 (1H, dd, $J = 9.4, 5.8$ Hz), 5.41 (1H, br s), 6.38 (1H, br s), 7.15 (1H, d, $J = 8.5$ Hz), 7.43 (2H, s), 8.08 (1H, d, $J = 8.5$ Hz). MS m/z : 526 (M-tBu+H) ⁺
BF5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.90 (6H, s), 1.15 (3H, s), 1.36–1.66 (16H, m), 1.67–1.79 (1H, m), 1.82–1.94 (3H, m), 1.94–2.61 (20H, m), 3.34–3.52 (4H, m), 3.65–3.91 (9H, m), 5.02 (1H, dd, $J = 9.7, 5.5$ Hz), 5.35 (1H, br s), 6.08–6.11 (1H, m), 6.34 (1H, br s), 6.80 (2H, d, $J = 8.5$ Hz), 6.93 (1H, d, $J = 7.9$ Hz), 6.98–7.03 (1H, m), 7.06–7.11 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 1041 (M+H) ⁺
BF6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.35–1.66 (4H, m), 1.68–1.80 (1H, m), 1.83–2.20 (7H, m), 2.21–2.57 (13H, m), 2.77–3.02 (4H, m), 3.32–3.53 (4H, m), 3.65–3.94 (11H, m), 5.19–5.29 (1H, m), 6.08–6.11 (1H, m), 6.67 (1H, d, $J = 7.9$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 6.93 (1H, d, $J = 7.9$ Hz), 7.07–7.12 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz), 8.03 (1H, s). MS m/z : 967 (M+H) ⁺
BG1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (9H, s), 1.89–2.07 (4H, m), 2.28–2.36 (1H, m), 2.48–2.56 (1H, m), 2.74–2.84 (2H, m), 3.46–3.98 (2H, m), 4.34–4.40 (1H, m), 5.33 (1H, br s), 5.82 (1H, br s), 6.65 (1H, br s), 7.33 (1H, d, $J = 8.5$ Hz), 7.37 (1H, d, $J = 8.5$ Hz). MS m/z : 540 [$\text{M}(^{79}\text{Br}^{79}\text{Br})+\text{Na}$] ⁺ , 542 [$\text{M}(^{79}\text{Br}^{81}\text{Br})+\text{Na}$] ⁺ , 544 [$\text{M}^{(81}\text{Br}^{81}\text{Br})+\text{Na}$] ⁺
BG2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (9H, s), 2.13–2.29 (4H, m), 2.31–2.42 (1H, m), 2.50–2.60 (1H, m), 2.83–2.88 (2H, m), 3.82–3.87 (2H, m), 4.99 (1H, dd, $J = 9.7, 6.1$ Hz), 5.39 (1H, br s), 6.36 (1H, br s), 6.90 (1H, d, $J = 7.9$ Hz), 7.19 (1H, d, $J = 7.9$ Hz). MS m/z : 460 [$\text{M}^{(79}\text{Br})+\text{Na}$] ⁺ , 462 [$\text{M}^{(81}\text{Br})+\text{Na}$] ⁺
BG3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (9H, s), 2.15–2.33 (4H, m), 2.37–2.48 (1H, m), 2.54–2.65 (1H, m), 3.31–3.37 (2H, m), 3.85–3.95 (2H, m), 5.07 (1H, dd, $J = 9.4, 5.8$ Hz), 5.41 (1H, br s), 6.38 (1H, br s), 7.15 (1H, d, $J = 8.5$ Hz), 7.43 (2H, s), 8.08 (1H, d, $J = 8.5$ Hz). MS m/z : 526 (M-tBu+H) ⁺
BG4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.91 (6H, s), 1.15 (3H, s), 1.42 (9H, s), 1.46–1.65 (6H, m), 1.68–1.80 (1H, m), 1.82–1.93 (3H, m), 1.95–2.60 (21H, m), 3.33–3.52 (4H, m), 3.66–3.91 (9H, m), 5.02 (1H, dd, $J = 9.4, 5.8$ Hz), 5.36 (1H, br s), 6.08–6.11 (1H, m), 6.34 (1H, br s), 6.80 (2H, d, $J = 8.5$ Hz), 6.93 (1H, d, $J = 7.9$ Hz), 6.99–7.02 (1H, m), 7.07–7.11 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz). MS m/z : 1041 (M+H) ⁺
BG5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.90 (6H, s), 1.16 (3H, s), 1.36–1.65 (4H, m), 1.67–1.78 (1H, m), 1.82–1.94 (3H, m), 1.94–2.21 (4H, m), 2.22–2.57 (13H, m), 2.61–3.02 (4H, m), 3.33–3.52 (4H, m), 3.63–3.94 (11H, m), 5.17–5.32 (1H, m), 6.08–6.11 (1H, m), 6.66 (1H, d, $J = 8.5$ Hz), 6.80 (2H, d, $J = 8.5$ Hz), 6.93 (1H, d, $J = 8.5$ Hz), 7.06–7.12 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz), 8.06 (1H, s). MS m/z : 967 (M+H) ⁺

[0916]

[Table 42]

Ex	Data
BH1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.45–1.93 (6H, m), 1.47 (9H, s), 2.05–2.15 (3H, m), 2.21–2.34 (1H, m), 2.34–2.49 (6H, m), 2.49–2.60 (1H, m), 3.40–3.52 (2H, m), 3.64–3.83 (2H, m), 3.78 (3H, s), 5.87–5.96 (1H, m), 6.65–6.90 (4H, m), 7.04–7.14 (3H, m).
BH2	MS m/z : 620 ($\text{M}+\text{H}$) $^+$.
BH3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–1.01 (2H, m), 1.40–1.98 (5H, m), 2.00–2.17 (2H, m), 2.17–2.28 (1H, m), 2.58–3.11 (9H, m), 2.64 (3H, s), 3.25–3.38 (1H, m), 3.65 (2H, td, $J = 8.2, 2.2$ Hz), 3.86 (2H, t, $J = 5.8$ Hz), 5.22 (1H, dd, $J = 13.4, 5.5$ Hz), 5.29 (2H, q, $J = 9.5$ Hz), 6.50–6.58 (1H, m), 6.65–6.74 (1H, m). MS m/z : 528 ($\text{M}+\text{H}$) $^+$.
BH4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.91–1.01 (2H, m), 0.93 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.39–1.99 (10H, m), 2.00–2.73 (17H, m), 2.73–2.98 (5H, m), 2.98–3.12 (3H, m), 3.46 (2H, dd, $J = 17.0, 14.6$ Hz), 3.60–3.80 (4H, m), 3.78 (3H, s), 3.83–3.90 (2H, m), 3.93–4.03 (1H, m), 4.52–4.71 (1H, m), 5.23 (1H, dd, $J = 14.9, 6.4$ Hz), 5.29 (2H, t, $J = 14.3$ Hz), 5.88–6.00 (1H, m), 6.56 (1H, d, $J = 8.5$ Hz), 6.73 (1H, d, $J = 8.5$ Hz), 6.79 (2H, d, $J = 9.1$ Hz), 6.85 (2H, d, $J = 10.3$ Hz), 7.04–7.14 (3H, m). MS m/z : 1129 ($\text{M}+\text{H}$) $^+$.
BH5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.44–1.66 (5H, m), 1.66–1.77 (1H, m), 1.77–2.00 (5H, m), 2.00–2.17 (3H, m), 2.17–2.76 (13H, m), 2.76–3.12 (8H, m), 3.37–3.53 (2H, m), 3.63–3.82 (5H, m), 3.82–3.95 (2H, m), 3.93–4.04 (1H, m), 4.53–4.72 (1H, m), 5.15–5.28 (1H, m), 5.91–6.01 (1H, m), 6.54–6.64 (1H, m), 6.72–6.82 (3H, m), 6.82–6.92 (2H, m), 7.03–7.14 (3H, m), 8.02 (1H, br s). MS m/z : 999 ($\text{M}+\text{H}$) $^+$.
BI1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.89–1.00 (8H, m), 1.15 (3H, s), 1.36–1.66 (2H, m), 1.69–1.79 (1H, m), 1.82–2.13 (8H, m), 2.18–2.58 (12H, m), 2.64–2.76 (1H, m), 2.83–2.96 (1H, m), 3.02–3.12 (1H, m), 3.43–3.53 (7H, m), 3.61–3.82 (10H, m), 5.21–5.33 (3H, m), 6.08–6.12 (1H, m), 6.76–6.82 (3H, m), 7.07–7.16 (6H, m), 7.24–7.29 (2H, m). MS m/z : 1071 ($\text{M}+\text{H}$) $^+$.
BI2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.37–1.65 (4H, m), 1.68–1.79 (1H, m), 1.82–1.94 (3H, m), 1.95–2.18 (3H, m), 2.22–2.57 (14H, m), 2.65–3.01 (3H, m), 3.41–3.53 (6H, m), 3.65–3.84 (7H, m), 5.24 (1H, dd, $J = 12.8, 5.5$ Hz), 6.07–6.12 (1H, m), 6.77–6.83 (3H, m), 7.07–7.18 (6H, m), 7.24–7.28 (2H, m), 8.06 (1H, s). MS m/z : 941 ($\text{M}+\text{H}$) $^+$.

[0917]

[Table 43]

Ex	Data
BJ1	$^1\text{H-NMR}$ (CDCl_3) δ : 2.88 (3H, d, $J = 5.5$ Hz), 3.02 (2H, br s), 4.31 (1H, br s), 6.58 (1H, s), 7.62 (1H, s). MS m/z : 202 $[\text{M}(^{79}\text{Br})+\text{H}]^+$, 204 $[\text{M}(^{81}\text{Br})+\text{H}]^+$.
BJ2	$^1\text{H-NMR}$ (DMSO-D_6) δ : 3.26 (3H, s), 7.45 (1H, s), 7.92 (1H, s), 11.29 (1H, br s).
BJ3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.01 (9H, s), 0.92–0.98 (2H, m), 2.24–2.30 (1H, m), 2.61–2.77 (1H, m), 2.86–2.95 (1H, m), 3.05–3.15 (1H, m), 3.44 (3H, s), 3.57–3.70 (2H, m), 5.17 (1H, dd, $J = 13.4, 5.5$ Hz), 5.24 (1H, d, $J = 9.2$ Hz), 5.29 (1H, d, $J = 9.2$ Hz), 7.17 (1H, s), 7.83 (1H, s).
BJ4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–1.00 (2H, m), 2.29–2.36 (1H, m), 2.70–2.84 (1H, m), 2.90–2.99 (1H, m), 3.08–3.16 (1H, m), 3.55 (3H, s), 3.60–3.70 (2H, m), 5.22–5.34 (3H, m), 7.45 (2H, s), 8.05 (1H, s), 8.31 (1H, s).
BJ5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.87–0.99 (8H, m), 1.15 (3H, s), 1.37–1.64 (4H, m), 1.69–1.77 (1H, m), 1.82–2.13 (6H, m), 2.23–2.60 (13H, m), 2.65–2.77 (1H, m), 2.85–2.97 (1H, m), 3.06–3.15 (1H, m), 3.41–3.53 (5H, m), 3.59–3.90 (11H, m), 5.20–5.33 (3H, m), 6.10 (1H, br s), 6.79 (2H, d, $J = 8.5$ Hz), 7.06–7.12 (4H, m), 7.26 (2H, d, $J = 8.5$ Hz), 7.47 (1H, s), 8.01 (1H, s). MS m/z : 1072 (M+H) $^+$.
BJ6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (6H, s), 1.16 (3H, s), 1.35–1.80 (5H, m), 1.83–1.95 (3H, m), 1.97–2.04 (1H, m), 2.07–2.13 (2H, m), 2.24–2.63 (13H, m), 2.66–2.79 (1H, m), 2.83–2.92 (1H, m), 2.96–3.04 (1H, m), 3.41–3.54 (5H, m), 3.64–3.92 (9H, m), 5.25 (1H, dd, $J = 13.4, 5.5$ Hz), 6.10 (1H, br s), 6.80 (2H, d, $J = 8.5$ Hz), 7.06–7.13 (4H, m), 7.23–7.29 (3H, m), 7.48 (1H, s), 8.05 (1H, s). MS m/z : 942 (M+H) $^+$.
BK1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.89–1.95 (2H, m), 2.97 (2H, t, $J = 6.4$ Hz), 3.41–3.46 (2H, m), 4.83 (1H, br s), 7.01 (1H, d, $J = 8.5$ Hz), 7.35 (1H, d, $J = 8.5$ Hz). MS m/z : 257 $[\text{M}(^{79}\text{Br})+\text{H}]^+$, 259 $[\text{M}(^{81}\text{Br})+\text{H}]^+$.
BK2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.83–1.95 (1H, m), 1.97–2.10 (2H, m), 2.66–2.86 (3H, m), 2.99–3.14 (2H, m), 3.55–3.98 (2H, m), 4.46–4.53 (1H, m), 5.38–5.45 (1H, m), 7.67 (1H, d, $J = 8.5$ Hz), 7.70 (1H, d, $J = 8.5$ Hz), 7.87 (1H, s). MS m/z : 411 $[\text{M}(^{79}\text{Br})+\text{H}]^+$, 413 $[\text{M}(^{81}\text{Br})+\text{H}]^+$.
BK3	$^1\text{H-NMR}$ (CDCl_3) δ : –0.02 (9H, s), 0.90–0.96 (2H, m), 1.78–1.91 (1H, m), 1.95–2.10 (2H, m), 2.65–2.73 (1H, m), 2.75–2.86 (1H, m), 2.90–2.97 (1H, m), 3.02–3.14 (2H, m), 3.56–3.62 (2H, m), 3.64–3.95 (2H, m), 4.47–4.54 (1H, m), 5.14 (1H, d, $J = 9.7$ Hz), 5.24 (1H, d, $J = 9.7$ Hz), 5.53–5.59 (1H, m), 7.68 (1H, d, $J = 9.1$ Hz), 7.72 (1H, d, $J = 9.1$ Hz). MS m/z : 513 $[\text{M}(^{79}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$, 515 $[\text{M}(^{81}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$.

[0918]

[Table 44]

Ex	Data
BK4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.01 (9H, s), 0.93–0.97 (2H, m), 2.16–2.31 (3H, m), 2.63–2.74 (1H, m), 2.85–2.95 (1H, m), 3.05–3.12 (1H, m), 3.34 (2H, t, $J = 6.1$ Hz), 3.62–3.67 (2H, m), 3.91 (2H, t, $J = 5.8$ Hz), 5.19–5.33 (3H, m), 6.71 (1H, d, $J = 9.1$ Hz), 7.96 (1H, d, $J = 9.1$ Hz). MS m/z : 433 ($\text{M-C}_2\text{H}_4+\text{H}$) $^+$.
BK5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93–0.97 (2H, m), 2.12–2.25 (3H, m), 2.61–2.69 (3H, m), 2.82–2.92 (1H, m), 3.00–3.08 (1H, m), 3.47–3.51 (2H, m), 3.61–3.67 (2H, m), 3.81–3.87 (2H, m), 5.18 (1H, dd, $J = 13.1, 5.2$ Hz), 5.26 (1H, d, $J = 9.7$ Hz), 5.31 (1H, d, $J = 9.7$ Hz), 6.36 (1H, d, $J = 7.9$ Hz), 6.44 (1H, d, $J = 8.5$ Hz). MS m/z : 453 ($\text{M}+\text{Na}$) $^+$.
BK6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.94–0.98 (2H, m), 1.24–1.39 (2H, m), 1.47 (9H, s), 1.99–2.08 (2H, m), 2.10–2.25 (3H, m), 2.55–2.69 (3H, m), 2.80–2.97 (3H, m), 2.99–3.07 (1H, m), 3.13 (1H, br s), 3.59–3.68 (2H, m), 3.79–3.86 (2H, m), 4.04 (1H, br s), 5.18 (1H, dd, $J = 13.1, 5.2$ Hz), 5.26 (1H, d, $J = 9.7$ Hz), 5.30 (1H, d, $J = 9.7$ Hz), 6.32 (1H, d, $J = 8.5$ Hz), 6.48 (1H, d, $J = 8.5$ Hz). MS m/z : 614 ($\text{M}+\text{H}$) $^+$.
BK7	MS m/z : 514 ($\text{M}+\text{H}$) $^+$.
BK8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.91–0.99 (8H, m), 1.15 (3H, s), 1.30–1.44 (2H, m), 1.45–1.64 (3H, m), 1.65–1.76 (1H, m), 1.82–1.99 (3H, m), 2.03–2.34 (9H, m), 2.35–2.69 (7H, m), 2.79–2.93 (4H, m), 3.00–3.07 (1H, m), 3.14–3.30 (2H, m), 3.43–3.53 (3H, m), 3.60–3.75 (4H, m), 3.78 (3H, s), 3.81–3.87 (2H, m), 3.95–4.04 (1H, m), 4.51–4.61 (1H, m), 5.14–5.33 (3H, m), 5.94–5.98 (1H, m), 6.33 (1H, d, $J = 8.5$ Hz), 6.50 (1H, d, $J = 8.5$ Hz), 6.77–6.87 (4H, m), 7.06–7.11 (3H, m). MS m/z : 1115 ($\text{M}+\text{H}$) $^+$.
BK9	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.94 (6H, s), 1.16 (3H, s), 1.31–1.44 (2H, m), 1.45–1.64 (2H, m), 1.68–1.78 (1H, m), 1.82–2.00 (3H, m), 2.05–2.72 (17H, m), 2.78–2.99 (4H, m), 3.13–3.30 (2H, m), 3.42–3.57 (3H, m), 3.64–3.77 (3H, m), 3.78 (3H, s), 3.81–3.87 (2H, m), 3.96–4.03 (1H, m), 4.53–4.64 (1H, m), 5.14–5.23 (1H, m), 5.94–5.98 (1H, m), 6.36 (1H, d, $J = 8.6$ Hz), 6.53 (1H, d, $J = 8.0$ Hz), 6.77–6.87 (4H, m), 7.06–7.12 (3H, m), 8.07 (1H, s). MS m/z : 985 ($\text{M}+\text{H}$) $^+$.
BL1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.42–1.65 (3H, m), 1.48 (9H, s), 1.66–1.92 (3H, m), 2.02–2.16 (3H, m), 2.22–2.34 (1H, m), 2.34–2.50 (6H, m), 2.50–2.60 (1H, m), 3.46 (2H, t, $J = 15.2$ Hz), 3.65–3.80 (2H, m), 3.78 (3H, s), 5.87–5.95 (1H, m), 6.76–6.87 (4H, m), 7.03–7.12 (3H, m).
BL2	MS m/z : 620 ($\text{M}+\text{H}$) $^+$.

[0919]

[Table 45]

Ex	Data
BL3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.90–1.01 (8H, m), 1.16 (3H, s), 1.31–1.66 (4H, m), 1.68–1.79 (1H, m), 1.81–2.01 (2H, m), 2.01–2.73 (17H, m), 2.78–2.96 (5H, m), 2.99–3.09 (1H, m), 3.13–3.29 (2H, m), 3.41–3.56 (3H, m), 3.59–3.80 (7H, m), 3.80–3.89 (2H, m), 3.90–4.06 (1H, m), 4.53–4.61 (1H, m), 5.15–5.23 (1H, m), 5.25–5.33 (2H, m), 5.94–5.98 (1H, m), 6.34 (1H, d, $J = 8.6$ Hz), 6.50 (1H, d, $J = 8.6$ Hz), 6.77–6.87 (4H, m), 7.06–7.11 (3H, m). MS m/z : 1115 ($\text{M}+\text{H}$) $^+$.
BL4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.93 (6H, s), 1.15 (3H, s), 1.24–1.64 (5H, m), 1.68–1.76 (1H, m), 1.82–1.99 (3H, m), 2.04–2.71 (17H, m), 2.78–2.97 (4H, m), 3.13–3.30 (2H, m), 3.43–3.57 (3H, m), 3.66–3.75 (2H, m), 3.78 (3H, s), 3.81–3.86 (2H, m), 3.95–4.03 (1H, m), 4.53–4.62 (1H, m), 5.14–5.23 (1H, m), 5.94–5.98 (1H, m), 6.36 (1H, d, $J = 8.5$ Hz), 6.53 (1H, d, $J = 7.9$ Hz), 6.77–6.87 (4H, m), 7.05–7.12 (3H, m), 8.02 (1H, s). MS m/z : 985 ($\text{M}+\text{H}$) $^+$.
BM1	$^1\text{H-NMR}$ (CDCl_3) δ : 3.52 (2H, td, $J = 4.3, 2.4$ Hz), 4.21 (1H, br s), 4.36 (2H, t, $J = 4.3$ Hz), 6.73 (1H, d, $J = 2.4$ Hz), 7.19 (1H, d, $J = 2.4$ Hz).
BM2	$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.45 (2H, t, $J = 4.6$ Hz), 4.24 (2H, t, $J = 4.6$ Hz), 6.78 (1H, s).
BM3	$^1\text{H-NMR}$ (CDCl_3) δ : 2.00 (1H, dq, $J = 27.2, 6.8$ Hz), 2.62–2.68 (1H, m), 2.72–2.81 (1H, m), 2.88 (1H, dq, $J = 18.1, 2.3$ Hz), 3.75–4.14 (2H, m), 4.44 (2H, t, $J = 4.9$ Hz), 4.53 (1H, dt, $J = 13.0, 5.3$ Hz), 5.69 (1H, d, $J = 4.9$ Hz), 7.99 (1H, br s). MS m/z : 524 [$\text{M}(^{79}\text{Br}^{79}\text{Br})+\text{H}$] $^+$, 526 [$\text{M}(^{79}\text{Br}^{81}\text{Br})+\text{H}$] $^+$, 528 [$\text{M}(^{81}\text{Br}^{81}\text{Br})+\text{H}$] $^+$.
BM4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93 (2H, td, $J = 8.7, 4.0$ Hz), 1.89 (1H, ddd, $J = 26.6, 13.2, 4.7$ Hz), 2.58–2.65 (1H, m), 2.75–2.84 (1H, m), 2.95 (1H, dq, $J = 18.2, 2.4$ Hz), 3.59 (2H, dt, $J = 9.5, 3.8$ Hz), 3.73–4.11 (2H, br m), 4.36–4.44 (2H, m), 4.50 (1H, dt, $J = 13.2, 5.0$ Hz), 5.14 (1H, d, $J = 9.1$ Hz), 5.24 (1H, d, $J = 9.1$ Hz), 5.75 (1H, d, $J = 4.9$ Hz).
BM5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.01 (9H, s), 0.92–1.01 (2H, m), 2.32 (1H, dq, $J = 15.0, 3.3$ Hz), 2.71–2.86 (1H, m), 2.95 (1H, tt, $J = 15.9, 6.0$ Hz), 3.04–3.12 (1H, m), 3.59–3.72 (2H, m), 3.99–4.20 (3H, m), 4.49–4.64 (2H, m), 5.25–5.32 (2H, m), 5.47–5.83 (1H, m). MS m/z : 573 [$\text{M}(^{79}\text{Br})-\text{H}$] $^+$, 575 [$\text{M}(^{81}\text{Br})-\text{H}$] $^+$.
BM6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.96 (2H, dq, $J = 10.8, 3.6$ Hz), 2.20–2.26 (1H, m), 2.64 (1H, ddd, $J = 26.7, 13.4, 4.3$ Hz), 2.82–2.91 (1H, m), 3.04 (1H, dq, $J = 17.6, 2.4$ Hz), 3.55 (2H, s), 3.64 (2H, dq, $J = 14.0, 2.4$ Hz), 4.01 (2H, dd, $J = 5.8, 3.9$ Hz), 4.42 (2H, t, $J = 4.6$ Hz), 5.16 (1H, dd, $J = 13.1, 5.2$ Hz), 5.28 (2H, q, $J = 9.7$ Hz), 6.23 (1H, d, $J = 8.5$ Hz), 6.39 (1H, d, $J = 8.5$ Hz). MS m/z : 455 ($\text{M}+\text{Na}$) $^+$.

[0920]

[Table 46]

Ex	Data
BM7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.99 (2H, m), 1.28–1.40 (1H, m), 1.47 (s, 9H), 1.97–2.08 (1H, m), 2.20–2.26 (1H, m), 2.64 (1H, ddd, $J = 26.7, 13.4, 4.3$ Hz), 2.81–2.99 (3H, m), 3.01–3.08 (1H, m), 3.34–3.44 (1H, m), 3.51 (1H, br s), 3.64 (2H, td, $J = 8.4, 1.8$ Hz), 3.93–4.08 (4H, m), 4.40 (2H, t, $J = 4.9$ Hz), 5.16 (1H, dd, $J = 13.1, 5.2$ Hz), 5.26 (1H, d, $J = 9.1$ Hz), 5.31 (1H, d, $J = 9.1$ Hz), 6.27 (1H, d, $J = 8.5$ Hz), 6.32 (1H, d, $J = 8.5$ Hz). MS m/z : 638 ($\text{M}+\text{Na}$) $^+$.
BM8	$^1\text{H-NMR}$ (CDCl_3) δ : -0.01 (9H, s), 0.91–0.98 (2H, m), 2.05 (3H, dd, $J = 10.9, 2.4$ Hz), 2.19–2.26 (1H, m), 2.58–2.73 (3H, m), 2.82–2.91 (1H, m), 3.00–3.14 (3H, m), 3.32 (1H, s), 3.52 (1H, d, $J = 1.8$ Hz), 3.63 (2H, tdd, $J = 11.9, 6.8, 5.2$ Hz), 4.00 (2H, dd, $J = 5.5, 3.6$ Hz), 4.40 (2H, t, $J = 4.6$ Hz), 5.15 (1H, dd, $J = 13.4, 4.9$ Hz), 5.27 (2H, q, $J = 9.5$ Hz), 6.26 (1H, d, $J = 7.9$ Hz), 6.32 (1H, d, $J = 8.5$ Hz). MS m/z : 516 ($\text{M}+\text{H}$) $^+$.
BM9	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.90–0.98 (8H, m), 1.16 (3H, s), 1.31–1.75 (7H, m), 1.83–1.98 (3H, m), 2.05–2.71 (13H, m), 2.83–2.92 (2H, m), 2.99–3.09 (1H, m), 3.17–3.31 (1H, m), 3.42–3.82 (11H, m), 3.93–4.05 (3H, m), 4.38–4.44 (2H, m), 4.47–4.59 (1H, m), 5.13–5.20 (1H, m), 5.26 (1H, d, $J = 9.1$ Hz), 5.31 (1H, d, $J = 9.1$ Hz), 5.96 (1H, br s), 6.28 (1H, d, $J = 8.5$ Hz), 6.35 (1H, d, $J = 8.5$ Hz), 6.79 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.07–7.10 (3H, m). MS m/z : 1117 ($\text{M}+\text{H}$) $^+$.
BM10	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.94 (6H, br s), 1.16 (3H, s), 1.33–1.63 (5H, m), 1.66–1.77 (1H, m), 1.83–1.98 (3H, m), 2.05–2.18 (4H, m), 2.21–2.72 (9H, m), 2.79–2.97 (4H, m), 3.17–3.32 (1H, m), 3.41–3.62 (4H, m), 3.67–3.75 (2H, m), 3.78 (3H, s), 3.93–4.07 (3H, m), 4.37–4.45 (2H, m), 4.51–4.57 (1H, m), 5.12–5.20 (1H, m), 5.93–5.99 (1H, m), 6.32 (1H, d, $J = 8.5$ Hz), 6.37 (1H, d, $J = 8.5$ Hz), 6.79 (2H, d, $J = 9.1$ Hz), 6.85 (2H, d, $J = 9.1$ Hz), 7.07–7.10 (3H, m), 8.09 (1H, s). MS m/z : 987 ($\text{M}+\text{H}$) $^+$.
BN1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.93–0.98 (8H, m), 1.16 (3H, s), 1.34–1.58 (7H, m), 1.69–1.75 (1H, m), 1.84–1.95 (3H, m), 2.04–2.71 (11H, m), 2.86–2.91 (3H, m), 3.02–3.08 (1H, m), 3.18–3.28 (1H, m), 3.42–3.54 (4H, m), 3.61–3.67 (2H, m), 3.70–3.75 (2H, m), 3.78 (3H, s), 3.95–4.02 (3H, m), 4.40–4.43 (2H, m), 4.50–4.56 (1H, m), 5.14–5.20 (1H, m), 5.24–5.32 (2H, m), 5.95–5.97 (1H, m), 6.28 (1H, d, $J = 8.6$ Hz), 6.35 (1H, d, $J = 8.6$ Hz), 6.78–6.81 (2H, m), 6.84–6.87 (2H, m), 7.06–7.11 (3H, m). MS m/z : 1117 ($\text{M}+\text{H}$) $^+$.

[0921]

[Table 47]

Ex	Data
BN2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.35–1.57 (4H, m), 1.68–1.75 (1H, m), 1.83–1.95 (3H, m), 2.05–2.33 (7H, m), 2.36–2.38 (2H, m), 2.40–2.72 (5H, m), 2.78–2.97 (4H, m), 3.21–3.28 (1H, m), 3.43–3.47 (2H, m), 3.49–3.56 (2H, m), 3.66–3.76 (2H, m), 3.78 (3H, s), 3.97–4.03 (3H, m), 4.40–4.42 (2H, m), 4.52–4.57 (1H, m), 5.12–5.20 (1H, m), 5.95–5.97 (1H, m), 6.31 (1H, d, $J=8.0$ Hz), 6.37 (1H, d, $J=8.0$ Hz), 6.78–6.81 (2H, m), 6.83–6.87 (2H, m), 7.06–7.11 (3H, m), 8.08 (1H, s). MS m/z : 987 ($\text{M}+\text{H}$) $^+$.
BO1	MS m/z : 602 ($\text{M}+\text{H}$) $^+$.
BO2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.26–1.49 (1H, m), 1.47 (9H, s), 1.98–2.09 (2H, m), 2.13–2.24 (1H, m), 2.31 (1H, ddd, $J=26.0, 12.9, 5.0$ Hz), 2.72–3.02 (5H, m), 3.41–3.59 (1H, m), 3.93–4.16 (3H, m), 4.23 (1H, d, $J=15.2$ Hz), 4.38 (1H, d, $J=15.2$ Hz), 5.19 (1H, dd, $J=13.1, 5.2$ Hz), 6.56 (1H, s), 6.64 (1H, dd, $J=8.5, 1.8$ Hz), 7.66 (1H, d, $J=8.5$ Hz), 7.90 (1H, br s). MS m/z : 387 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
BO3	MS m/z : 343 ($\text{M}+\text{H}$) $^+$.
BO4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.33–1.67 (4H, m), 1.67–1.79 (1H, m), 1.79–2.41 (13H, m), 2.41–2.67 (3H, m), 2.73–3.00 (5H, m), 3.20–3.35 (1H, m), 3.47 (2H, dd, $J=20.7, 14.0$ Hz), 3.55–3.84 (6H, m), 3.93–4.09 (2H, m), 4.24 (1H, d, $J=15.8$ Hz), 4.39 (1H, d, $J=15.8$ Hz), 4.50–4.71 (1H, m), 5.14–5.25 (1H, m), 6.09–6.17 (1H, m), 6.59 (1H, s), 6.66 (1H, d, $J=8.5$ Hz), 6.80 (2H, d, $J=8.5$ Hz), 7.10 (4H, d, $J=8.5$ Hz), 7.25 (2H, d, $J=7.3$ Hz), 7.67 (1H, d, $J=7.9$ Hz), 7.96 (1H, s). MS m/z : 926 ($\text{M}+\text{H}$) $^+$.
BP1	MS m/z : 245 [$\text{M}(^{79}\text{Br})+\text{H}$] $^+$, 247 [$\text{M}(^{81}\text{Br})+\text{H}$] $^+$.
BP2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.04 (9H, s), 0.98 (2H, t, $J=8.4$ Hz), 2.24–2.34 (1H, m), 2.46–2.63 (1H, m), 2.85–3.00 (1H, m), 3.04–3.12 (1H, m), 3.46 (3H, s), 3.59–3.72 (2H, m), 5.30 (2H, d, $J=2.0$ Hz), 5.36–5.47 (1H, m), 7.03 (1H, s), 7.04 (1H, d, $J=9.0$ Hz). MS m/z : 458 [$\text{M}(^{79}\text{Br})-\text{C}_2\text{H}_4+\text{H}$] $^+$, 460 [$\text{M}(^{81}\text{Br})-\text{C}_2\text{H}_4+\text{H}$] $^+$.
BP3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.04 (9H, s), 0.99 (2H, t, $J=8.6$ Hz), 1.50 (9H, s), 2.36–2.46 (1H, m), 2.64–2.71 (4H, m), 2.85–3.00 (1H, m), 3.00–3.13 (1H, m), 3.36–3.55 (10H, m), 3.60–3.71 (2H, m), 5.32 (2H, d, $J=1.2$ Hz), 5.37–5.50 (1H, m), 6.85 (1H, d, $J=13.3$ Hz), 6.86 (1H, s). MS m/z : 522 ($\text{M}-\text{tBu}-\text{C}_2\text{H}_4+\text{H}$) $^+$.
BP4	MS m/z : 506 ($\text{M}+\text{H}$) $^+$.
BP5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.03 (9H, s), 0.69 (3H, s), 0.94 (6H, s), 0.99 (2H, t, $J=8.2$ Hz), 1.19 (3H, s), 1.46–2.18 (10H, m), 2.24–2.42 (5H, m), 2.44–2.65 (8H, m), 2.78–2.90 (1H, m), 3.03–3.13 (1H, m), 3.49–3.78 (15H, m), 3.82 (3H, s), 5.32 (2H, d, $J=1.2$ Hz), 5.39–5.50 (1H, m), 6.14–6.19 (1H, m), 6.81–6.89 (4H, m), 7.11–7.16 (4H, m), 7.29 (2H, d, $J=8.6$ Hz). MS m/z : 1089 ($\text{M}+\text{H}$) $^+$.

[0922]

[Table 48]

Ex	Data
BP6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.19 (3H, s), 1.47–2.21 (12H, m), 2.28–3.02 (13H, m), 3.44–3.79 (13H, m), 3.81 (3H, s), 5.36–5.50 (1H, m), 6.14–6.19 (1H, m), 6.80–6.92 (4H, m), 7.11–7.16 (4H, m), 7.28 (2H, d, $J = 9.4$ Hz), 8.00 (1H, s). MS m/z : 959 ($\text{M}+\text{H}$) $^+$.
BQ1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.96 (2H, t, $J = 8.5$ Hz), 1.46 (9H, s), 2.15–2.27 (1H, m), 2.33–2.45 (4H, m), 2.71 (1H, ddd, $J = 26.1, 13.1, 4.3$ Hz), 2.81–2.94 (1H, m), 2.99–3.10 (1H, m), 3.36–3.48 (4H, m), 3.44 (3H, s), 3.53 (2H, s), 3.60–3.70 (2H, m), 5.23 (1H, dd, $J = 14.3, 6.4$ Hz), 5.29 (2H, q, $J = 9.1$ Hz), 6.71 (1H, d, $J = 7.9$ Hz), 6.98 (1H, d, $J = 8.5$ Hz), 7.04 (1H, s). MS m/z : 588 ($\text{M}+\text{H}$) $^+$.
BQ2	MS m/z : 488 ($\text{M}+\text{H}$) $^+$.
BQ3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.91–0.99 (8H, m), 1.16 (2H, s), 1.45–1.64 (4H, m), 1.68–1.77 (1H, m), 1.83–1.99 (3H, m), 2.04–2.14 (2H, m), 2.18–2.33 (3H, m), 2.34–2.60 (8H, m), 2.66–2.97 (5H, m), 3.02–3.10 (1H, m), 3.43–3.48 (5H, m), 3.53–3.75 (9H, m), 3.78 (3H, s), 5.20–5.33 (3H, m), 5.94–5.98 (1H, m), 6.72 (1H, d, $J = 7.9$ Hz), 6.77–6.87 (4H, m), 6.99 (1H, d, $J = 7.9$ Hz), 7.03–7.11 (4H, m). MS m/z : 1089 ($\text{M}+\text{H}$) $^+$.
BQ4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.93 (6H, s), 1.16 (3H, s), 1.44–1.64 (4H, m), 1.66–1.76 (1H, m), 1.82–1.98 (3H, m), 2.05–2.14 (2H, m), 2.21–2.60 (12H, m), 2.67–3.00 (4H, m), 3.42–3.51 (4H, m), 3.53–3.60 (4H, m), 3.63–3.79 (7H, m), 5.22 (1H, dd, $J = 12.8, 5.5$ Hz), 5.94–5.97 (1H, m), 6.73–6.88 (5H, m), 6.99–7.12 (5H, m), 8.08 (1H, s). MS m/z : 959 ($\text{M}+\text{H}$) $^+$.
BR1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.18–1.40 (2H, m), 1.47 (9H, s), 1.98–2.10 (2H, m), 2.15–2.28 (1H, m), 2.68 (1H, ddd, $J = 26.1, 12.8, 4.9$ Hz), 2.75–2.87 (1H, m), 2.87–3.02 (3H, m), 3.35–3.46 (2H, m), 3.38 (3H, s), 3.92–4.17 (2H, m), 5.17 (1H, dd, $J = 13.1, 5.2$ Hz), 6.31 (1H, d, $J = 1.8$ Hz), 6.34 (1H, dd, $J = 8.2, 2.1$ Hz), 6.60 (1H, d, $J = 8.5$ Hz), 7.94–8.30 (1H, br m). MS m/z : 402 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
BR2	MS m/z : 358 ($\text{M}+\text{H}$) $^+$.
BR3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.29–1.44 (2H, m), 1.44–1.66 (3H, m), 1.66–1.79 (1H, m), 1.79–2.02 (3H, m), 2.02–2.61 (12H, m), 2.62–2.76 (1H, m), 2.76–2.99 (4H, m), 3.20–3.32 (1H, m), 3.39 (3H, s), 3.40–3.59 (4H, m), 3.64–3.80 (2H, m), 3.78 (3H, s), 3.94–4.06 (1H, m), 4.48–4.65 (1H, m), 5.17 (1H, dd, $J = 13.1, 5.2$ Hz), 5.93–5.99 (1H, m), 6.32–6.39 (2H, m), 6.62 (1H, d, $J = 7.9$ Hz), 6.79 (2H, d, $J = 9.1$ Hz), 6.85 (2H, d, $J = 9.7$ Hz), 7.04–7.13 (3H, m), 8.02 (1H, br s). MS m/z : 959 ($\text{M}+\text{H}$) $^+$.

[0923]

[Table 49]

Ex	Data
BS1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.24–1.40 (2H, m), 1.47 (9H, s), 2.00–2.12 (2H, m), 2.15–2.27 (1H, m), 2.35 (1H, ddd, $J = 26.1, 13.1, 5.2$ Hz), 2.76–2.99 (4H, m), 3.41–3.58 (1H, m), 3.59–3.85 (1H, m), 3.91–4.17 (2H, m), 4.24 (1H, d, $J = 15.2$ Hz), 4.37 (1H, d, $J = 15.2$ Hz), 5.21 (1H, dd, $J = 13.4, 5.5$ Hz), 6.80 (1H, dd, $J = 8.2, 2.1$ Hz), 7.06 (1H, d, $J = 2.4$ Hz), 7.22 (1H, t, $J = 3.9$ Hz), 7.91 (1H, br s). MS m/z : 387 (M-tBu+H) $^+$.
BS2	MS m/z : 343 (M+H) $^+$.
BS3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.29–1.67 (4H, m), 1.67–1.80 (1H, m), 1.81–2.67 (15H, m), 2.74–3.03 (6H, m), 3.16–3.35 (1H, m), 3.41–3.55 (2H, m), 3.55–3.85 (7H, m), 3.92–4.06 (1H, m), 4.25 (1H, d, $J = 15.2$ Hz), 4.38 (1H, d, $J = 15.2$ Hz), 4.54–4.70 (1H, m), 5.13–5.31 (1H, m), 6.08–6.18 (1H, m), 6.68–6.91 (3H, m), 7.00–7.16 (5H, m), 7.16–7.32 (3H, m), 7.83–7.93 (1H, m). MS m/z : 926 (M+H) $^+$.
BT1	$^1\text{H-NMR}$ (CDCl_3) δ : 3.39 (3H, s), 6.88 (1H, d, $J = 7.4$ Hz), 7.26 (1H, d, $J = 5.9$ Hz), 8.61 (1H, s). MS m/z : 293 (M+H) $^+$.
BT2	MS m/z : 506 ($\text{M-C}_2\text{H}_4\text{+H}$) $^+$.
BT3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.03 (9H, s), 0.95–1.04 (2H, m), 1.57 (9H, s), 2.18–2.31 (1H, m), 2.58–2.80 (1H, m), 2.82–2.98 (1H, m), 3.05–3.16 (1H, m), 3.46 (3H, s), 3.63–3.73 (2H, m), 5.15–5.26 (1H, m), 5.26–5.38 (2H, m), 6.56–6.65 (1H, m), 6.66–6.99 (1H, m), 7.84–7.93 (1H, m).
BT4	MS m/z : 293 ($\text{M-CH}_2\text{OH+H}$) $^+$.
BT5	$^1\text{H-NMR}$ (CDCl_3) δ : 1.36–1.67 (4H, m), 1.51 (9H, s), 2.03–2.11 (1H, m), 2.20–2.31 (1H, m), 2.62–3.11 (5H, m), 3.39–3.50 (1H, m), 3.43 (3H, s), 4.04–4.15 (1H, m), 5.13–5.23 (1H, m), 5.35–5.51 (1H, m), 6.43 (1H, d, $J = 7.0$ Hz), 6.59 (1H, dd, $J = 10.6, 2.7$ Hz), 8.03–8.12 (1H, m). MS m/z : 420 (M-tBu+H) $^+$.
BT6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.94 (6H, s), 1.19 (3H, s), 1.25–2.77 (22H, m), 2.80–3.04 (5H, m), 3.25–3.83 (7H, m), 3.44 (3H, s), 3.82 (3H, s), 3.97–4.09 (1H, m), 5.12–5.25 (1H, m), 6.13–6.19 (1H, m), 6.45 (1H, d, $J = 7.0$ Hz), 6.57–6.64 (1H, m), 6.83 (2H, d, $J = 9.0$ Hz), 7.11–7.15 (4H, m), 7.29 (2H, d, $J = 5.9$ Hz), 8.04 (1H, s). MS m/z : 959 (M+H) $^+$.
BU1	$^1\text{H-NMR}$ (CDCl_3) δ : 4.02 (2H, dd, $J = 6.1, 3.6$ Hz), 4.41 (2H, dd, $J = 6.1, 3.6$ Hz), 6.65 (1H, d, $J = 7.9$ Hz), 6.69 (1H, d, $J = 7.9$ Hz), 6.93 (1H, t, $J = 7.9$ Hz), 8.61 (1H, br s). MS m/z : 177 (M+H) $^+$.
BU2	$^1\text{H-NMR}$ (DMSO-D_6) δ : 3.88 (2H, t, $J = 4.6$ Hz), 4.44 (2H, t, $J = 4.6$ Hz), 6.50 (1H, d, $J = 8.5$ Hz), 7.20 (1H, d, $J = 8.5$ Hz), 10.87 (1H, s). MS m/z : 303 (M+H) $^+$.

[0924]

[Table 50]

Ex	Data
BU3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.89–1.01 (2H, m), 2.20–2.30 (1H, m), 2.57–2.72 (1H, m), 2.84–2.93 (1H, m), 3.02–3.12 (1H, m), 3.61–3.66 (2H, m), 4.00–4.09 (2H, m), 4.49–4.57 (2H, m), 5.18 (1H, dd, J = 13.4, 5.5 Hz), 5.23–5.31 (2H, m), 6.28 (1H, d, J = 7.9 Hz), 7.30 (1H, d, J = 7.9 Hz). MS m/z : 566 ($\text{M}+\text{Na}$) $^+$.
BU4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.99 (2H, m), 2.26–2.33 (1H, m), 2.62–2.77 (1H, m), 2.86–2.98 (1H, m), 3.05–3.14 (1H, m), 3.61–3.69 (2H, m), 4.05–4.14 (2H, m), 4.55–4.63 (2H, m), 5.21–5.32 (3H, m), 6.55 (1H, d, J = 8.5 Hz), 7.41 (2H, br s), 7.91 (1H, d, J = 8.5 Hz). MS m/z : 662 ($\text{M}+\text{Na}$) $^+$.
BU5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.88–1.00 (8H, m), 1.16 (3H, s), 1.35–1.65 (3H, m), 1.68–1.78 (1H, m), 1.82–2.15 (6H, m), 2.20–2.78 (14H, m), 2.83–2.95 (1H, m), 3.01–3.12 (1H, m), 3.36–3.53 (4H, m), 3.61–3.93 (9H, m), 4.01–4.12 (2H, m), 4.39–4.53 (2H, m), 5.15–5.35 (3H, m), 6.10 (1H, br s), 6.47 (1H, d, J = 7.9 Hz), 6.80 (2H, d, J = 8.5 Hz), 7.02 (1H, d, J = 8.5 Hz), 7.07–7.11 (4H, m), 7.26 (2H, d, J = 8.5 Hz). MS m/z : 1099 ($\text{M}+\text{H}$) $^+$.
BU6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.68 (3H, s), 0.93 (6H, s), 1.18 (3H, s), 1.35–1.69 (5H, m), 1.68–1.78 (1H, m), 1.84–1.96 (3H, m), 1.98–2.05 (1H, m), 2.07–2.17 (2H, m), 2.25–2.61 (13H, m), 2.62–2.73 (1H, m), 2.78–2.90 (1H, m), 2.91–3.01 (1H, m), 3.37–3.56 (4H, m), 3.66–3.93 (7H, m), 4.01–4.10 (2H, m), 4.39–4.51 (2H, m), 5.21–5.25 (1H, br m), 6.12 (1H, br s), 6.53 (1H, d, J = 8.5 Hz), 6.82 (2H, d, J = 8.5 Hz), 7.06 (1H, d, J = 8.5 Hz), 7.10–7.13 (4H, m), 7.28 (1H, d, J = 8.5 Hz), 8.29 (1H, br s). MS m/z : 969 ($\text{M}+\text{H}$) $^+$.
BV1	$^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (9H, s), 3.61–3.70 (1H, m), 3.96–4.05 (1H, m), 4.10–4.23 (2H, m), 4.51–4.58 (1H, m), 4.82–4.89 (1H, m), 7.17–7.25 (2H, m), 7.62–7.66 (1H, m). MS m/z : 243 [$(\text{M}-\text{Boc})+\text{H}$] $^+$.
BV2	$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.83–3.90 (2H, m), 3.96–4.14 (3H, m), 5.15–5.21 (1H, m), 7.37 (1H, td, J = 8.5, 1.5 Hz), 7.69–7.76 (2H, m), 8.49 (3H, br s). MS m/z : 243 ($\text{M}+\text{H}$) $^+$.
BV3	$^1\text{H-NMR}$ (CDCl_3) δ : 3.59–3.65 (1H, m), 4.13–4.24 (3H, m), 4.26–4.34 (2H, m), 6.62 (1H, dd, J = 8.5, 1.5 Hz), 7.10 (1H, d, J = 8.5 Hz), 7.82 (1H, dd, J = 8.5, 1.5 Hz), 8.08 (1H, br s). MS m/z : 223 ($\text{M}+\text{H}$) $^+$.
BV4	$^1\text{H-NMR}$ (CDCl_3) δ : 3.40 (3H, brs), 3.54–3.60 (1H, m), 4.01–4.13 (3H, m), 4.17–4.23 (2H, m), 6.39 (1H, dd, J = 7.9, 1.5 Hz), 6.48 (1H, dd, J = 7.9, 1.5 Hz), 6.63 (1H, t, J = 7.9 Hz). MS m/z : 193 ($\text{M}+\text{H}$) $^+$.
BV5	$^1\text{H-NMR}$ (CDCl_3) δ : 3.80–3.85 (1H, m), 4.15 (1H, m), 4.32 (2H, m), 4.66–4.77 (2H, m), 6.70 (1H, d, J = 8.5 Hz), 6.73 (1H, d, J = 8.5 Hz), 6.97 (1H, t, J = 8.5 Hz), 8.72 (1H, br s). MS m/z : 219 ($\text{M}+\text{H}$) $^+$.

[0925]

[Table 51]

Ex	Data
BV6	$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 3.56–3.63 (1H, m), 3.89–3.94 (1H, m), 4.06–4.16 (2H, m), 4.66–4.74 (1H, m), 4.84–4.89 (1H, m), 6.51 (1H, d, $J = 8.5$ Hz), 7.22 (1H, d, $J = 8.5$ Hz), 11.01 (1H, br s). MS m/z : 345 (M+H) $^+$.
BV7	$^1\text{H-NMR}$ (CDCl_3) δ : -0.01 (9H, s), 0.89–1.01 (2H, m), 2.21–2.31 (1H, m), 2.56–2.72 (1H, m), 2.83–2.92 (1H, m), 3.03–3.09 (1H, m), 3.54–3.68 (2H, m), 3.79–3.84 (1H, m), 4.18–4.27 (1H, m), 4.30–4.40 (2H, m), 4.64–4.82 (2H, m), 5.10–5.30 (3H, m), 6.31 (1H, d, $J = 8.5$ Hz), 7.33 (1H, d, $J = 8.5$ Hz). MS m/z : 608 (M+Na) $^+$.
BV8	$^1\text{H-NMR}$ (CDCl_3) δ : 0.01 (9H, s), 0.93–1.00 (2H, m), 2.26–2.42 (1H, m), 2.56–2.80 (1H, m), 2.86–2.99 (1H, m), 3.06–3.16 (1H, m), 3.53–3.70 (2H, m), 3.89–3.97 (1H, m), 4.21–4.27 (1H, m), 4.31–4.38 (2H, m), 4.68–4.79 (1H, m), 4.86–4.97 (1H, m), 5.14–5.36 (3H, m), 6.56–6.60 (1H, m), 7.42 (2H, s), 7.92–7.95 (1H, m). MS m/z : 704 (M+Na) $^+$.
BV9	$^1\text{H-NMR}$ (CDCl_3) δ : 0.03 (9H, s), 0.68 (3H, s), 0.93 (6H, s), 0.93–0.99 (2H, m), 1.19 (3H, s), 1.37–1.68 (6H, m), 1.68–1.79 (1H, m), 1.86–1.93 (3H, m), 1.96–2.04 (1H, m), 2.05–2.15 (2H, m), 2.24–2.76 (13H, m), 2.83–2.97 (1H, m), 3.03–3.13 (1H, m), 3.36–3.56 (4H, m), 3.61–3.98 (11H, m), 4.15–4.23 (1H, m), 4.28–4.39 (2H, m), 4.65–4.82 (2H, m), 5.14–5.38 (3H, m), 6.13 (1H, br s), 6.54 (1H, d, $J = 7.9$ Hz), 6.83 (2H, d, $J = 9.2$ Hz), 7.10–7.13 (4H, m), 7.29 (1H, d, $J = 7.9$ Hz). MS m/z : 1141 (M+H) $^+$.
BV10	$^1\text{H-NMR}$ (CDCl_3) δ : 0.68 (3H, s), 0.93 (6H, s), 1.18 (3H, s), 1.37–1.69 (5H, m), 1.76 (1H, td, $J = 12.5, 3.4$ Hz), 1.85–1.97 (3H, m), 2.00–2.03 (1H, m), 2.10–2.13 (2H, m), 2.26–2.77 (14H, m), 2.82–2.91 (1H, m), 2.92–3.04 (1H, m), 3.37–3.57 (4H, m), 3.67–3.99 (8H, m), 4.15–4.24 (1H, m), 4.29–4.43 (2H, m), 4.69–4.84 (2H, m), 5.13–5.34 (1H, m), 6.12 (1H, br s), 6.57 (1H, dd, $J = 8.2, 2.7$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.08–7.16 (5H, m), 7.28 (1H, d, $J = 7.9$ Hz), 8.28 (1H, br s). MS m/z : 1011 (M+H) $^+$.
BW1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–0.99 (2H, m), 1.45 (9H, s), 2.09–2.27 (3H, m), 2.54–2.71 (3H, m), 2.80–2.93 (1H, m), 2.98–3.09 (1H, m), 3.57–3.68 (3H, m), 3.68–3.77 (2H, m), 3.77–3.90 (2H, m), 4.12–4.22 (1H, m), 4.25–4.35 (2H, m), 5.19 (1H, dd, $J = 13.1, 5.2$ Hz), 5.28 (2H, q, $J = 9.5$ Hz), 6.00 (1H, d, $J = 8.5$ Hz), 6.48 (1H, d, $J = 7.9$ Hz).
BW2	MS m/z : 386 (M+H) $^+$.

[0926]

[Table 52]

Ex	Data
BW3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.90–0.97 (6H, m), 1.16 (3H, s), 1.41–1.66 (2H, m), 1.66–1.79 (1H, m), 1.79–2.59 (16H, m), 2.59–2.76 (3H, m), 2.76–3.03 (2H, m), 3.35–3.54 (2H, m), 3.62–3.91 (10H, m), 3.91–4.01 (1H, m), 4.22–4.37 (1H, m), 4.39–4.51 (1H, m), 4.51–4.65 (1H, m), 5.09–5.27 (1H, m), 5.88–6.00 (1H, m), 6.00–6.09 (1H, m), 6.47–6.58 (1H, m), 6.72–6.91 (4H, m), 7.02–7.14 (3H, m), 7.96–8.06 (1H, m). MS m/z : 957 ($\text{M}+\text{H}$) $^+$.
BX1	$^1\text{H-NMR}$ (CDCl_3) δ : 3.58–3.62 (3H, m), 6.70 (1H, d, $J = 8.0$ Hz), 7.33–7.41 (1H, m), 9.32 (1H, s). MS m/z : 293 ($\text{M}+\text{H}$) $^+$.
BX2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.02 (9H, s), 0.91–1.00 (2H, m), 2.16–2.26 (1H, m), 2.61–2.74 (1H, m), 2.81–2.92 (1H, m), 3.01–3.10 (1H, m), 3.59–3.67 (2H, m), 3.61 (3H, d, $J = 1.8$ Hz), 5.18 (1H, dd, $J = 13.5, 5.5$ Hz), 5.27 (2H, dd, $J = 19.0, 9.2$ Hz), 6.39 (1H, d, $J = 8.6$ Hz), 7.36 (1H, dd, $J = 8.0, 5.5$ Hz). MS m/z : 506 ($\text{M}-\text{C}_2\text{H}_4+\text{H}$) $^+$.
BX3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.02 (9H, m), 0.95–1.02 (2H, m), 1.56 (9H, s), 2.18–2.28 (1H, m), 2.69–2.80 (1H, m), 2.84–2.95 (1H, m), 3.04–3.13 (1H, m), 3.62–3.70 (5H, m), 5.17 (1H, dd, $J = 12.9, 5.5$ Hz), 5.30 (2H, dd, $J = 16.8, 9.4$ Hz), 6.51–6.55 (1H, m), 6.54 (1H, d, $J = 8.6$ Hz), 7.63 (1H, s).
BX4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.36–1.45 (1H, m), 1.50 (9H, s), 1.85–1.94 (2H, m), 2.03–2.09 (1H, m), 2.21–2.31 (1H, m), 2.69–3.09 (5H, m), 3.62 (3H, d, $J = 2.0$ Hz), 3.83–3.93 (2H, m), 4.04–4.13 (2H, m), 5.14–5.23 (1H, m), 6.43–6.50 (2H, m), 8.13 (1H, s). MS m/z : 420 ($\text{M}-\text{tBu}+\text{H}$) $^+$.
BX5	MS m/z : 376 ($\text{M}+\text{H}$) $^+$.
BX6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.97 (6H, s), 1.19 (3H, s), 1.39–1.68 (5H, m), 1.69–2.01 (4H, m), 2.04–2.64 (12H, m), 2.66–3.05 (5H, m), 3.20–3.35 (1H, m), 3.43–3.66 (7H, m), 3.69–3.79 (2H, m), 3.81 (3H, s), 3.96–4.11 (1H, m), 4.53–4.69 (1H, m), 5.14–5.24 (1H, m), 6.00 (1H, s), 6.44–6.53 (2H, m), 6.83 (2H, d, $J = 9.0$ Hz), 6.86–6.93 (2H, m), 7.09–7.16 (3H, m), 8.00 (1H, s). MS m/z : 977 ($\text{M}+\text{H}$) $^+$.
BY1	$^1\text{H-NMR}$ (CDCl_3) δ : 3.48–3.50 (4H, m), 4.33 (2H, br s), 6.69 (2H, s).
BY2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.87–2.01 (1H, m), 2.59–2.84 (4H, m), 3.46–3.60 (3H, m), 4.49 (1H, br s), 4.78–4.84 (1H, m), 5.57 (1H, br s), 6.82 (1H, d, $J = 8.6$ Hz), 7.20 (1H, d, $J = 8.6$ Hz), 7.90 (1H, br s). MS m/z : 444 [$\text{M}(^{79}\text{Br}^{79}\text{Br})+\text{H}$] $^+$, 446 [$\text{M}(^{79}\text{Br}^{81}\text{Br})+\text{H}$] $^+$, 448 [$\text{M}(^{81}\text{Br}^{81}\text{Br})+\text{H}$] $^+$.

[0927]

[Table 53]

Ex	Data
BY3	$^1\text{H-NMR}$ (CDCl_3) δ : -0.02 (9H, s), 0.88-0.97 (2H, m), 1.81-1.97 (1H, m), 2.61-2.98 (4H, m), 3.50-3.62 (5H, m), 4.51 (1H, br s), 4.79-4.85 (1H, m), 5.12 (1H, d, J = 9.8 Hz), 5.23 (1H, d, J = 9.8 Hz), 5.70 (1H, br s), 6.84 (1H, d, J = 8.6 Hz), 7.22 (1H, d, J = 8.6 Hz). MS m/z : 547 $[\text{M}(^{79}\text{Br}^{79}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$, 549 $[\text{M}(^{79}\text{Br}^{81}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$, 551 $[\text{M}(^{81}\text{Br}^{81}\text{Br})-\text{C}_2\text{H}_4+\text{H}]^+$.
BY4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92-0.97 (2H, m), 2.20-2.27 (1H, m), 2.58-2.71 (1H, m), 2.82-2.93 (1H, m), 3.01-3.08 (1H, m), 3.58-3.66 (4H, m), 3.99-4.03 (2H, m), 4.34 (1H, br s), 5.18 (1H, dd, J = 13.2, 5.2 Hz), 5.25 (1H, d, J = 9.8 Hz), 5.30 (1H, d, J = 9.8 Hz), 6.17 (1H, d, J = 8.6 Hz), 7.03 (1H, d, J = 8.6 Hz). MS m/z : 517 $[\text{M}(^{79}\text{Br})+\text{Na}]^+$, 519 $[\text{M}(^{81}\text{Br})+\text{Na}]^+$.
BY5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.93-0.99 (2H, m), 2.24-2.32 (1H, m), 2.62-2.75 (1H, m), 2.85-2.96 (1H, m), 3.03-3.11 (1H, m), 3.59-3.71 (4H, m), 4.00-4.07 (2H, m), 5.19-5.34 (3H, m), 6.30 (1H, d, J = 8.6 Hz), 6.71 (1H, s), 7.42 (2H, s), 7.83 (1H, d, J = 8.6 Hz). MS m/z : 611 $(\text{M}-\text{C}_2\text{H}_4+\text{H})^+$.
BY6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 0.93-0.98 (2H, m), 1.15 (3H, s), 1.35-1.64 (4H, m), 1.69-1.77 (1H, m), 1.82-1.92 (3H, m), 1.96-2.51 (16H, m), 2.59-2.73 (1H, m), 2.83-2.94 (1H, m), 3.02-3.08 (1H, m), 3.41-3.76 (12H, m), 3.78 (3H, s), 3.98-4.02 (2H, m), 5.20 (1H, dd, J = 13.2, 5.2 Hz), 5.26 (1H, d, J = 9.8 Hz), 5.31 (1H, d, J = 9.8 Hz), 5.44 (1H, s), 6.09-6.13 (1H, m), 6.20 (1H, d, J = 8.0 Hz), 6.80 (2H, d, J = 8.5 Hz), 6.88 (1H, d, J = 8.0 Hz), 7.08-7.13 (4H, m), 7.26 (2H, d, J = 8.5 Hz). MS m/z : 1098 $(\text{M}+\text{H})^+$.
BY7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.36-1.65 (4H, m), 1.69-1.78 (1H, m), 1.82-2.14 (6H, m), 2.24-2.53 (13H, m), 2.61-2.74 (1H, m), 2.78-2.99 (2H, m), 3.43-3.76 (10H, m), 3.78 (3H, s), 3.98-4.04 (2H, m), 5.20 (1H, dd, J = 12.8, 5.5 Hz), 5.47 (1H, s), 6.09-6.11 (1H, m), 6.22 (1H, d, J = 8.5 Hz), 6.80 (2H, d, J = 8.5 Hz), 6.89 (1H, d, J = 8.5 Hz), 7.08-7.12 (4H, m), 7.25-7.27 (2H, m), 8.19 (1H, s). MS m/z : 968 $(\text{M}+\text{H})^+$.
BZ1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.44-1.64 (11H, m), 1.69-1.92 (3H, m), 2.04-2.19 (3H, m), 2.23-2.55 (9H, m), 3.42-3.52 (2H, m), 3.65-3.75 (2H, m), 3.78 (3H, s), 6.08-6.11 (1H, m), 6.79 (2H, d, J = 8.0 Hz), 7.06-7.11 (4H, m), 7.24 (2H, d, J = 8.0 Hz). MS m/z : 658 $(\text{M}+\text{H})^+$.
BZ2	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.92 (3H, s), 1.16 (3H, s), 1.36-1.66 (4H, m), 1.69-1.78 (1H, m), 1.80-1.93 (3H, m), 1.94-2.15 (4H, m), 2.25-2.40 (4H, m), 2.43-2.54 (2H, m), 3.42-3.53 (2H, m), 3.57-3.76 (4H, m), 3.78 (3H, s), 6.09-6.13 (1H, m), 6.80 (2H, d, J = 9.2 Hz), 7.07-7.12 (4H, m), 7.26 (2H, d, J = 8.6 Hz). MS m/z : 588 $(\text{M}+\text{H})^+$.

[0928]

[Table 54]

Ex	Data
BZ3	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.91 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.45–1.64 (4H, m), 1.69–1.77 (1H, m), 1.83–1.91 (1H, m), 1.97–2.18 (5H, m), 2.25–2.52 (6H, m), 3.04 (3H, s), 3.48 (2H, dd, $J = 20.0, 14.0$ Hz), 3.66–3.75 (2H, m), 3.78 (3H, s), 4.19 (2H, d, $J = 6.1$ Hz), 6.05–6.09 (1H, m), 6.80 (2H, d, $J = 9.1$ Hz), 7.08–7.11 (4H, m), 7.25 (2H, d, $J = 8.5$ Hz).
BZ4	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.34–1.65 (4H, m), 1.47 (9H, s), 1.68–1.78 (1H, m), 1.82–1.92 (3H, m), 1.95–2.02 (1H, m), 2.04–2.14 (2H, m), 2.25–2.48 (12H, m), 3.41–3.49 (6H, m), 3.66–3.76 (2H, m), 3.78 (3H, s), 6.08–6.12 (1H, m), 6.80 (2H, d, $J = 8.8$ Hz), 7.08 (2H, d, $J = 7.9$ Hz), 7.10 (2H, d, $J = 8.8$ Hz), 7.26 (2H, d, $J = 7.9$ Hz).
BZ5	MS m/z : 656 ($\text{M}+\text{H}$) $^+$.
BZ6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 0.94–0.99 (2H, m), 1.16 (3H, s), 1.39–1.64 (4H, m), 1.69–1.78 (1H, m), 1.84–1.91 (3H, m), 1.97–2.48 (16H, m), 2.60–2.72 (1H, m), 2.83–2.94 (1H, m), 3.02–3.09 (1H, m), 3.41–3.75 (12H, m), 3.78 (3H, s), 3.98–4.03 (2H, m), 5.20 (1H, dd, $J = 13.2, 5.2$ Hz), 5.27 (1H, d, $J = 9.8$ Hz), 5.31 (1H, d, $J = 9.8$ Hz), 5.45 (1H, s), 6.08–6.12 (1H, m), 6.19 (1H, d, $J = 8.0$ Hz), 6.79–6.81 (2H, m), 6.87 (1H, d, $J = 8.0$ Hz), 7.07–7.12 (4H, m), 7.24–7.28 (2H, m). MS m/z : 1098 ($\text{M}+\text{H}$) $^+$.
BZ7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.41–1.64 (4H, m), 1.70–1.77 (1H, m), 1.84–2.13 (6H, m), 2.25–2.48 (13H, m), 2.62–2.74 (1H, m), 2.79–3.00 (2H, m), 3.42–3.75 (10H, m), 3.78 (3H, s), 3.98–4.03 (2H, m), 5.20 (1H, dd, $J = 13.2, 5.2$ Hz), 5.46 (1H, s), 6.08–6.11 (1H, m), 6.22 (1H, d, $J = 8.0$ Hz), 6.78–6.81 (2H, m), 6.89 (1H, d, $J = 8.0$ Hz), 7.07–7.11 (4H, m), 7.24–7.27 (2H, m), 8.03 (1H, s). MS m/z : 968 ($\text{M}+\text{H}$) $^+$.
CA1	$^1\text{H-NMR}$ (CDCl_3) δ : 0.69 (3H, s), 0.91–0.95 (6H, m), 1.19 (3H, s), 1.33–1.86 (13H, m), 1.88–2.00 (1H, m), 2.04–2.42 (12H, m), 2.63–2.99 (3H, m), 3.05–3.17 (2H, m), 3.37–3.55 (5H, m), 3.73–3.84 (5H, m), 3.98–4.09 (2H, m), 5.13–5.21 (1H, m), 6.30–6.38 (3H, m), 6.62 (1H, d, $J = 7.9$ Hz), 6.87 (2H, d, $J = 9.1$ Hz), 7.12 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.24–7.29 (3H, m), 7.99 (1H, s). MS m/z : 958 ($\text{M}+\text{H}$) $^+$.
CB1	$^1\text{H-NMR}$ (CDCl_3) δ : 3.54–3.63 (2H, m), 3.75–3.82 (2H, m), 6.77 (1H, t, $J = 7.9$ Hz), 6.94 (1H, br s), 8.34–8.40 (2H, m), 9.07 (1H, br s). MS m/z : 208 ($\text{M}+\text{H}$) $^+$.
CB2	$^1\text{H-NMR}$ (CDCl_3) δ : 1.33–1.49 (9H, m), 3.44–3.66 (2H, m), 3.66–3.84 (2H, m), 4.43–4.73 (2H, m), 6.59–6.80 (1H, m), 7.22–7.46 (2H, m), 7.93–8.27 (2H, m). MS m/z : 238 ($\text{M}+\text{tBu}+\text{H}$) $^+$.

[0929]

[Table 55]

Ex	Data
CB3	$^1\text{H-NMR}$ (CDCl_3) δ : 1.35–1.55 (9H, m), 3.73–3.96 (2H, m), 3.96–4.18 (2H, m), 4.63–4.99 (2H, m), 6.78–7.10 (3H, m), 8.86–9.33 (1H, m). MS m/z : 234 (M-tBu+H) ⁺ .
CB4	$^1\text{H-NMR}$ (CDCl_3) δ : 1.39–1.57 (9H, m), 3.77–3.93 (2H, m), 4.01–4.19 (2H, m), 4.78–4.91 (2H, m), 6.68–6.79 (1H, m), 7.49–7.58 (1H, m), 9.39–9.68 (1H, br m). MS m/z : 360 (M-tBu+H) ⁺ .
CB5	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.91–0.99 (2H, m), 1.44–1.52 (9H, m), 2.15–2.27 (1H, m), 2.59–2.79 (1H, m), 2.80–2.95 (1H, m), 3.00–3.11 (1H, m), 3.58–3.70 (2H, m), 3.79–3.94 (2H, m), 4.07–4.21 (2H, m), 4.70–4.97 (2H, m), 5.13–5.23 (1H, m), 5.27 (2H, q, $J = 9.1$ Hz), 6.41 (1H, d, $J = 8.5$ Hz), 7.52 (1H, t, $J = 8.8$ Hz). MS m/z : 679 (M+Na) ⁺ .
CB6	$^1\text{H-NMR}$ (CDCl_3) δ : 0.01 (9H, s), 0.91–0.99 (2H, m), 1.35–1.51 (9H, m), 2.13–2.32 (1H, m), 2.63–2.96 (2H, m), 3.00–3.14 (1H, m), 3.56–3.74 (2H, m), 3.78–3.98 (2H, m), 4.05–4.23 (2H, m), 5.17–5.37 (5H, m), 6.81–6.87 (1H, m), 7.50–7.59 (1H, m), 10.07 (1H, d, $J = 11.0$ Hz). MS m/z : 581 (M+Na) ⁺ .
CB7	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.92–1.00 (2H, m), 1.40–1.51 (9H, m), 2.15–2.28 (1H, m), 2.30–2.44 (4H, m), 2.64–2.81 (1H, m), 2.81–2.95 (1H, m), 3.00–3.13 (1H, m), 3.37–3.73 (8H, m), 3.77–3.97 (2H, m), 4.05–4.22 (2H, m), 4.75–5.04 (2H, m), 5.13 (2H, s), 5.16–5.25 (1H, m), 5.29 (2H, q, $J = 8.7$ Hz), 6.54–6.62 (1H, m), 6.82–6.93 (1H, m), 7.29–7.38 (5H, m). MS m/z : 763 (M+H) ⁺ .
CB8	MS m/z : 629 (M+H) ⁺ .
CB9	$^1\text{H-NMR}$ (CDCl_3) δ : 0.00 (9H, s), 0.65 (3H, s), 0.90–1.02 (2H, m), 0.94 (6H, s), 1.16 (3H, s), 1.38–1.78 (13H, m), 1.80–1.99 (3H, m), 2.02–2.15 (2H, m), 2.16–2.62 (12H, m), 2.64–2.95 (3H, m), 3.00–3.12 (1H, m), 3.38–3.81 (12H, m), 3.78 (3H, s), 3.81–4.01 (2H, m), 4.07–4.23 (2H, m), 4.81–5.06 (2H, m), 5.17–5.25 (1H, m), 5.29 (2H, dd, $J = 16.4, 9.7$ Hz), 5.92–5.99 (1H, m), 6.56–6.65 (1H, m), 6.79 (2H, d, $J = 9.1$ Hz), 6.82–6.94 (3H, m), 7.03–7.13 (3H, m). MS m/z : 1230 (M+H) ⁺ .
CB10	$^1\text{H-NMR}$ (CDCl_3) δ : 0.65 (3H, s), 0.94 (6H, s), 1.16 (3H, s), 1.40–1.80 (4H, m), 1.80–2.00 (3H, m), 2.02–2.17 (2H, m), 2.17–2.66 (15H, m), 2.66–2.91 (3H, m), 2.91–3.06 (1H, m), 3.06–3.24 (2H, m), 3.35–3.86 (13H, m), 4.01–4.10 (2H, m), 4.17–4.33 (2H, m), 5.20 (1H, dd, $J = 12.5, 5.2$ Hz), 5.90–5.99 (1H, m), 6.61 (1H, d, $J = 7.9$ Hz), 6.79 (2H, d, $J = 9.1$ Hz), 6.82–6.95 (3H, m), 7.04–7.17 (3H, m), 7.93–8.28 (1H, m). MS m/z : 1014 (M+H) ⁺ .

[0930]

[Table 56]

Ex	Data
CC1	¹ H-NMR (CDCl ₃) δ : -0.02 (9H, s), 0.89-0.98 (2H, m), 2.00-2.12 (2H, m), 2.15-2.26 (1H, m), 2.63 (1H, ddd, J = 26.6, 13.2, 4.7 Hz), 2.79-2.93 (3H, m), 3.04 (1H, dt, J = 17.2, 3.6 Hz), 3.62 (2H, t, J = 8.5 Hz), 3.83 (2H, t, J = 5.8 Hz), 5.16 (1H, dd, J = 13.4, 5.5 Hz), 5.26 (2H, q, J = 8.9 Hz), 6.47 (1H, d, J = 7.9 Hz), 6.63 (1H, d, J = 8.5 Hz), 7.07-7.13 (1H, m), 7.58-7.65 (1H, m), 7.70-7.81 (1H, m), 7.91 (1H, d, J = 7.9 Hz).
CC2	¹ H-NMR (CDCl ₃) δ : 0.00 (9H, s), 0.90-1.00 (2H, m), 1.39-1.54 (2H, m), 1.49 (9H, s), 2.07-2.34 (5H, m), 2.53-2.74 (3H, m), 2.78-2.95 (2H, m), 2.98-3.09 (1H, m), 3.59-3.69 (2H, m), 3.69-3.92 (6H, m), 3.98-4.08 (1H, m), 4.12-4.20 (1H, m), 4.54-4.75 (1H, m), 5.12-5.22 (1H, m), 5.28 (2H, dd, J = 17.0, 9.7 Hz), 6.42 (1H, d, J = 8.5 Hz), 6.48 (1H, d, J = 8.5 Hz). MS m/z: 678 (M+Na) ⁺ .
CC3	¹ H-NMR (CDCl ₃) δ : 0.65 (3H, s), 0.91-0.97 (6H, s), 1.16 (3H, s), 1.39-1.80 (10H, m), 1.80-3.04 (20H, m), 3.40-3.54 (2H, m), 3.62-3.89 (9H, m), 3.92-4.04 (2H, m), 4.04-4.12 (1H, m), 4.65-4.84 (2H, m), 5.13-5.24 (1H, m), 5.88-6.00 (1H, m), 6.46 (1H, d, J = 8.5 Hz), 6.50-6.54 (1H, m), 6.79 (2H, d, J = 9.1 Hz), 6.83-6.91 (2H, m), 7.02-7.15 (3H, m), 8.01 (1H, br s). MS m/z: 1027 (M+H) ⁺ .
CD1	¹ H-NMR (CDCl ₃) δ : 1.34-1.51 (1H, m), 1.48 (9H, s), 1.56-1.66 (1H, m), 2.02-2.11 (2H, m), 2.17-2.25 (1H, m), 2.68-3.02 (5H, m), 3.39-3.48 (1H, m), 3.54-3.66 (1H, m), 3.75 (3H, s), 3.97-4.10 (2H, m), 5.13-5.21 (1H, m), 6.33 (1H, d, J = 7.8 Hz), 6.52 (1H, d, J = 7.8 Hz), 6.94 (1H, t, J = 8.0 Hz), 8.05-8.23 (1H, m).
CD2	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.95 (3H, s), 0.95 (3H, s), 1.17 (3H, s), 1.39-1.78 (6H, m), 1.83-2.64 (15H, m), 2.69-3.02 (5H, m), 3.20-3.34 (1H, m), 3.43-3.65 (4H, m), 3.66-3.80 (8H, m), 3.95-4.07 (1H, m), 4.50-4.63 (1H, m), 5.11-5.25 (1H, m), 5.94-6.00 (1H, m), 6.32-6.40 (1H, m), 6.55 (1H, d, J = 8.6 Hz), 6.80 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.4 Hz), 6.96 (1H, t, J = 8.0 Hz), 7.04-7.15 (3H, m), 8.03 (1H, s). MS m/z: 959 (M+H) ⁺ .
CE1	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.37-1.64 (4H, m), 1.69-1.77 (1H, m), 1.83-2.14 (6H, m), 2.24-2.51 (13H, m), 2.61-2.73 (1H, m), 2.78-2.99 (2H, m), 3.42-3.75 (10H, m), 3.78 (3H, s), 3.96-4.04 (2H, m), 5.20 (1H, dd, J = 12.8, 5.5 Hz), 5.46 (1H, s), 6.08-6.11 (1H, m), 6.22 (1H, d, J = 8.5 Hz), 6.79-6.81 (2H, m), 6.89 (1H, d, J = 8.5 Hz), 7.07-7.11 (4H, m), 7.25-7.27 (2H, m), 8.15 (1H, s). MS m/z: 968 (M+H) ⁺ .

[0931]

[Table 57]

Ex	Data
CF1	¹ H-NMR (CDCl ₃) δ : 0.66 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 1.16 (3H, s), 1.36-1.64 (4H, m), 1.69-1.77 (1H, m), 1.82-2.13 (6H, m), 2.25-2.51 (13H, m), 2.61-2.73 (1H, m), 2.79-2.99 (2H, m), 3.42-3.75 (10H, m), 3.78 (3H, s), 3.96-4.05 (2H, m), 5.20 (1H, dd, J = 12.8, 5.5 Hz), 5.46 (1H, s), 6.08-6.12 (1H, m), 6.22 (1H, d, J = 8.5 Hz), 6.79-6.81 (2H, m), 6.89 (1H, d, J = 8.5 Hz), 7.08-7.11 (4H, m), 7.25-7.27 (2H, m), 8.11 (1H, s). MS m/z: 968 (M+H) ⁺ .
CG1	¹ H-NMR (CDCl ₃) δ : 0.65 (3H, s), 0.93 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.30-1.43 (2H, m), 1.45-1.65 (2H, m), 1.67-1.76 (1H, m), 1.82-2.02 (3H, m), 2.03-2.74 (17H, m), 2.77-2.99 (4H, m), 3.12-3.31 (2H, m), 3.41-3.58 (3H, m), 3.65-3.76 (3H, m), 3.78 (3H, s), 3.80-3.89 (2H, m), 3.92-4.05 (1H, m), 4.52-4.63 (1H, m), 5.13-5.24 (1H, m), 5.96 (1H, d, J = 4.4 Hz), 6.36 (1H, d, J = 8.5 Hz), 6.53 (1H, d, J = 8.5 Hz), 6.76-6.89 (4H, m), 7.05-7.13 (3H, m), 8.04 (1H, s). MS m/z: 985 (M+H) ⁺ .
CH1	¹ H-NMR (CDCl ₃) δ : 0.65 (3H, s), 0.94 (6H, s), 1.16 (3H, s), 1.31-1.45 (2H, m), 1.45-1.67 (2H, m), 1.67-1.77 (1H, m), 1.82-2.01 (3H, m), 2.04-2.74 (17H, m), 2.77-2.99 (4H, m), 3.12-3.30 (2H, m), 3.40-3.57 (3H, m), 3.65-3.76 (3H, m), 3.78 (3H, s), 3.81-3.89 (2H, m), 3.92-4.04 (1H, m), 4.52-4.63 (1H, m), 5.14-5.24 (1H, m), 5.96 (1H, d, J = 4.4 Hz), 6.36 (1H, d, J = 8.5 Hz), 6.53 (1H, d, J = 8.5 Hz), 6.76-6.89 (4H, m), 7.05-7.13 (3H, m), 8.04 (1H, s). MS m/z: 985 (M+H) ⁺ .

[0932]

5 The structural formulas of the compounds described in the Examples are shown below in Table 58 to Table 92.

 In the Tables, Ex indicates the Example number and Structure indicates the structural formula.

 The following symbols may be used in the structural
10 formulas.

Bn: benzyl group

Boc: tert-butoxycarbonyl group

Cbz: benzyloxycarbonyl group

Et: ethyl group

15 tBu: tert-butyl group

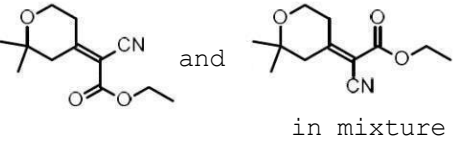
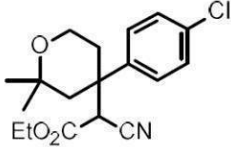
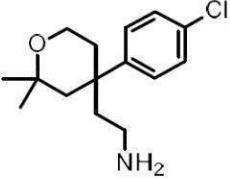
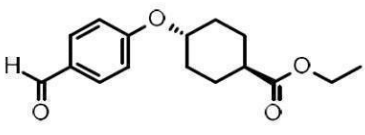
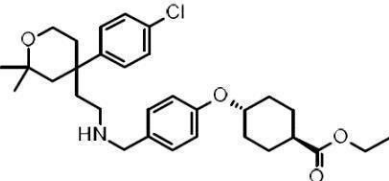
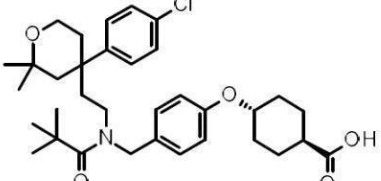
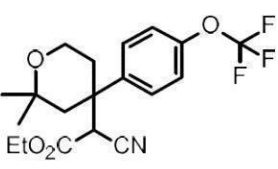
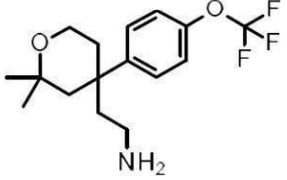
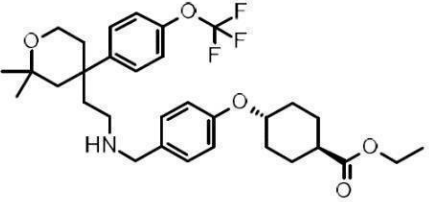
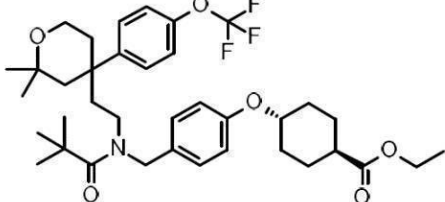
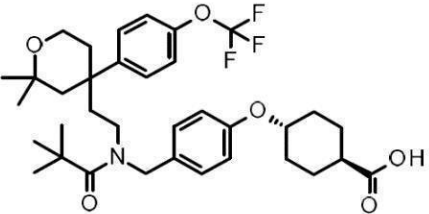
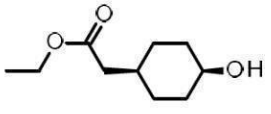
Ms: methanesulfonyl group

Ns: 2-nitrobenzenesulfonyl group

SEM: 2-(trimethylsilyl)ethoxymethyl group

[0933]

[Table 58]

Ex	Structure	Ex	Structure
A1	 in mixture	A2	
A3		A4	
A5		A6	
B1		B2	
B3		B4	
B5		C1	

[0934]

[Table 59]

Ex	Structure	Ex	Structure
C2		C3	
C4		C5	
C6		C7	
C8		D1	
D2		D3	
E1		E2	

[0935]

[Table 60]

Ex	Structure	Ex	Structure
F1		F2	
F3		F4	
G1		G2	
G3		H1	
I1		I2	

[0936]

[Table 61]

Ex	Structure	Ex	Structure
J1		J2	
J3		J4	
K1		K2	
K3		K4	
K5		L1	
L2		M1	

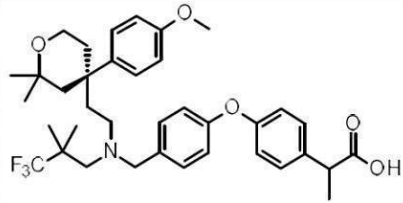
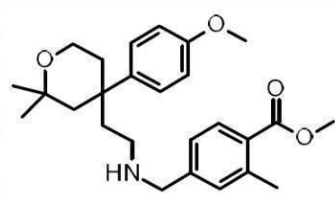
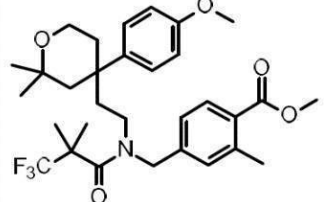
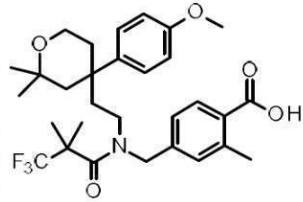
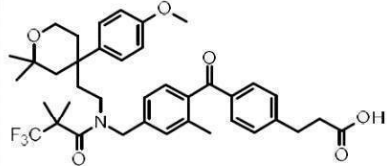
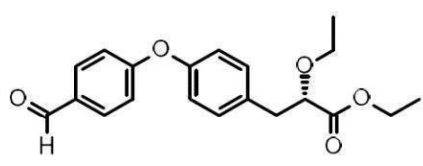
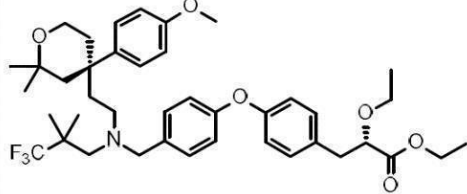
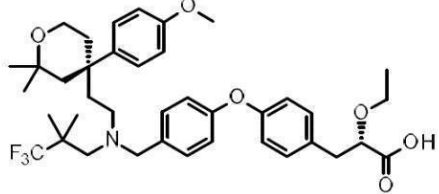
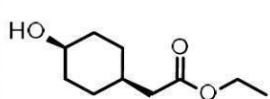
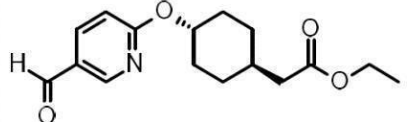
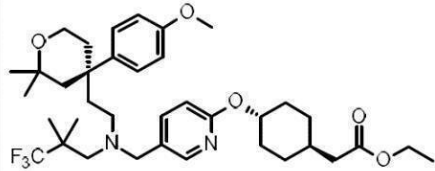
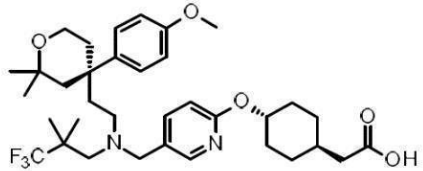
[0937]

[Table 62]

Ex	Structure	Ex	Structure
M2		M3	
M4		M5	
N1		N2	
O1		O2	
P1		P2	

[0938]

[Table 63]

Ex	Structure	Ex	Structure
P3		Q1	
Q2		Q3	
Q4		R1	
R2		R3	
S1		S2	
S3		S4	

[0939]

[Table 64]

Ex	Structure	Ex	Structure
T1		T2	
U1		U2	
U3		U4	
U5		U6	
U7		U8	
U9		U10	

[0940]

[Table 65]

Ex	Structure	Ex	Structure
U11		V1	
V2		V3	
V4		V5	
W1		W2	
W3		W4	

[0941]

[Table 66]

Ex	Structure	Ex	Structure
W5		X1	
X2		Y1	
Y2		Y3	
Y4		Y5	
Y6		Z1	
Z2		Z3	

[0942]

[Table 67]

Ex	Structure	Ex	Structure
Z4		Z5	
Z6		Z7	
Z8		AA1	
AA2		AA3	
AA4		AB1	
AB2		AB3	

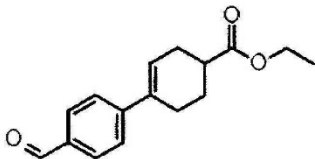
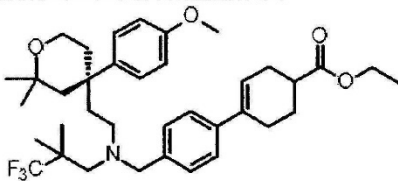
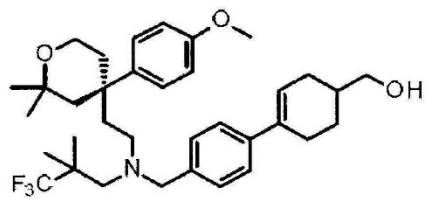
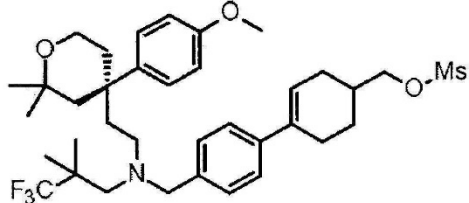
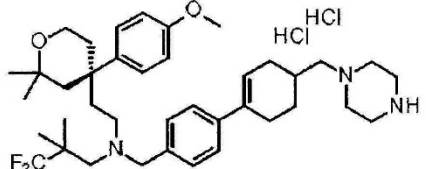
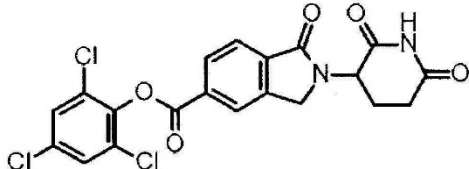
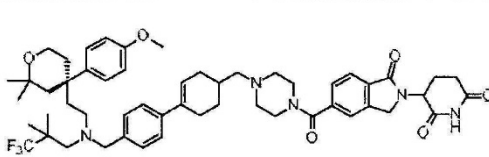
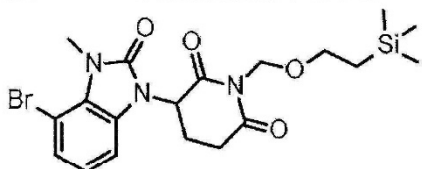
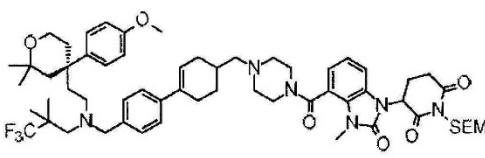
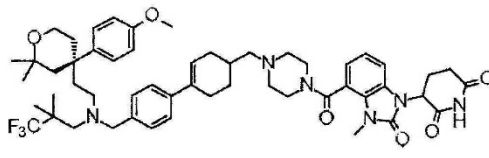
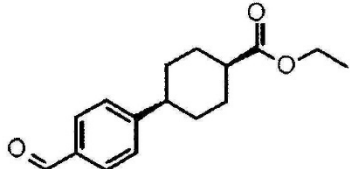
[0943]

[Table 68]

Ex	Structure	Ex	Structure
AB4		AB5	
AB6		AC1	
AC2		AC3	
AC4		AC5	
AC6		AD1	
AE1		AF1	

[0944]

[Table 69]

Ex	Structure	Ex	Structure
AG1		AG2	
AG3		AG4	
AG5		AG6	
AG7		AH1	
AH2		AH3	
AH4		AI1	

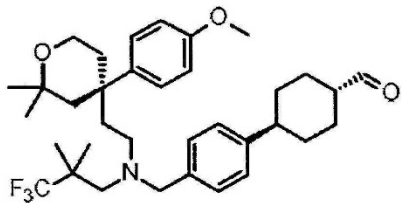
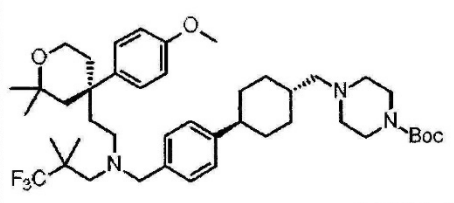
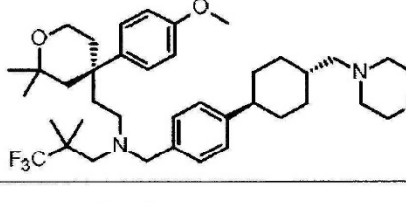
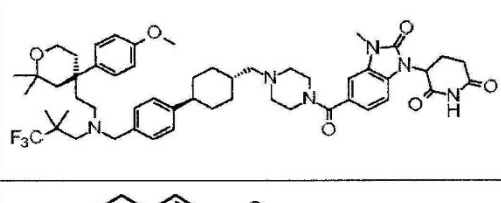
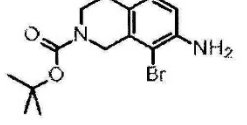
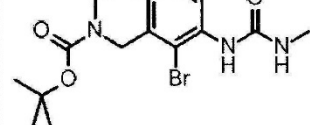
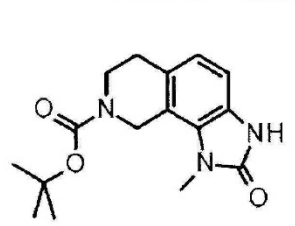
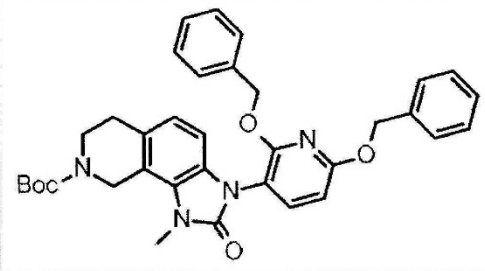
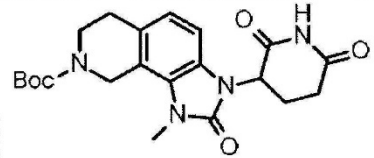
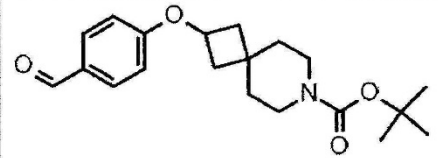
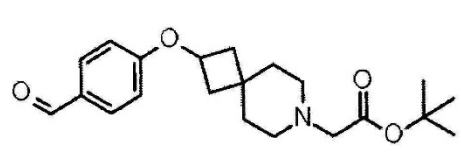
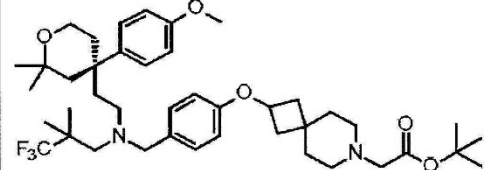
[0945]

[Table 70]

Ex	Structure	Ex	Structure
AI2		AI3	
AI4		AI5	
AI6		AI7	
AI8		AI9	
AI10		AI11	
AJ1		AJ2	

[0946]

[Table 71]

Ex	Structure	Ex	Structure
AJ3		AJ4	
AJ5		AJ6	
AK1		AK2	
AK3		AK4	
AK5		AK6	
AK7		AK8	

[Table 72]

Ex	Structure	Ex	Structure
AK9		AK10	
AL1		AL2	
AL3		AL4	
AM1		AM2	
AM3		AM4	

[0948]

[Table 73]

Ex	Structure	Ex	Structure
AM5		AM6	
AM7		AM8	
AM9		AM10	
AN1		AN2	
AN3		AN4	

[0949]

[Table 74]

Ex	Structure	Ex	Structure
AN5		A01	
A02		A03	
A04		A05	
A06		A07	
AP1		AP2	
AP3		AP4	

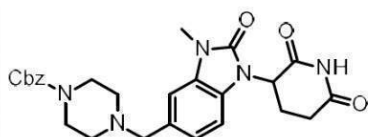
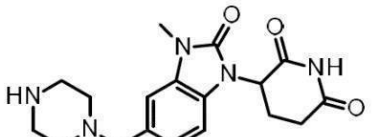
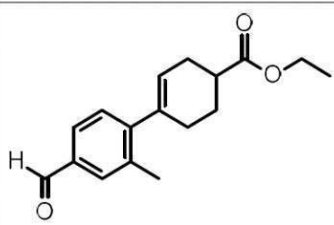
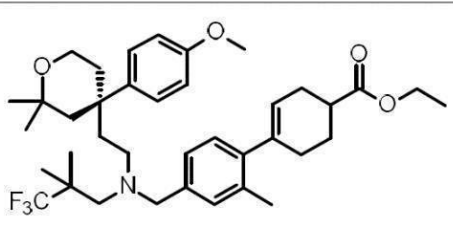
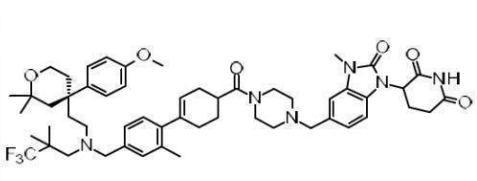
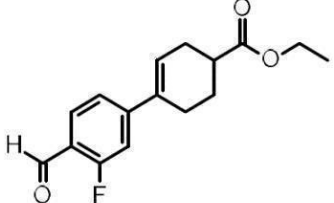
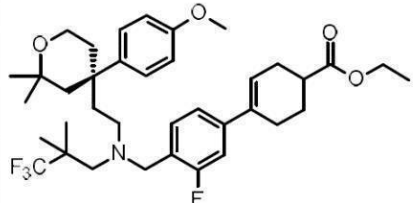
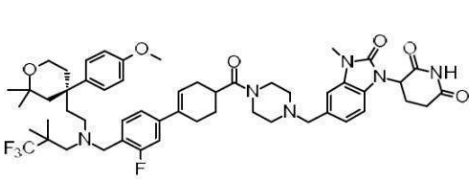
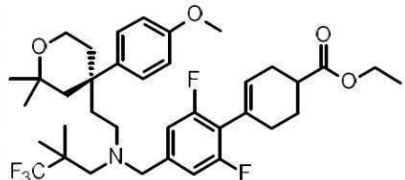
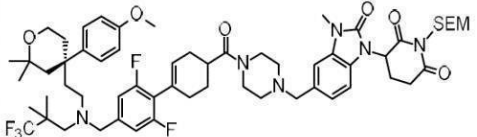
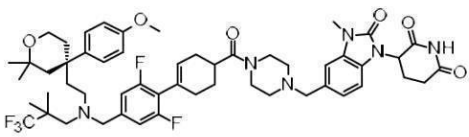
[0950]

[Table 75]

Ex	Structure	Ex	Structure
AP5		AP6	
AQ1		AR1	
AR2		AR3	
AR4		AR5	
AR6		AR7	
AS1		AS2	

[0951]

[Table 76]

Ex	Structure	Ex	Structure
AS3		AS4	
AS5		AS6	
AS7		AT1	
AT2		AT3	
AU1		AU2	
AU3		AU4	

[0952]

[Table 77]

Ex	Structure	Ex	Structure
AV1		AV2	
AW1		AW2	
AW3		AW4	
AW5		AX1	
AX2		AX3	

[0953]

[Table 78]

Ex	Structure	Ex	Structure
AY1		AY2	
AY3		AY4	
AY5		AY6	
AY7		AY8	
AZ1		AZ2	

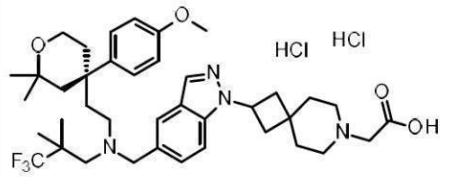
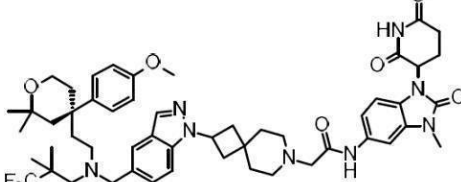
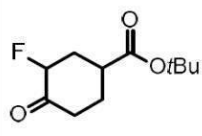
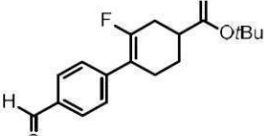
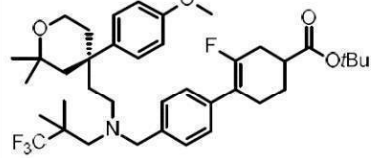
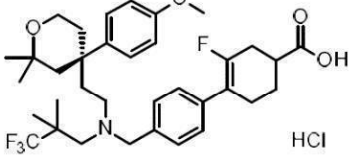
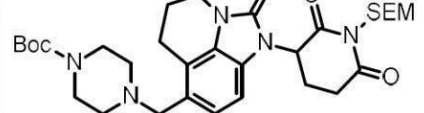
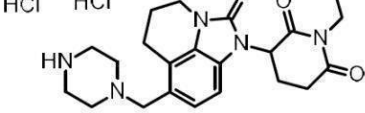
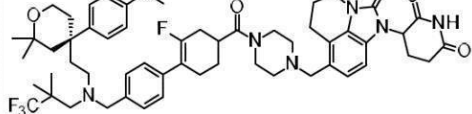
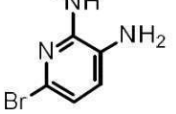
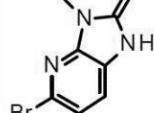
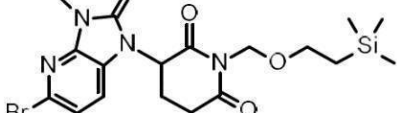
[0954]

[Table 79]

Ex	Structure	Ex	Structure
AZ3		AZ4	
AZ5		AZ6	
AZ7		AZ8	
BA1		BA2	
BA3		BA4	

[0955]

[Table 80]

Ex	Structure	Ex	Structure
BA5		BA6	
BB1		BB2	
BB3		BB4	
BB5		BB6	
BB7		BC1	
BC2		BC3	

[0956]

[Table 81]

Ex	Structure	Ex	Structure
BC4		BC5	
BC6		BD1	
BD2		BD3	
BD4		BD5	
BD6		BE1	
BE2		BE3	

[0957]

[Table 82]

Ex	Structure	Ex	Structure
BE4		BE5	
BF1		BF2	
BF3		BF4	
BF5		BF6	
BG1		BG2	
BG3		BG4	

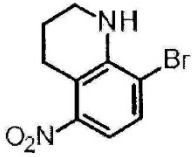
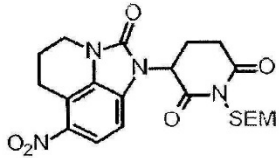
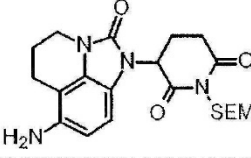
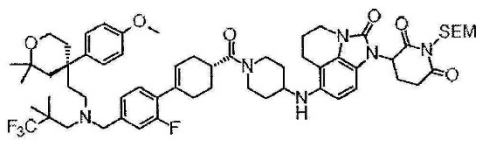
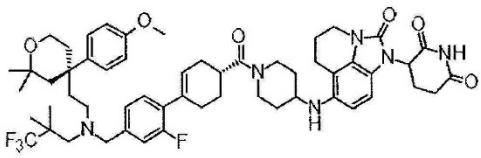
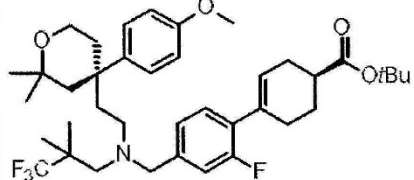
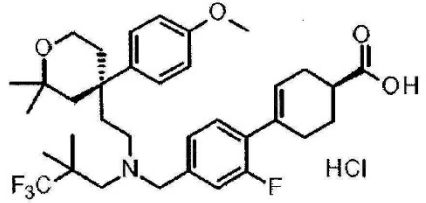
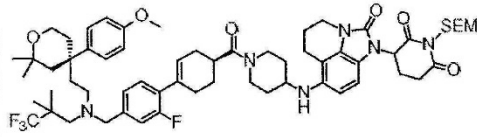
[0958]

[Table 83]

Ex	Structure	Ex	Structure
BG5		BH1	
BH2		BH3	
BH4		BH5	
BI1		BI2	
BJ1		BJ2	
BJ3		BJ4	
BJ5		BJ6	

[0959]

[Table 84]

Ex	Structure	Ex	Structure
BK1		BK2	
BK3		BK4	
BK5		BK6	
BK7		BK8	
BK9		BL1	
BL2		BL3	

[0960]

[Table 85]

Ex	Structure	Ex	Structure
BL4		BM1	
BM2		BM3	
BM4		BM5	
BM6		BM7	
BM8		BM9	
BM10		BN1	
BN2		B01	

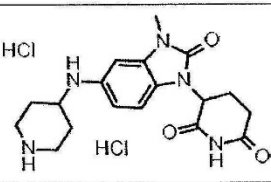
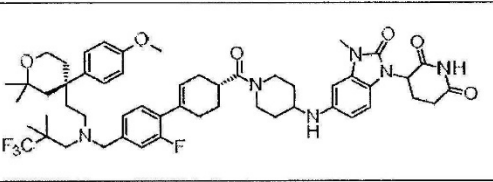
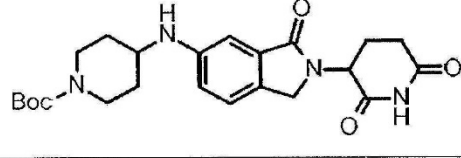
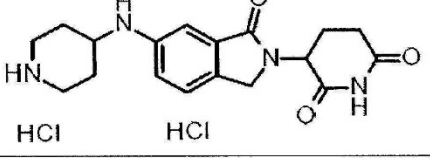
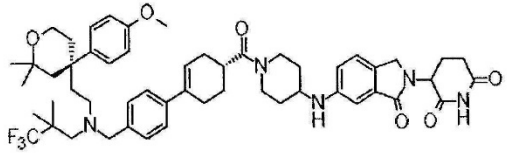
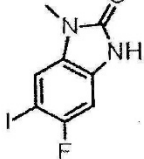
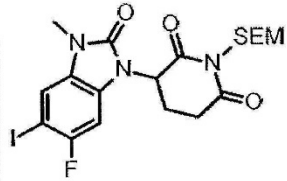
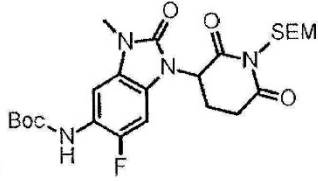
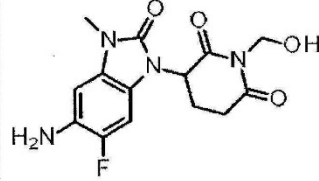
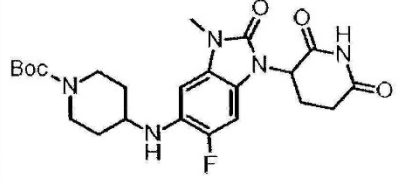
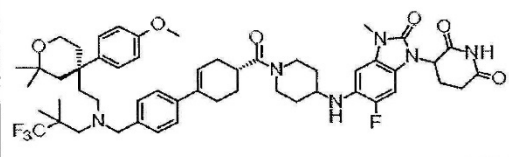
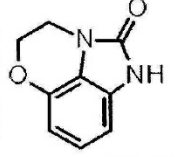
[0961]

[Table 86]

Ex	Structure	Ex	Structure
B02		B03	
B04		BP1	
BP2		BP3	
BP4		BP5	
BP6		BQ1	
BQ2		BQ3	
BQ4		BR1	

[0962]

[Table 87]

Ex	Structure	Ex	Structure
BR2		BR3	
BS1		BS2	
BS3		BT1	
BT2		BT3	
BT4		BT5	
BT6		BU1	

[0963]

[Table 88]

Ex	Structure	Ex	Structure
BU2		BU3	
BU4		BU5	
BU6		BV1	
BV2		BV3	
BV4		BV5	
BV6		BV7	
BV8		BV9	

[0964]

[Table 89]

Ex	Structure	Ex	Structure
BV10		BW1	
BW2		BW3	
BX1		BX2	
BX3		BX4	
BX5		BX6	
BY1		BY2	

[0965]

[Table 90]

Ex	Structure	Ex	Structure
BY3		BY4	
BY5		BY6	
BY7		BZ1	
BZ2		BZ3	
BZ4		BZ5	
BZ6		BZ7	

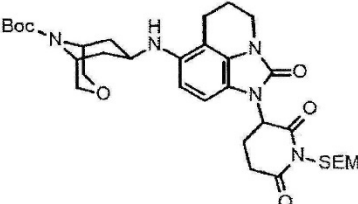
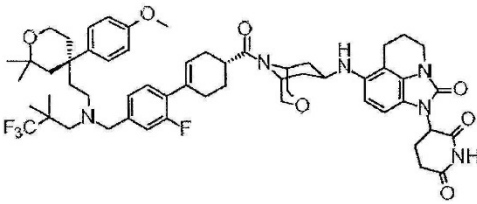
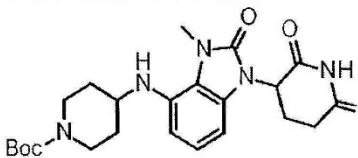
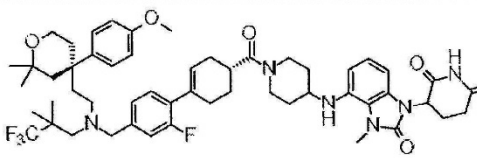
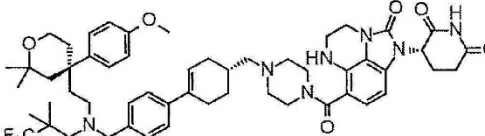
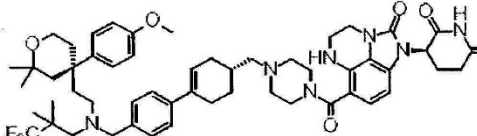
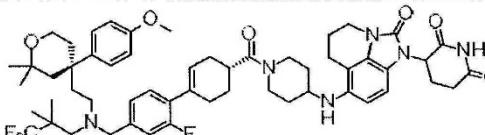
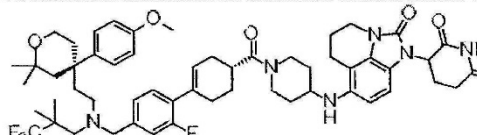
[0966]

[Table 91]

Ex	Structure	Ex	Structure
CA1		CB1	
CB2		CB3	
CB4		CB5	
CB6		CB7	
CB8		CB9	
CB10		CC1	

[0967]

[Table 92]

Ex	Structure	Ex	Structure
CC2		CC3	
CD1		CD2	
CE1		CF1	
CG1		CH1	

[0968]

5 <Experimental Example 1> Evaluation of inhibitory activity of compound against binding of DAX1 to SF1-LBD

The binding activity of each compound to the SF-1 ligand binding domain (LBD) was evaluated using the binding inhibitory activity of each compound against binding of DAX1 to SF1-LBD as an index. 100 nM His-SF1-LBD, 2 nM Biotin-DAX1 peptide (Biotin-MAGENHQWQGSILYNMLMSAKQT-NH₂) and each compound (8-point dilution series with common ratio 2 from final concentration 2 μM) were mixed in assay buffer [25 mM HEPES (pH 7.5), 100 mM NaCl, 0.1% BSA, 0.01% CHAPS, 1 mM DTT] and reacted at room temperature for 30 min. Anti-6xHis AlphaLISA Acceptor beads and Streptavidin-coated AlphaScreen Donor beads were mixed to a final concentrations of 5 μg/ml and 10 μg/ml, respectively, and reacted in the dark at room temperature for 60 min. AlphaLISA signals were detected using a multimode plate reader (EnVision Xcite, PerkinElmer). The binding rate of DAX1 peptide to SF1

was calculated from the luminescence amount (C) of the compound-free group and the luminescence amount (T) of the compound-added group, based on the following formula.

[0969]

5 [Math. 1]

DAX1 peptide binding rate (%) = $100 \times T/C$

[0970]

The DAX1 peptide binding rate at each concentration was analyzed using GraphPad Prism6 (GraphPad Software Inc.) to
10 calculate the concentration (IC₅₀ value) of each compound that inhibits 50% of the binding of DAX1 to SF1-LBD. The IC₅₀ value (unit: nM) of the compound corresponding to each Example number is shown in Table 93.

[0971]

15 [Table 93]

Example No.	cell-free SF1 IC ₅₀
A6	19
B5	20
C8	<16
D3	29
E2	19
F4	31
G3	54
H1	32
I2	47
J4	39
K5	29
L2	32
M5	18
N2	41
O2	36
P3	30
Q4	35
R3	27
S4	22
T2	26
U11	21

[0972]

<Experimental Example 2> Evaluation of changes in SF1 target gene expression for NCI-H295R

5 NCI-H295R cells were cultured in a 5% CO₂ incubator at 37°C using DMEM/F12 medium (Thermo Fisher Scientific Inc.) containing 2.5% Nu-Serum (registered trademark) Growth Medium Supplement (Corning) and 1% Corning ITS+ Premix Universal Culture Supplement (Corning). The DMSO solution of each
10 compound was serially diluted with DMSO using a D300e Digital Dispenser (TECAN), and the compounds were added to a 96-well plate (FALCON). NCI-H295R cells were seeded at 1×10⁴ cells/50 μL/well on the 96-well plate containing the compounds added

thereto, and cultured for 24 hr in a 5% CO₂ incubator at 37°C. The final DMSO concentration in the medium was adjusted to 0.1% (v/v) in all cases, and the concentration range of the compounds was set to 1000 nM to 0.32 nM with a common ratio of 5 times. After the completion of culture, the medium was discarded, 50 µL/well of chilled D-PBS (Sigma Aldrich) was added to wash the cells, and D-PBS was discarded. After washing, 25 µL/well of Cells-to-CT (registered trademark) Bulk Lysis Reagents (Thermo Fisher Scientific, Inc.) was added to the wells, the mixture was stirred for 5 min with a plate mixer, and 2.5 µL/well of the reaction quenching liquid was added to prepare cell lysate. The cell lysate was dispensed into a 96-well plate (Corning) at 10 µL/well, and 40 µL/well of Cells-to-CT Bulk RT Reagents (Thermo Fisher Scientific, Inc.) was added. A reverse transcription reaction was performed at 37°C for 50 min using a thermal cycler, and the reverse transcriptase was inactivated by heating at 95°C for 5 min, and then stored at 10°C. PrimeTime (registered trademark) Gene Expression Master Mix (Integrated DNA Technologies), the target genes CYP11A1, CYP17A1, CYP21A2, or STAR, and the control gene ACTB PrimeTime (registered trademark) qPCR Probe Assays (Integrated DNA Technologies), and Nuclease free water were mixed at a ratio of 20:1:1:10 to prepare a PrimerProbe mix. The prepared PrimerProbe mix was added to a 384-well plate at 8 µL/well, and the cDNA obtained by reverse transcription was added at 2 µL/well. Real-Time PCR was performed under fast cycling conditions (95°C for 3 min, followed by 40 cycles of 95°C for 5 seconds and 62°C for 30 seconds) to measure the fluorescent signal. The obtained data was analyzed using GraphPad Prism9 (GraphPad Software Inc.) to calculate the concentration (IC₅₀ value) that reduces the mRNA expression level by 50%. The IC₅₀ values (unit: nM) for CYP11A1, CYP17A1, CYP21A2, and STAR, of the compounds corresponding to each Example number are shown in Table 94.

[0973]

[Table 94]

Example No.	CYP11A1	CYP17A1	CYP21A2	STAR
A6	102	283	142	159
B5	10	56	17	24
C8	7.8	70	13	26
D3	53	144	78	76
E2	17	189	33	65
F4	14	166	23	69
G3	32	73	42	35
H1	25	80	39	37
I2	29	117	52	55
J4	4.1	70	8.1	14
K5	12	141	28	47
L2	17	238	46	83
M5	2.8	13	4.3	3.9
N2	19	113	30	39
O2	35	211	82	75
P3	4.4	137	9.8	19
Q4	8.5	189	19	44
R3	3.3	28	4.3	6.2
S4	1.2	12	2.2	3.2
T2	1.2	24	2.4	4.1
U11	10	140	24	54
V5	9.8	71	21	18
W5	90	372	138	131
X2	511	1228	581	776

[0974]

<Experimental Example 3> Evaluation of SF1 degradation

5 induction action on human adrenocortical carcinoma cell line
NCI-H295R

Human adrenocortical carcinoma cell line NCI-H295R cells
(ATCC, CRL-2128) were used as hosts, and NCI-H295R SF-1-HiBiT
cells with HiBiT tag knocked in at the endogenous SF1 locus
10 were cultured in a 5% CO₂ incubator at 37°C using DMEM/F12
medium (Thermo Fisher Scientific Inc.) containing 2.5% Nu-Serum
(registered trademark) Growth Medium Supplement (Corning) and
1% Corning ITS+ Premix Universal Culture Supplement (Corning).
NCI-H295R SF-1-HiBiT cells were seeded in a 384-well plate

(Thermo Fisher Scientific Inc.) at 1×10^4 cells/50 μ L/well and cultured at 37°C in a 5% CO₂ incubator for 24 hr. DMSO solutions of each compound were serially diluted with DMSO using a D300e Digital Dispenser (TECAN), added to a 384-well plate, and cultured in a 5% CO₂ incubator at 37°C for 24 hr. The final DMSO concentration in the medium was adjusted to 0.1% (v/v) for all, and the concentration range of the compounds was set to 10000 nM to 4.6 nM or 1000 nM to 0.46 nM with a common ratio of 3. After completion of culture, the medium was discarded, and Nano-Glo (registered trade mark) HiBiT Lytic Detection System (Promega, Cat. No. N3040) was added at 20 μ L/well and stirred with a plate mixer. Luminescence signals were then detected using a multimode plate reader (EnVision Xcite, PerkinElmer). The SF-1 protein degradation rate was calculated from the amount of luminescence (C) in the compound-free group and the amount of luminescence (T) in the compound-added group, based on the following formula.

[0975]

[Math. 2]

SF-1 protein degradation rate (%) = $100 \times (1 - T/C)$

[0976]

The obtained data was analyzed using GraphPad Prism9 (GraphPad Software Inc.) or Genedata Screener (Genedata AG) to calculate the concentration that induces 50% degradation of SF-1 (DC₅₀ value). The HiBiT DC₅₀ values (unit: nM) of the compounds corresponding to each Example number are shown in Table 95 to Table 97.

[0977]

<Experimental Example 4> Evaluation of proliferation inhibitory action on NCI-H295R

NCI-H295R cells were cultured in DMEM/F12 medium (Thermo Fisher Scientific, Inc.) containing 2.5% US Charcoal/Dextran Treated FBS (Hyclone) and 1% Corning ITS+ Premix Universal Culture Supplement (Corning). DMSO solutions of each compound were serially diluted with DMSO using a D300e Digital Dispenser

(TECAN), and added to a 384-well plate (Thermo Fisher Scientific Inc.). NCI-H295R cells were seeded in a 384-well plate at 2×10^3 cells/40 μ L/well and cultured for 7 days in a 37°C, 5% CO₂ incubator. The final concentration of DMSO in the medium was adjusted to 0.1% (v/v) for all, and the concentration range of the compounds was set to 10000 nM to 0.038 nM with a common ratio of 4. On the first day of culture (day 0) and the seventh day of culture (day 7), 10 μ L/well of CellTiter-Glo (registered trademark) 2.0 Assay (Promega) was added, and the luminescence signal was detected using a multimode plate reader (EnVision, PerkinElmer). The cell proliferation rate was calculated from the luminescence amount on the day of compound addition (C0), the luminescence amount of the compound-free group after 7 days of culture (C7), and the luminescence amount of the compound-added group (T7), based on the following formula.

[0978]

[Math. 3]

cell proliferation rate (%) = $100 \times [(T7-C0)/(C7-C0)]$

[0979]

The concentration of each compound that inhibits the proliferation of NCI-H295R cells by 50% (GI₅₀ value) was calculated by a one-log plot of the cell survival rate and compound concentration at each concentration. The H295R GI₅₀ values (unit: nM) of the compounds corresponding to each Example No. are shown in Table 95 to Table 97.

[0980]

[Table 95]

Example No.	HiBiT DC ₅₀	H295R GI ₅₀
Y6	12	199
Z8	10	43
AA4	12	488
AB6	29	165
AC6	26	73
AD1	6.9	47
AE1	8.5	40
AF1	6.9	121
AG7	8.7	147
AH4	5.7	123
AI11	6.2	90
AJ6	5.3	58
AK10	4.9	82
AL4	4.5	83
AM10	7.3	106
AN5	12	92
A07	5.4	39
AP6	4.1	68
AQ1	56	286
AR7	6.5	82
AS7	4.1	56
AT3	7.7	45
AU4	9.3	60
AV2	7.4	61
AW5	12	85
AX3	7.1	61
AY8	7.3	71
AZ8	7.0	28
BA6	4.9	23
BB7	9.0	62

[0981]

[Table 96]

Example No.	HiBiT DC ₅₀	H295R GI ₅₀
BC6	6.2	48
BD6	3.0	57
BE5	2.6	124
BF6	10	75
BG5	9.2	84
BH5	7.7	79
BI2	11	79
BJ6	17	97
BK9	3.2	24
BL4	3.1	43
BM10	2.2	22
BN2	2.3	31
BO4	15	129
BP6	12	71
BQ4	4.5	28
BR3	2.2	23
BS3	14	70
BT6	3.5	48
BU6	18	64
BV10	14	123
BW3	9.1	86
BX6	7.1	52
BY7	7.3	54
BZ7	4.0	27
CA1	5.5	48
CB10	13	85
CC3	4.9	36
CD2	7.0	33

[0982]

[Table 97]

Example No.	HiBiT DC ₅₀	H295R GI ₅₀
CE1	4.3	70
CF1	5.1	84
CG1	1.8	18
CH1	2.8	25

[0983]

<Experimental Example 5> Evaluation of antitumor activity
against NCI-H295R cell subcutaneous transplant model
(adrenocortical carcinoma)

5 NCI-H295R cells were subcutaneously transplanted at 1.0
to 2.0×10^7 cells/head into the right flank of female NSG mice
and, when the estimated tumor volume (major axis $\times$ minor axis $\times$
minor axis/2) reached 100 to 300 mm³, the mice were divided
into groups of 4 to 5 mice each such that no difference was
10 present between groups. Female NSG mice were purchased from
Charles River Japan Co., Ltd. From the day of grouping, each
compound was orally administered at a dose of 30 mg/kg/day once
a day for 10 to 11 consecutive days (QD $\times$ 10 to 11). Individual
estimated tumor volumes were measured from the day of grouping
15 until 11 to 12 days after grouping (the day the test was
terminated). To the vehicle-control group was administered
0.5% methylcellulose containing 6.2-6.4 mM mesylic acid.

[0984]

The antitumor activity against the NCI-H295R cell
20 subcutaneous transplant model in Experimental Example 5 was
calculated by the following formula on the day the test was
terminated.

[0985]

[Math. 4]

25 tumor growth inhibition rate (%) = $(1 - \text{TVCT}/\text{TVCC}) \times 100$
TVC = (individual tumor volume on test termination day) -
(individual tumor volume on grouping day)
TVCT = TVC average value of administered group
TVCC = TVC average value of administration-free group

30 [0986]

The tumor growth inhibition rate (unit: %) of the
compound corresponding to each Example No. is shown in Table
98.

[0987]

35 [Table 98]

Example No.	tumor growth inhibition rate (%)
AW5	109
BK9	131
BY7	118

[0988]

<Experimental Example 6> Evaluation of antitumor activity in human prostate cancer cell subcutaneous transplant model

5 (prostate cancer)

A xenograft model derived from a prostate cancer patient (obtained from the National Institute of Biomedical Innovation (NIBIO)) was used for antitumor evaluation. Tumors excised from seed mice were cut into about 4-5 mm squares and
10 subcutaneously transplanted into the right flank of male NSG mice. On the fourth day after transplantation, the mice were divided into groups of 8 to 10 mice each to ensure uniformity of the seed mice. From the day of grouping, each compound was orally administered once a day at a dose of 100 mg/kg/day for
15 28 to 32 consecutive days (QD × 28 to 32). Individual estimated tumor volumes were measured from the day of grouping until the day after the final administration (the day of completion of test). To the vehicle-control group was administered 0.5% methylcellulose containing 21.3 mM mesylic
20 acid.

[0989]

The antitumor activity in the human prostate cancer cell subcutaneous transplant model was calculated by the following formula on the day of completion of each test.

25 [0990]

[Math. 5]

tumor growth inhibition rate (%) = $(1 - TVCt / TVCc) \times 100$

TVC = (individual tumor volume on test termination day) -
(individual tumor volume on grouping day)

30 TVCt = TVC average value of administered group

TVCC =TVC average value of administration-free group

[0991]

The tumor growth inhibition rate (unit: %) of the compound corresponding to each Example No. is shown in Table

5 99.

[0992]

[Table 99]

Example No.	tumor growth inhibition rate (%)
AW5	10
BK9	43
BY7	38

[0993]

10 <Experimental Example 7> Inhibitory activity on normal mouse uterine weight (inhibitory action on estrogen activity)

Female NSG mice were purchased from Charles River Japan, Inc. From the day of grouping, each compound was orally administered at a dose of 100 mg/kg/day once a day for 8
15 consecutive days (QD x 8). To the vehicle-control group was administered 0.5% methylcellulose. 24 hr after the final administration, the wet weight of the mouse uterus was measured, and the relative uterine weight (%) to the vehicle control group was calculated by the following formula.

20 [0994]

[Math. 6]

relative uterine weight (%) = (average uterine weight of administered group/average uterine weight of administration-free group) × 100

25 [0995]

The relative uterine weight (unit: %) of the compound corresponding to each Example No. to the vehicle control group is shown in Table 100.

[0996]

30

[Table 100]

Example No.	relative uterine weight (%)
AW5	74
BK9	56
BY7	42

[0997]

<Experimental Example 8> Evaluation of binding activity to CRBN

5 The binding activity of each compound to CRBN can be evaluated as follows using, for example, the competition with HTRF Thalidomide-Red ligand for the CRBN partial protein as an index.

15 150 nM His-Avi-3C-hCRBN (318-426, C366S), 80 nM HTRF Thalidomide-Red ligand, 0.8 µg/mL MAb Anti 6His-Eu cryptate, and each test compound (8-point dilution series with common ratio 3 from final concentration 50 µM) are mixed in HTRF PROTAC Binding Buffer 1, and reacted for 3 hr at room temperature. HTRF signals are measured using a plate reader
15 (Biotek SynergyNEO2, Agilent). The ratio value for each well is calculated by the following formula.

[0998]

[Math. 7]

ratio value = (fluorescence intensity at 665 nm)/(fluorescence
20 intensity at 620 nm) × 10⁴

[0999]

Then, T/C for each test compound treatment is calculated using the following formula.

[1000]

25 [Math. 8]

$$T/C = (\text{ratio value of test compound-added group} - \text{Min}) / (\text{Max} - \text{Min})$$

Max: ratio value of well containing His-CRBN, Thalidomide-Red and Anti-His Eu and not containing evaluation sample

30 Min: ratio value of well containing Thalidomide-Red and Anti-His Eu and not containing evaluation sample

[1001]

The T/C at each concentration is analyzed using GraphPad Prism9 for Windows 64-bit (GraphPad Software Inc. Version 9.1.0) to calculate the concentration (IC₅₀ value) of each test
5 compound that inhibits 50% of the binding of HTRF Thalidomide-Red ligand to CRBN.

[1002]

One embodiment of the compound or a pharmaceutically acceptable salt thereof of the present invention showed an IC₅₀
10 value of the order of μ M or less.

[1003]

[Industrial Applicability]

[1004]

Since a compound represented by the formula (1) or a
15 pharmaceutically acceptable salt thereof of the present invention has an SF-1 antagonist activity, it can be used as an SF-1 antagonist or SF-1 inhibitor. In addition, since SF-1 is known to be involved in the development or progression of various diseases such as adrenocortical carcinoma and
20 castration-resistant prostate cancer, the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention can be used in the treatment of such diseases. In addition, since the compound represented by the formula (1) or a pharmaceutically acceptable salt
25 thereof of the present invention has SF-1 antagonist activity, it can be used as a partial structure in a larger molecule (e.g., polyfunctional molecule) by combining a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present
30 invention with other functional moieties.

Furthermore, since the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention specifically binds to SF-1, it can also be used as an SF-1 binder, and further can be used as an SF-1-
35 binding moiety in a larger molecule (e.g., polyfunctional

molecule) by combining a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention with other functional moieties. Among these, a polyfunctional molecule containing a moiety corresponding to the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof of the present invention and an E3 ligase-binding moiety, particularly, a compound represented by the formula (2) or a pharmaceutically acceptable salt thereof of the present invention, or a crystal thereof, can degrade SF-1 protein and inhibit the proliferation of tumor cells, and thus can be used as an SF-1 inhibitor and an SF-1 degrader, as well as for the treatment of SF-1-related diseases such as adrenocortical carcinoma, castration-resistant prostate cancer, and the like.

[1005]

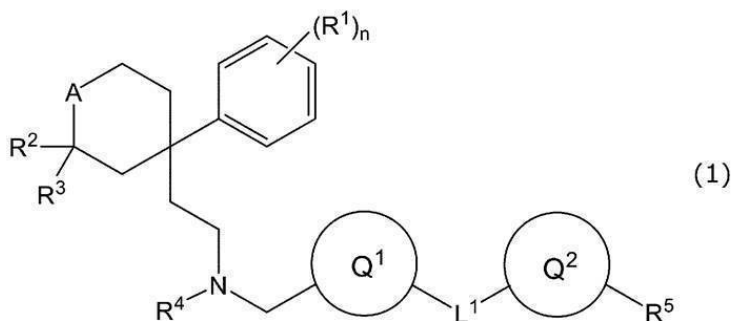
This application is based on a patent application No. 2023-169833 filed in Japan (filing date: September 29, 2023), the contents of which are incorporated in full herein.

[CLAIMS]

[Claim 1]

A compound represented by the following formula (1):

[Chem. 1]



5

wherein

A is $-O-$, $-S-$, $-NR^a-$, or $-CR^bR^c-$,

wherein

R^a is hydrogen or C_{1-3} alkyl,

10 R^b and R^c are each independently hydrogen, halogen, or C_{1-3} alkyl, and

the alkyl is unsubstituted or substituted by 1 to 3 halogens,

each R^1 in the number of n is independently halogen,
15 hydroxy, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, $-O-C_{1-6}$ alkyl, $-N(H)-C_{1-3}$ alkyl, $-N(C_{1-3} \text{ alkyl})_2$, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl,

wherein

the alkyl and alkenyl are each independently
20 unsubstituted or substituted by 1 to 3 halogens,

the cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

25 the heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R^2 and R^3 are each independently hydrogen, halogen, C_{1-6} alkyl, or C_{2-6} alkenyl,

wherein

the alkyl and alkenyl are each independently
unsubstituted or substituted by 1 to 3 halogens,

R^4 is C_{1-6} alkyl, $-C(=O)-R^d$ (R^d indicates C_{1-6} alkyl, C_{2-5}
alkenyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl),
5 C_{6-12} aryl, or 6- to 12-membered heteroaryl,

wherein

the C_{1-6} alkyl is unsubstituted or substituted by 1 to 3
halogens, C_{3-7} cycloalkyl, or 3- to 7-membered heterocycloalkyl,

the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl
10 are each independently unsubstituted or substituted by 1 to 3
groups selected from the group consisting of halogen,
unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

the heteroaryl and heterocycloalkyl have 1 or 2 hetero
atoms selected from oxygen, nitrogen, and sulfur as ring member
15 atoms,

ring Q^1 is a C_{6-12} monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C_{3-7} cycloalkane ring, a 3- to 7-
membered heterocycloalkane ring, a C_{3-7} cycloalkene ring, or a
20 3- to 7-membered heterocycloalkene ring,

wherein

the aromatic hydrocarbocycle, aromatic heterocycle,
cycloalkane ring, heterocycloalkane ring, cycloalkene ring, and
heterocycloalkene ring are each independently unsubstituted or
25 substituted by 1 to 3 groups selected from the group consisting
of halogen, unsubstituted C_{1-3} alkyl, and C_{1-3} haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring, and
heterocycloalkene ring have 1 or 2 hetero atoms selected from
oxygen, nitrogen, and sulfur as ring member atoms,

30 L^1 is a single bond, $-O-$, $-S-$, $-NH-$, C_{1-3} alkylene, C_{2-3}
alkenylene, $-C(=O)-$, $-C(=O)NH-$, $-NHC(=O)-$, $-C(=O)O-$, or $-$
 $OC(=O)-$,

wherein

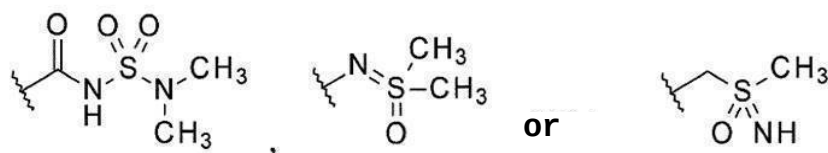
the alkylene and alkenylene are each independently
35 unsubstituted or substituted by 1 to 3 halogens,

ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3- to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane ring, or a 5- to 12-membered spiroheterocycloalkane ring, wherein

the aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, heterocycloalkene ring, spirocycloalkane ring, and spiroheterocycloalkane ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring, heterocycloalkene ring, and spiroheterocycloalkane ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

R⁵ is C₁₋₆ alkyl, carboxy, hydroxy, or a group represented by the following formula:
[Chem. 2]



wherein

the C₁₋₆ alkyl is unsubstituted or substituted by 1 or 2 groups selected from the group consisting of carboxy, hydroxy, and -O-C₁₋₆ alkyl, and

n is an integer of 0 to 3, or a pharmaceutically acceptable salt thereof.

[Claim 2]

The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein A is -O- or -CR^bR^c-.

[Claim 3]

The compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein

each R¹ in the number of n is independently halogen, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, or 3- to 7-membered
5 heterocycloalkyl,

wherein the heterocycloalkyl has 1 or 2 nitrogen atoms as ring member atoms.

[Claim 4]

The compound according to any one of claims 1 to 3 or a
10 pharmaceutically acceptable salt thereof, wherein

R² and R³ are each independently hydrogen or C₁₋₆ alkyl.

[Claim 5]

The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein

15 R⁴ is C₁₋₆ alkyl, -C(=O)-R^d, or 6- to 12-membered heteroaryl,

wherein

the R^d is C₁₋₆ alkyl,

the C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3
20 halogens or C₃₋₇ cycloalkyl, and

the heteroaryl has 1 or 2 nitrogen atoms as ring member atoms.

[Claim 6]

The compound according to any one of claims 1 to 5 or a
25 pharmaceutically acceptable salt thereof, wherein

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, or a C₃₋₇ cycloalkene ring, and the aromatic heterocycle has 1 or 2
30 nitrogen atoms as ring member atoms.

[Claim 7]

The compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein

L¹ is a single bond, -O-, C₁₋₃ alkylene, or -C(=O)-.

35 [Claim 8]

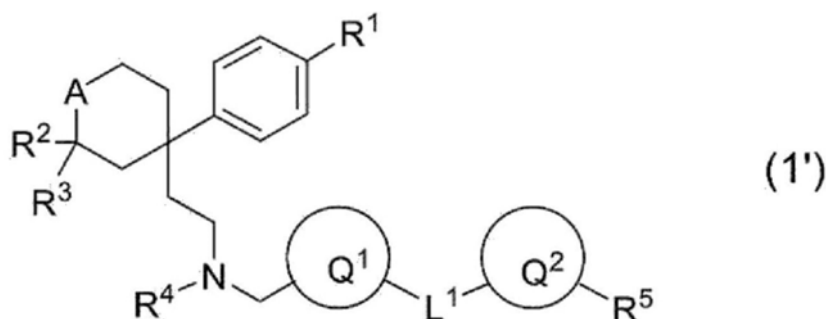
The compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein

ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered
5 heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 5- to 12-membered spiroheterocycloalkane ring, and the heterocycloalkane ring and spiroheterocycloalkane ring have 1 or 2 nitrogen atoms as ring member atoms.

[Claim 9]

10 A compound represented by the following formula (1'):

[Chem. 3]



wherein

A is -O- or -CF₂-,

15 R¹ is halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom,

R² and R³ are each independently hydrogen or C₁₋₆ alkyl,

20 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally
25 substituted by one halogen),

ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇

cycloalkane ring, or a C₄₋₇ cycloalkene ring,

L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,

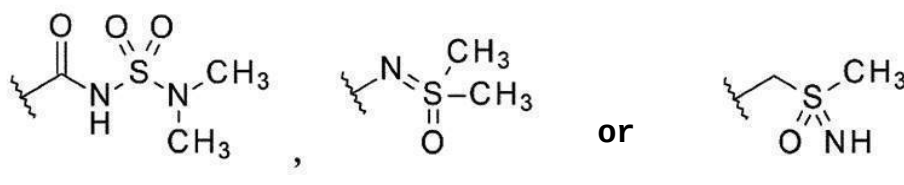
ring Q² is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring

5 optionally substituted by one halogen, a piperidine ring, or a 7-azaspiro[3.5]nonane ring, and

R⁵ is C₁₋₆ alkyl optionally having 1 or 2 groups selected from the group consisting of carboxy, hydroxy, and -O-C₁₋₆ alkyl, carboxy, hydroxy, or a group represented by the

10 following formula:

[Chem. 4]



or a pharmaceutically acceptable salt thereof.

[Claim 10]

15 The compound according to claim 9 or a pharmaceutically acceptable salt thereof, wherein

A is -O-,

R² is methyl,

R³ is methyl,

20 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, or 6-membered heteroaryl having 1 or 2 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen),

25 ring Q¹ is a benzene ring optionally having one group selected from the group consisting of halogen and C₁₋₃ alkyl, or a pyridine ring,

L¹ is a single bond, -O-, or -C(=O)-, and

30 ring Q² is a benzene ring, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring.

[Claim 11]

The compound according to claim 9 or 10 or a

pharmaceutically acceptable salt thereof, wherein

R¹ is methoxy, and

R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl.

[Claim 12]

5 Any one compound selected from the following group:

trans-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)cyclohexanecarboxylic acid,

2-[4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)phenyl]propanoic acid,

{trans-4-[(5-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}pyridin-2-yl)oxy]cyclohexyl}acetic
15 acid,

[trans-4-(4-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}phenoxy)cyclohexyl]acetic acid,

(4R)-2'-fluoro-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-carboxylic acid,

[(4R)-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl]-2,3,4,5-tetrahydro[biphenyl]-4-yl]methanol, and

tert-butyl 4-{{(4R)-4'-{{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyltetrahydro-2H-pyran-4-yl]ethyl}}(3,3,3-trifluoro-2,2-dimethylpropyl)amino)methyl}-2,3,4,5-tetrahydro[biphenyl]-4-yl]methyl}piperazine-1-carboxylate,

or a pharmaceutically acceptable salt thereof.

[Claim 13]

A polyfunctional molecule comprising a moiety corresponding to the compound or a pharmaceutically acceptable
35 salt thereof according to any one of claims 1 to 12.

[Claim 14]

The polyfunctional molecule according to claim 13,
further comprising another functional moiety, wherein the
moiety corresponding to the compound or a pharmaceutically
5 acceptable salt thereof is linked to the other functional
moiety directly or is linked via a linker at any position in
R⁵.

[Claim 15]

The polyfunctional molecule according to claim 14,
10 wherein

said other functional moiety is an E3 ligase-binding
moiety, an autophagy-recruiting moiety, a lysosome-recruiting
moiety, a kinase-recruiting moiety, a phosphatase-recruiting
moiety, a glycosyltransferase-recruiting moiety, an
15 acetyltransferase-recruiting moiety, or ADC.

[Claim 16]

The polyfunctional molecule according to claim 14,
wherein

said other functional moiety is an E3 ligase-binding
20 moiety.

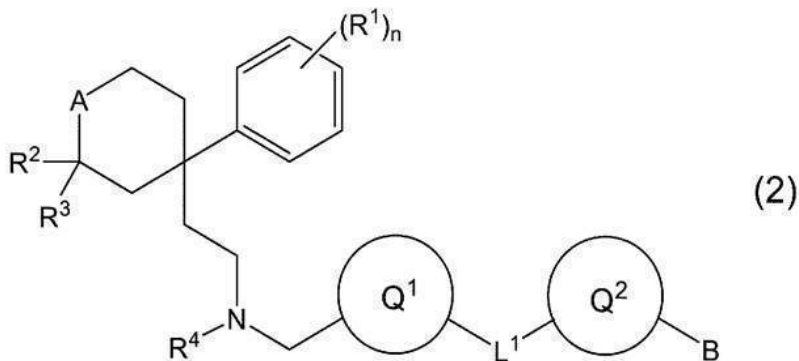
[Claim 17]

The polyfunctional molecule according to claim 16,
wherein the E3 ligase-binding moiety is a cereblon (CRBN)-
binding moiety.

25 [Claim 18]

A compound represented by the following formula (2):

[Chem. 5]



wherein

A is -O-, -S-, -NR^a-, or -CR^bR^c-,
 wherein
 R^a is hydrogen or C₁₋₃ alkyl,
 R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and
 the alkyl is unsubstituted or substituted by 1 to 3 halogens,
 each R¹ in the number of n is independently halogen, hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,
 wherein
 the alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,
 the cycloalkyl and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
 the heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,
 R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, or C₂₋₆ alkenyl,
 wherein
 the alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,
 R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅ alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl), C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,
 wherein
 the C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3 halogens, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,
 the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the heteroaryl and heterocycloalkyl have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

wherein

the aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, and heterocycloalkene ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring, and heterocycloalkene ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

L¹ is a single bond, -O-, -S-, -NH-, C₁₋₃ alkylene, C₂₋₃ alkenylene, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -OC(=O)-,

wherein

the alkylene and alkenylene are each independently unsubstituted or substituted by 1 to 3 halogens,

ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3- to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, heterocycloalkene ring, spirocycloalkane ring, and spiroheterocycloalkane ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the

group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring, heterocycloalkene ring, and spiroheterocycloalkane ring have 1
5 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

B is -L²-L³-L⁴-R⁶,

L² is a single bond, C₁₋₆ alkylene, -C(=O)-, -C(=O)NH-, -
(CH₂)_k-C(=O)NH- (k indicates an integer of 1 to 3), or -
10 NHC(=O)-,

L³ is a single bond, C₁₋₆ alkylene, C₃₋₆ cycloalkylene, piperazinediyl, piperazin-2-onediyl, piperidinediyl, pyrrolidinediyl, azetidinediyl, or 3-oxa-9-azabicyclo[3.3.1]nonanediyl,

15 L⁴ is a single bond, -NH-, -N(-R⁷)- (R⁷ indicates C₁₋₆ alkyl), -CH₂-, or -C(=O)-, and

R⁶ is an E3 ligase-binding moiety, an autophagy-recruiting moiety, a lysosome-recruiting moiety, a kinase-recruiting moiety, a phosphatase-recruiting moiety, a
20 glycosyltransferase-recruiting moiety, an acetyltransferase-recruiting moiety, or ADC, and

n is an integer of 0 to 3, or a pharmaceutically acceptable salt thereof.

[Claim 19]

25 The compound according to claim 18 or a pharmaceutically acceptable salt thereof, wherein A is -O- or -CR^bR^c-.

[Claim 20]

The compound according to claim 18 or 19 or a pharmaceutically acceptable salt thereof, wherein

30 each R¹ in the number of n is independently halogen, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, or 3- to 7-membered heterocycloalkyl, and the heterocycloalkyl has 1 or 2 nitrogen atoms as ring member atoms.

[Claim 21]

35 The compound according to any one of claims 18 to 20 or a

pharmaceutically acceptable salt thereof, wherein

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl.

[Claim 22]

The compound according to any one of claims 18 to 21 or a
5 pharmaceutically acceptable salt thereof, wherein

R^4 is C_{1-6} alkyl, $-C(=O)-R^d$, or 6- to 12-membered
heteroaryl,

wherein

the R^d is C_{1-6} alkyl,

10 the C_{1-6} alkyl is unsubstituted or substituted by 1 to 3
halogens or C_{3-7} cycloalkyl, and

the heteroaryl has 1 or 2 nitrogen atoms as ring member
atoms.

[Claim 23]

15 The compound according to any one of claims 18 to 22 or a
pharmaceutically acceptable salt thereof, wherein

ring Q^1 is a C_{6-12} monocyclic or bicyclic aromatic
hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic
aromatic heterocycle, a C_{3-7} cycloalkane ring, or a C_{3-7}
20 cycloalkene ring, and the aromatic heterocycle has 1 or 2
nitrogen atoms as ring member atoms.

[Claim 24]

The compound according to any one of claims 18 to 23 or a
pharmaceutically acceptable salt thereof, wherein

25 L^1 is a single bond, $-O-$, C_{1-3} alkylene, or $-C(=O)-$.

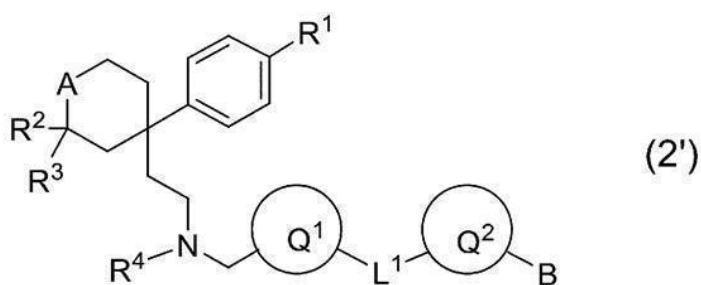
[Claim 25]

The compound according to any one of claims 18 to 24 or a
pharmaceutically acceptable salt thereof, wherein

ring Q^2 is a C_{6-12} monocyclic or bicyclic aromatic
30 hydrocarbocycle, a C_{3-7} cycloalkane ring, a 3- to 7-membered
heterocycloalkane ring, a C_{3-7} cycloalkene ring, or a 5- to 12-
membered spiroheterocycloalkane ring, and the heterocycloalkane
ring and spiroheterocycloalkane ring have 1 or 2 nitrogen atoms
as ring member atoms.

35 [Claim 26]

A compound represented by the following formula (2'):
 [Chem. 6]



wherein

5 A is -O- or -CF₂-,

 R¹ is halogen, -O-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂ or 4- to 6-membered heterocycloalkyl having one nitrogen atom as a ring member atom,

10 R² and R³ are each independently hydrogen or C₁₋₆ alkyl,

 R⁴ is C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, -C(=O)-C₁₋₆ alkyl optionally substituted by 1 to 3 halogens, C₃₋₆ cycloalkylmethyl optionally substituted by one trifluoromethyl, or 6-membered heteroaryl having 1 or 2

15 nitrogen atoms as ring member atoms (the heteroaryl is optionally substituted by one halogen),

 ring Q¹ is a benzene ring optionally having 1 or 2 groups selected from the group consisting of halogen and C₁₋₃ alkyl, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle
 20 having 1 or 2 nitrogen atoms as ring member atoms, a C₄₋₇ cycloalkane ring, or a C₄₋₇ cycloalkene ring,

 L¹ is a single bond, -O-, -CH₂-, or -C(=O)-,

 ring Q² is a benzene ring optionally substituted by one halogen, a C₄₋₇ cycloalkane ring, a C₄₋₇ cycloalkene ring
 25 optionally substituted by one halogen, a piperidine ring, or a 7-azaspiro[3.5]nonane ring,

 B is -L²-L³-L⁴-R⁶,

 L² is a single bond, C₁₋₆ alkylene, -C(=O)-, -C(=O)NH-, -
 (CH₂)_k-C(=O)NH- (k indicates an integer of 1 to 3), or -
 30 NHC(=O)-,

L³ is a single bond, C₁₋₆ alkylene, C₃₋₆ cycloalkylene, piperazinediyl, piperazin-2-onediyl, piperidinediyl, pyrrolidinediyl, azetidinediyl, or 3-oxa-9-azabicyclo[3.3.1]nonanediyl,

5 L⁴ is a single bond, -NH-, -N(-R⁷)- (R⁷ indicates C₁₋₆ alkyl), -CH₂-, or -C(=O)-, and

R⁶ is an E3 ligase-binding moiety, an autophagy-recruiting moiety, a lysosome-recruiting moiety, a kinase-recruiting moiety, a phosphatase-recruiting moiety, a
10 glycosyltransferase-recruiting moiety, an acetyltransferase-recruiting moiety, or ADC, or a pharmaceutically acceptable salt thereof.

[Claim 27]

The compound according to any one of claims 18 to 26,
15 wherein R⁶ is an E3 ligase-binding moiety, or a pharmaceutically acceptable salt thereof.

[Claim 28]

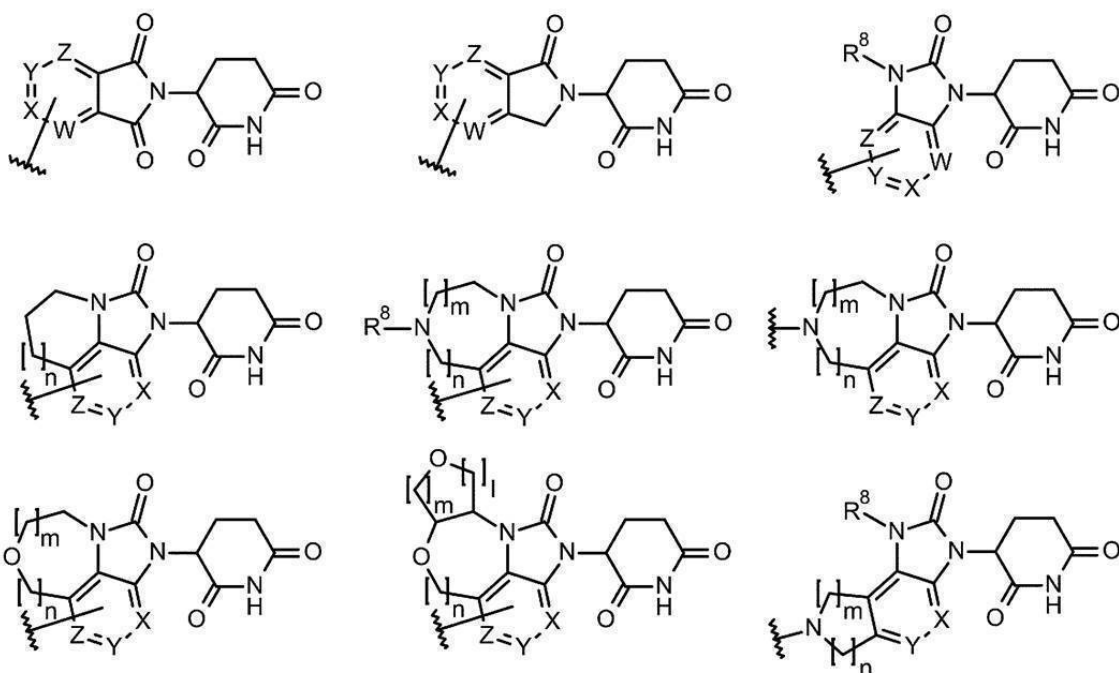
The compound according to claim 27 or a pharmaceutically acceptable salt thereof, wherein the E3 ligase-binding moiety
20 is a cereblon (CRBN)-binding moiety.

[Claim 29]

The compound according to any one of claims 18 to 28 or a pharmaceutically acceptable salt thereof, wherein

R⁶ is any substituent selected from the following
25 formulas:

[Chem. 7]



wherein,

R^8 is hydrogen or C_{1-6} alkyl,

W, X, Y, and Z are each independently a nitrogen atom or
 5 a carbon atom optionally having one group selected from the
 group consisting of halogen, C_{1-6} alkyl, and $-O-C_{1-6}$ alkyl,

l, m, and n indicate each independently an integer of 0
 to 3, and

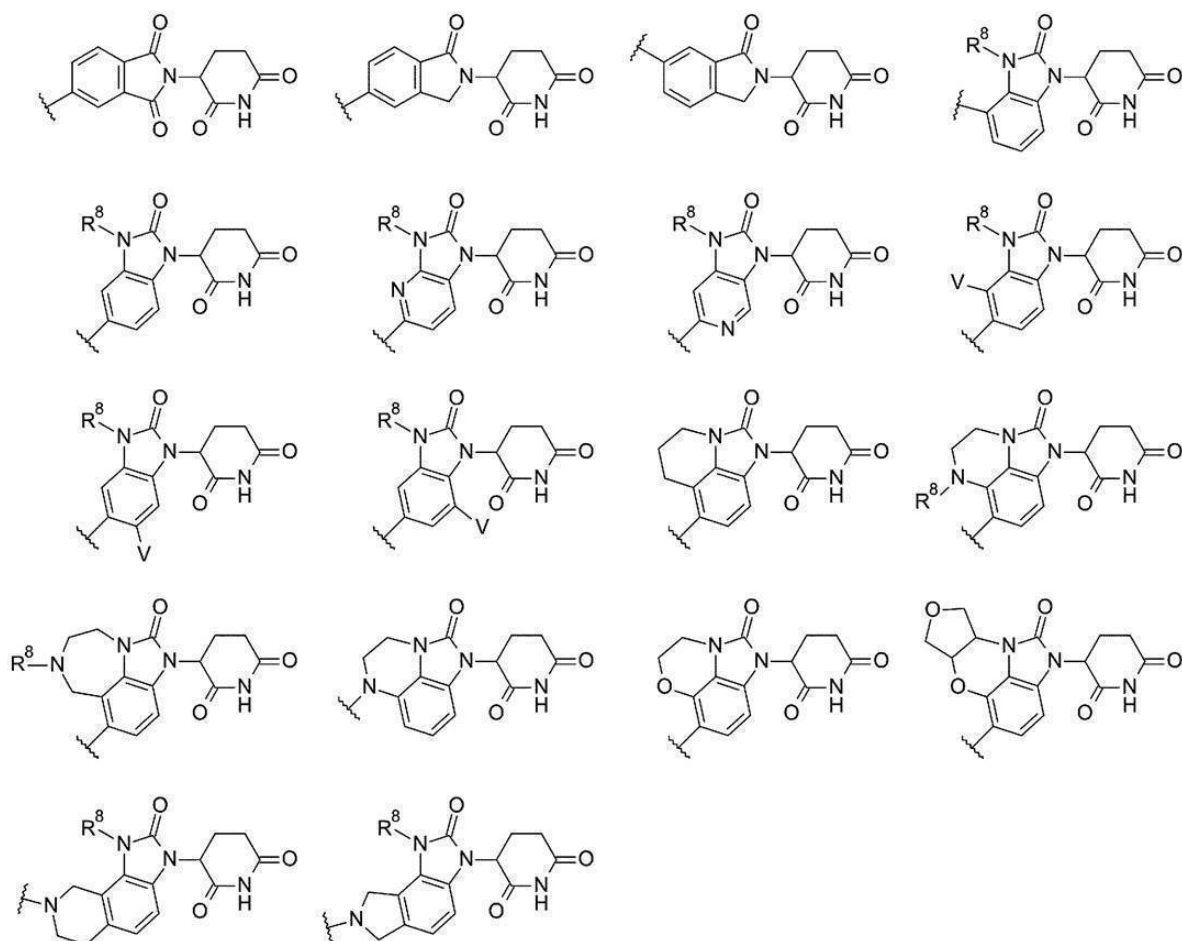
a wavy line indicates the bonding position with L^4 .

10 [Claim 30]

The compound according to claim 29 or a pharmaceutically
 acceptable salt thereof, wherein

R^6 is any substituent selected from the following
 formulas:

15 [Chem. 8]



wherein

R^8 is hydrogen or C_{1-6} alkyl,

V is halogen, and

5 a wavy line indicates the bonding position with L^4 .

[Claim 31]

The compound according to any one of claims 18 to 30 or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-O-C_{1-6}$ alkyl optionally substituted by 1 to 3

10 halogens,

R^4 is C_{1-6} alkyl optionally substituted by 1 to 3 halogens or C_{3-6} cycloalkylmethyl optionally substituted by one trifluoromethyl,

ring Q^1 is a benzene ring optionally having 1 or 2 groups
 15 selected from the group consisting of halogen and C_{1-6} alkyl, a 9- to 10-membered bicyclic aromatic heterocycle having 1 or 2 nitrogen atoms as ring member atoms, a C_{4-7} cycloalkane ring, or a C_{4-7} cycloalkene ring, and

L¹ is a single bond or -O-.

[Claim 32]

The compound according to any one of claims 18 to 31 or a pharmaceutically acceptable salt thereof, wherein

5 A is -O-,

R² is methyl, and

R³ is methyl.

[Claim 33]

The compound according to any one of claims 18 to 32 or a
10 pharmaceutically acceptable salt thereof, wherein

R¹ is methoxy, and

R⁴ is 3,3,3-trifluoro-2,2-dimethylpropyl.

[Claim 34]

The compound according to any one of claims 18 to 33 or a
15 pharmaceutically acceptable salt thereof, wherein

ring Q¹ is a benzene ring optionally having one halogen,

L¹ is a single bond, and

ring Q² is a cyclohexene ring.

[Claim 35]

20 Any one compound selected from the following group:

(3RS)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-
25 1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3R)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-
30 1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3S)-3-[5-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-3-methyl-2-oxo-2,3-dihydro-
35 1H-benzimidazol-1-yl]piperidine-2,6-dione,

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
5 imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3R)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
10 imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3S)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
15 imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-
20 4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3R)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-
25 4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3S)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-[(4R)-4-(4-
methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-
30 4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione,
(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-
2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-
dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-
4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-
35 imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione,

(3R)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione, and
5 (3S)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione,
10 or a pharmaceutically acceptable salt thereof.

[Claim 36]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
15 monobenzenesulfonate.

[Claim 37]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
20 monoethanesulfonate.

[Claim 38]

(3RS)-3-[7-({1-[(4R)-2'-Fluoro-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl}amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
30 mono-10-camphorsulfonate.

[Claim 39]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-

35

dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione monoethanesulfonate.

5 [Claim 40]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione monosalicylate.

[Claim 41]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione monobenzenesulfonate.

[Claim 42]

(3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione mono-10-camphorsulfonate.

[Claim 43]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl) amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate, the crystal having peaks at diffraction angles (2 θ) of 2.15 $\pm$ 0.2, 8.30 $\pm$ 0.2, 10.29 $\pm$ 0.2, 14.75 $\pm$ 0.2, 17.19 $\pm$ 0.2, 20.00 $\pm$ 0.2, 21.34 $\pm$ 0.2, 22.68 $\pm$ 0.2, 23.77 $\pm$ 0.2, and 25.23 $\pm$ 0.2 in a powder X-ray diffraction pattern obtained by

irradiation with copper K α ray ($\lambda=1.54$ angstroms).

[Claim 44]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
5 2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
ethanesulfonate, the crystal having peaks at diffraction angles
(2θ) of 2.21 ± 0.2 , 12.04 ± 0.2 , 14.87 ± 0.2 , 17.69 ± 0.2 , 18.93 ± 0.2 ,
10 20.41 ± 0.2 , 22.42 ± 0.2 , 23.19 ± 0.2 , 24.13 ± 0.2 , and 27.98 ± 0.2 in a
powder X-ray diffraction pattern obtained by irradiation with
copper K α ray ($\lambda=1.54$ angstroms).

[Claim 45]

A crystal of (3RS)-3-[7-({1-[(4R)-2'-fluoro-4'-{[{2-
15 [(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-carbonyl]piperidin-4-yl)amino)-2-oxo-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2H)-yl]piperidine-2,6-dione
10-camphorsulfonate, the crystal having
20 peaks at diffraction angles (2θ) of 3.89 ± 0.2 , 6.81 ± 0.2 ,
 7.68 ± 0.2 , 8.20 ± 0.2 , 10.28 ± 0.2 , 13.15 ± 0.2 , 15.97 ± 0.2 , 16.81 ± 0.2 ,
 18.58 ± 0.2 , and 23.56 ± 0.2 in a powder X-ray diffraction pattern
obtained by irradiation with copper K α ray ($\lambda=1.54$ angstroms).

[Claim 46]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-
2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-
biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-
4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione
30 ethanesulfonate ethanesulfonate, the crystal having peaks at
diffraction angles (2θ) of 2.27 ± 0.2 , 8.18 ± 0.2 , 9.88 ± 0.2 ,
 13.09 ± 0.2 , 14.57 ± 0.2 , 15.80 ± 0.2 , 16.91 ± 0.2 , 17.77 ± 0.2 ,
 18.87 ± 0.2 , and 20.14 ± 0.2 in a powder X-ray diffraction pattern
obtained by irradiation with copper K α ray ($\lambda=1.54$ angstroms).

35 [Claim 47]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione salicylate, the crystal having peaks at diffraction angles (2θ) of 2.20±0.2, 4.34±0.2, 9.45±0.2, 10.97±0.2, 13.23±0.2, 16.98±0.2, 18.09±0.2, 20.20±0.2, 21.32±0.2, and 25.19±0.2 in a powder X-ray diffraction pattern obtained by irradiation with
10 copper Kα ray (λ=1.54 angstroms).

[Claim 48]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione benzenesulfonate, having peaks at diffraction angles (2θ) of 2.19±0.2, 8.87±0.2, 10.86±0.2, 12.55±0.2, 13.05±0.2, 14.99±0.2, 17.84±0.2, 20.62±0.2, 21.43±0.2, and 25.27±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms).
20

[Claim 49]

A crystal of (3RS)-3-[7-(4-{[(4R)-4'-{[{2-[(4R)-4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(3,3,3-trifluoro-2,2-dimethylpropyl)amino]methyl}-2,3,4,5-tetrahydro[1,1'-biphenyl]-4-yl]methyl}piperazine-1-carbonyl)-2-oxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-1(2H)-yl]piperidine-2,6-dione 10-camphorsulfonate, having peaks at diffraction angles (2θ) of 2.20±0.2, 7.82±0.2, 11.05±0.2, 12.42±0.2, 13.34±0.2, 15.23±0.2, 16.49±0.2, 17.86±0.2, 20.15±0.2, and 24.36±0.2 in a powder X-ray diffraction pattern obtained by irradiation with copper Kα ray (λ=1.54 angstroms) crystal.
30

[Claim 50]

A composition for inhibiting Steroidogenic Factor 1,
35 comprising the compound or a pharmaceutically acceptable salt

thereof according to any one of claims 1 to 12, the
polyfunctional molecule according to any one of claims 13 to
17, or the compound or a pharmaceutically acceptable salt
thereof, or the crystal thereof according to any one of claims
5 18 to 49.

[Claim 51]

A composition for inducing degradation of Steroidogenic
Factor 1, comprising the polyfunctional molecule according to
any one of claims 13 to 17 or the compound or a
10 pharmaceutically acceptable salt thereof, or the crystal
thereof according to any one of claims 18 to 49.

[Claim 52]

A pharmaceutical composition comprising the compound or a
pharmaceutically acceptable salt thereof according to any one
15 of claims 1 to 12, the polyfunctional molecule according to any
one of claims 13 to 17, or the compound or a pharmaceutically
acceptable salt thereof, or the crystal thereof according to
any one of claims 18 to 49.

[Claim 53]

20 The pharmaceutical composition according to claim 52,
which is for the treatment of castration-resistant prostate
cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-
sensitive prostate cancer, breast cancer, Cushing's syndrome,
or primary aldosteronism.

25 [Claim 54]

A method for treating castration-resistant prostate
cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-
sensitive prostate cancer, breast cancer, Cushing's syndrome,
or primary aldosteronism, comprising administering an effective
30 amount of the compound or a pharmaceutically acceptable salt
thereof according to any one of claims 1 to 12, the
polyfunctional molecule according to any one of claims 13 to
17, or the compound or a pharmaceutically acceptable salt
thereof, or the crystal thereof according to any one of claims
35 18 to 49 to a subject in need of a treatment of castration-

resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.

[Claim 55]

5 The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, the polyfunctional molecule according to any one of claims 13 to 17 or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of claims 18 to 49,
10 which is for use in the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.

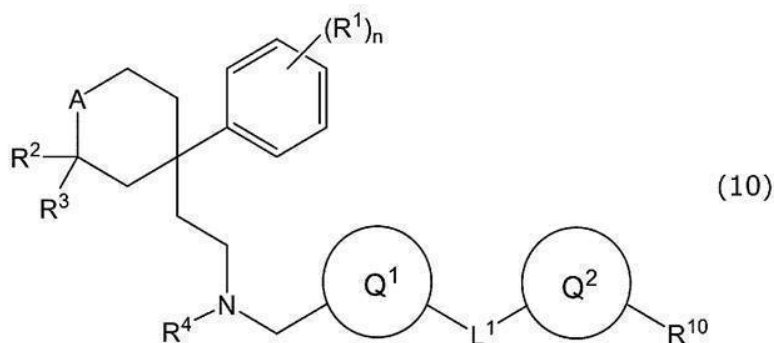
[Claim 56]

15 Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, the polyfunctional molecule according to any one of claims 13 to 17, or the compound or a pharmaceutically acceptable salt thereof, or the crystal thereof according to any one of claims
20 18 to 49 in the production of a medicament for the treatment of castration-resistant prostate cancer, adrenocortical carcinoma, Leydig cell tumor, hormone-sensitive prostate cancer, breast cancer, Cushing's syndrome, or primary aldosteronism.

[Claim 57]

25 A compound represented by the following formula (10):

[Chem. 9]



wherein

A is -O-, -S-, -NR^a-, or -CR^bR^c-,

wherein
 R^a is hydrogen or C₁₋₃ alkyl,
 R^b and R^c are each independently hydrogen, halogen, or C₁₋₃ alkyl, and
 5 the alkyl is unsubstituted or substituted by 1 to 3 halogens,
 each R¹ in the number of n is independently halogen, hydroxy, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, -O-C₁₋₆ alkyl, -N(H)-C₁₋₃ alkyl, -N(C₁₋₃ alkyl)₂, C₃₋₇ cycloalkyl, or 3- to 7-membered
 10 heterocycloalkyl,
 wherein
 the alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,
 the cycloalkyl and heterocycloalkyl are each
 15 independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
 the heterocycloalkyl has 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,
 20 R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, or C₂₋₆ alkenyl,
 wherein
 the alkyl and alkenyl are each independently unsubstituted or substituted by 1 to 3 halogens,
 25 R⁴ is C₁₋₆ alkyl, -C(=O)-R^d (R^d indicates C₁₋₆ alkyl, C₂₋₅ alkenyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl), C₆₋₁₂ aryl, or 6- to 12-membered heteroaryl,
 wherein
 the C₁₋₆ alkyl is unsubstituted or substituted by 1 to 3
 30 halogens, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocycloalkyl,
 the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and
 35 the heteroaryl and heterocycloalkyl have 1 or 2 hetero

atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

ring Q¹ is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, or a 3- to 7-membered heterocycloalkene ring,

wherein

the aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, and heterocycloalkene ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃ haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring and heterocycloalkene ring have 1 or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as ring member atoms,

L¹ is a single bond, -O-, -S-, -NH-, C₁₋₃ alkylenes, C₂₋₃ alkenylenes, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, or -OC(=O)-,

wherein

the alkylenes and alkenylenes are each independently unsubstituted or substituted by 1 to 3 halogens,

ring Q² is a C₆₋₁₂ monocyclic or bicyclic aromatic hydrocarbocycle, a 6- to 12-membered monocyclic or bicyclic aromatic heterocycle, a C₃₋₇ cycloalkane ring, a 3- to 7-membered heterocycloalkane ring, a C₃₋₇ cycloalkene ring, a 3- to 7-membered heterocycloalkene ring, a C₅₋₁₂ spirocycloalkane ring, or a 5- to 12-membered spiroheterocycloalkane ring,

wherein

the aromatic hydrocarbocycle, aromatic heterocycle, cycloalkane ring, heterocycloalkane ring, cycloalkene ring, heterocycloalkene ring, spirocycloalkane ring, and spiroheterocycloalkane ring are each independently unsubstituted or substituted by 1 to 3 groups selected from the group consisting of halogen, unsubstituted C₁₋₃ alkyl, and C₁₋₃

haloalkyl, and

the aromatic heterocycle, heterocycloalkane ring,
heterocycloalkene ring, and spiroheterocycloalkane ring have 1
or 2 hetero atoms selected from oxygen, nitrogen, and sulfur as
5 ring member atoms,

R^{10} is C_{1-6} alkyl,

wherein

the C_{1-6} alkyl is substituted by one or two 3- to 7-
membered heterocycloalkyls,

10 the heterocycloalkyl has 1 or 2 hetero atoms selected
from oxygen, nitrogen, and sulfur as ring member atoms, and

the heterocycloalkyl is unsubstituted or substituted by
an amino-protecting group, and

n is an integer of 0 to 3, or a pharmaceutically
15 acceptable salt thereof.