



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION

(13) **A1**

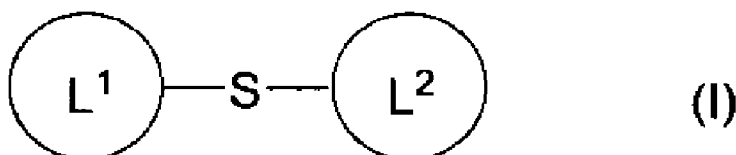
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(54) Titre : AGENT DE DEGRADATION DE BET
(54) Title: BET DEGRADER



(57) Abrégé/Abstract:

Provided is a BET degrader. A BET degrader including a compound represented by formula (I) or a pharmaceutically acceptable salt thereof is used. (In the formula, L¹ and L² are the same or different and represent a low molecular ligand for a BET protein, and S represents a group represented by one formula selected from the group consisting of formulas (S1)-(S18).)

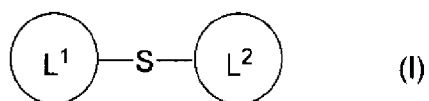


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ABSTRACT

The present invention provides a BET (protein) degrader, specifically a BET degrader containing a compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



wherein L1 and L2 are the same or different and each represents a small molecular ligand for BET protein, and S represents a group represented by a formula selected from the group consisting of formulas (S1) to (S18).

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

BET DEGRADER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001]

5 The present patent application claims priority to Japanese Patent Application No. 2019-180349 filed on September 30, 2018, and the entire disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 Field of the Invention

[0002]

 The present invention relates to a BET degrader with a degrading action on BET protein.

15 Background Art

[0003]

 In humans, 46 bromodomain proteins that recognize the acetylated lysine in histone proteins are known. The BET (bromodomain and extra-terminal domain) family has been reported as one of the families, and a member of the BET family recognizes acetyllysine in histones H3 and H4. BRD (bromodomain containing protein) 2, BRD3, BRD4 and BRDT (bromodomain testis specific protein) are known as the BET family. BET family proteins have two bromo domains (BD1, BD2) at the N-terminus, and the sequences are strongly conserved between the members of the family. Further, it has been reported that the BET protein is involved in cancer growth [see non-patent documents 1 and 2] and progression of inflammation [see non-patent document 3].

[0004]

 BRD4 enhances expression of genes that promote growth by recruiting P-TEBb on mitotic chromosomes. In NUT-midline carcinoma

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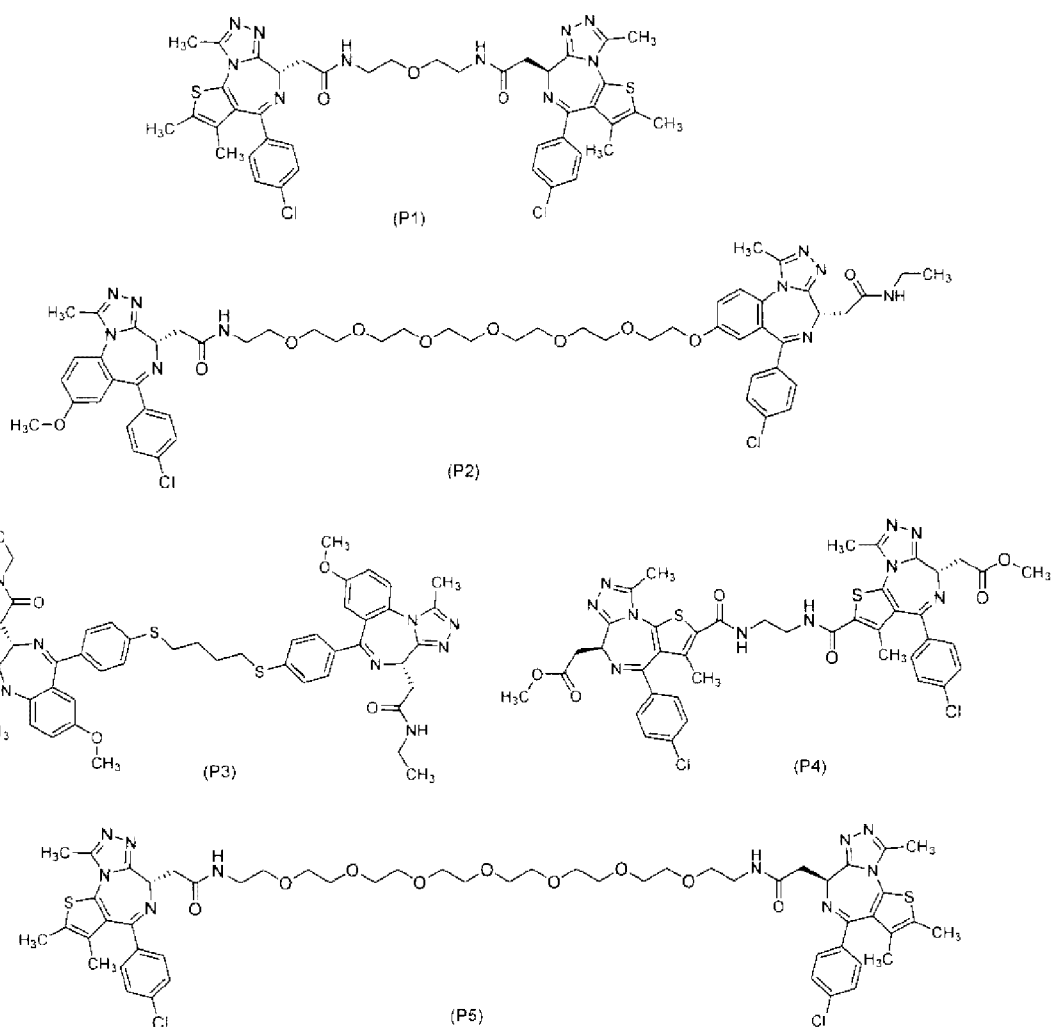
(NMC), increased expression of c-MYC protein by the BRD4-NUT fusion protein has been confirmed [see non-patent document 4]. It has also been reported that the degree of decrease in expression of the MYC gene is the most significant level in the human multiple myeloma-derived MM1.S cells, among the genes whose expression is decreased by the BET inhibitor JQ-1 treatment [See non-patent document 5].

[0005]

As typical BET inhibitors, clinical trials of RVX-208/Apabetalone [see non-patent document 6], I-BET762/GSK-525762A [see non-patent document 7], OTX-015/MK8628 [see non-patent document 8], CPI-0610 [see non-patent document 9], TEN-010 [see non-patent document 10], and ABBV-075 [see non-patent document 11] are in progress. Among these drugs, all but RVX-208 are being developed as cancer treatment drugs.

[0006]

In addition, in recent years, a compound, as a bivalent BET inhibitor, having a more potent BET inhibitory activity by simultaneously inhibiting the BD1 and BD2 domains has also been reported (see non-patent document 12). As the bivalent BET inhibitor described above, for example, compounds represented by the following formulas (P1) to (P5) are known (see non-patent document 12, patent documents 1, 2 and 3).



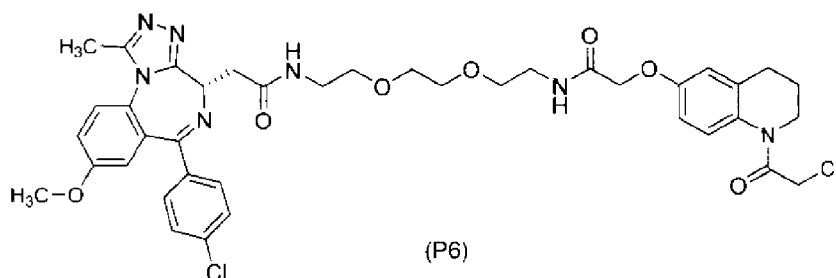
[0007]

In recent years, as a new BET function regulator, a compound that degrades BET proteins in the ubiquitin-proteasome system have been reported. It is known that the compound induces apoptosis of cancer cells by the degradation of BET protein more efficiently than BET inhibitors (see non-patent document 13). Therefore, it can be expected that the BET degrader will be an anticancer drug superior to the inhibitor thereof. In addition, in clinical trials of BET inhibitors, hematological toxicity such as thrombocytopenia and the like has been reported as an adverse event (see non-patent document 14).

[0008]

A typical example of the BET degrader is PROTAC, which is a chimeric molecule of a small molecular ligand for BET protein and a ligand for E3 ubiquitin ligase. Among them, as PROTAC using DCAF16, the compound
5 represented by (P6) is known (see non-patent document 15).

[0009]



[0010]

However, the degrading action on BET protein by these drugs is still
10 insufficient, and there is a demand for a drug having a more potent degrading action of BET protein.

Prior Art Documents

Patent Documents

[0011]

15 Patent Document 1: WO 2013/033268

Patent Document 2: WO 2015/081284

Patent Document 3: WO 2017/091673

Non-Patent Documents

20 [0012]

Non-Patent Document 1: Nature, 2011, Vol. 478, p. 524-528

Non-Patent Document 2: Cell, 2011, Vol. 146, p. 904-917

Non-Patent Document 3: Nature, 2010, Vol. 468, p. 1119-1123

Non-Patent Document 4: Cancer Research, 2003, Vol. 63, p. 304-307

- Non-Patent Document 5: Cell, 2013, Vol. 153, p. 320-334
- Non-Patent Document 6: Proceeding of the National Academy of Science, 2013, Vol. 110, p. 19754-19759
- Non-Patent Document 7: Journal of Medicinal Chemistry, 2013, Vol. 56, p. 7501-7515
- Non-Patent Document 8: Oncotarget, 2015, Vol. 6, p. 17698-17712
- Non-Patent Document 9: Blood, 2015, Vol. 126, p. 4255-4255
- Non-Patent Document 10: Molecular Cancer Therapeutech, 2015, Vol. 14, A49
- Non- Patent Document 11: Cancer Research, 2016, Vol. 76, p. 4718-4718
- Non-Patent Document 12: Nature Chemical Biology, 2016, Vol. 112, p. 1089-1096
- Non-Patent Document 13: Science, 2015, Vol. 348, p.1376-1381
- Non-Patent Document 14: Lancet Haematology, 2016, Vol. 3, e196-204
- Non-Patent Document 15: Nature Chemical Biology, 2018, Vol. 15, p.737-746

SUMMARY OF THE INVENTION

[0013]

- The present invention provides a BET (protein) degrader or compound having a degrading action on BET protein or a pharmaceutically acceptable salt thereof.

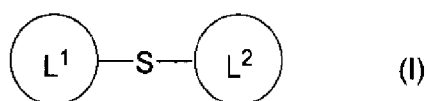
[0014]

- In the present invention, it has been found that a compound containing two small molecular ligands for BET protein that are linked by a spacer having a specific structure or a pharmaceutically acceptable salt thereof can be used as a BET degrader. It has also been found that the BET degrader or compound of the present invention or a pharmaceutically acceptable salt thereof has a potent anticancer activity.

- [0015]

The present invention relates to the following (1) to (91).

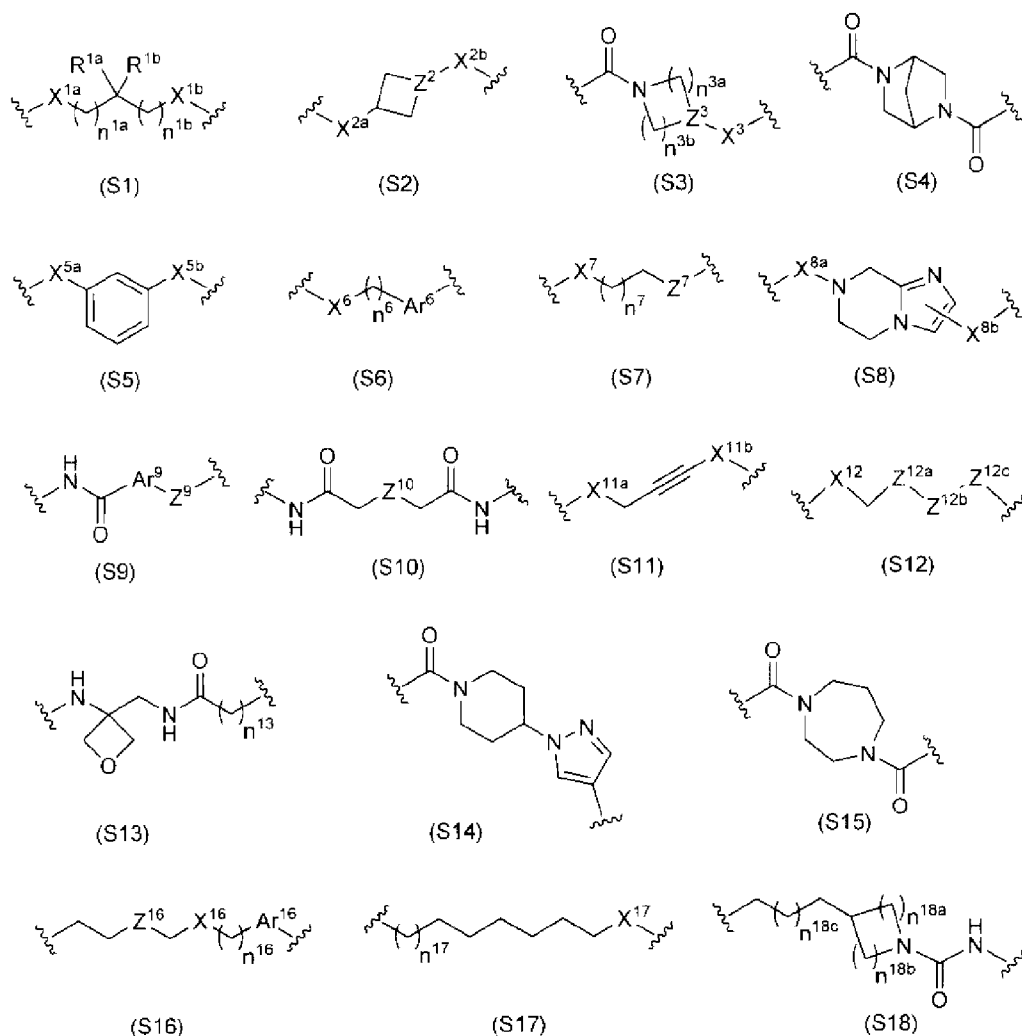
(1) A BET degrader, containing as an active ingredient a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein

L¹ and L² are the same or different and each represents a small molecular ligand for BET protein, and

S represents a group represented by a formula selected from the
10 group consisting of the following formulas (S1) to (S18):



wherein

the wavy lines each represents the bonding site to L¹ or L²,

n^{1a} and n^{1b} are the same or different and each represents 0 or 1,

5 X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-,

R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom or lower alkyl, or R^{1a} and R^{1b} together represent carbonyl,

10 X^{2a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,

X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -

- CH₂-,
- Z² represents CH or N,
- n^{3a} and n^{3b} are the same or different and each represents 1 or 2,
- X³ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-
- 5 C(=O)-NH-, or -NH-CH₂-,
- Z³ represents CH or N,
- X^{5a} and X^{5b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,
- n⁶ represents 1 or 2,
- 10 Ar⁶ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl,
- X⁶ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -CH₂-NH-, -NH-CH₂-, or -NH-C(=O)-NH-,
- X⁷ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-C(=O)-
- 15 NH-,
- n⁷ represents 1, 2, or 3,
- Z⁷ represents S, SO, or SO₂,
- X^{8a} represents -C(=O)-, -CH₂-, or -NH-C(=O)-,
- X^{8b} represents a bond, -C(=O)-, -CH₂-, or -CH(OH)-,
- 20 Ar⁹ represents triazolediyl or oxazolediyl,
- Z⁹ represents CH₂ or NH,
- Z¹⁰ represents O or NH,
- X^{11a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,
- 25 X^{11b} represents -C(=O)-NH-, -NH-C(=O)-, or -C(=O)-,
- X¹² represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,
- Z^{12a} represents CH₂ or NH,
- Z^{12b} represents CH₂ or O,
- 30 Z^{12c} represents a bond, CH₂, or O,

n^{13} represents 0, 1, or 2,

n^{16} represents 1 or 2,

Z^{16} represents a bond, CH_2 , or O,

X^{16} represents $-\text{CH}_2-\text{O}-$, $-\text{C}(=\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(=\text{O})-$, or $-\text{NH}-\text{C}(=\text{O})-$

5 $\text{NH}-$,

Ar^{16} represents triazolediyl, oxadiazolediyl, or pyrazolediyl,

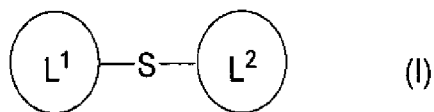
n^{17} represents 1 or 2,

X^{17} represents $-\text{C}(=\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(=\text{O})-$, $-\text{NH}-\text{SO}_2-$, or $-\text{NH}-\text{C}(=\text{O})-$

$\text{NH}-$, and

10 n^{18a} , n^{18b} , and n^{18c} are the same or different and each represents 1 or 2.

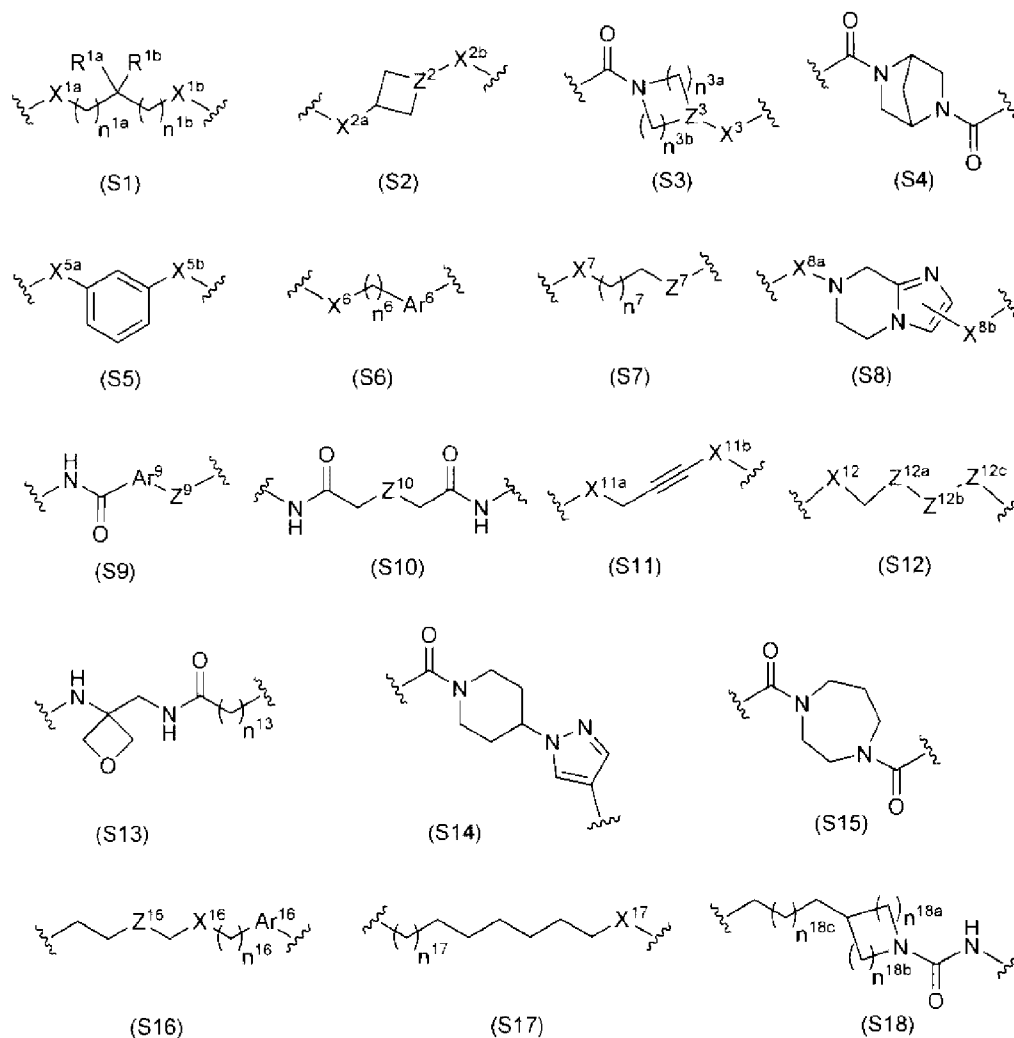
(2) A BET degrader, containing as an active ingredient a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein

L^1 and L^2 are the same or different and each represents a small molecular ligand for BET protein, and

S represents a group represented by a formula selected from the
20 group consisting of the following formulas (S1) to (S18):



wherein

the wavy lines each represents the bonding site to L¹ or L²,

n^{1a} and n^{1b} are the same or different and each represents 0 or 1,

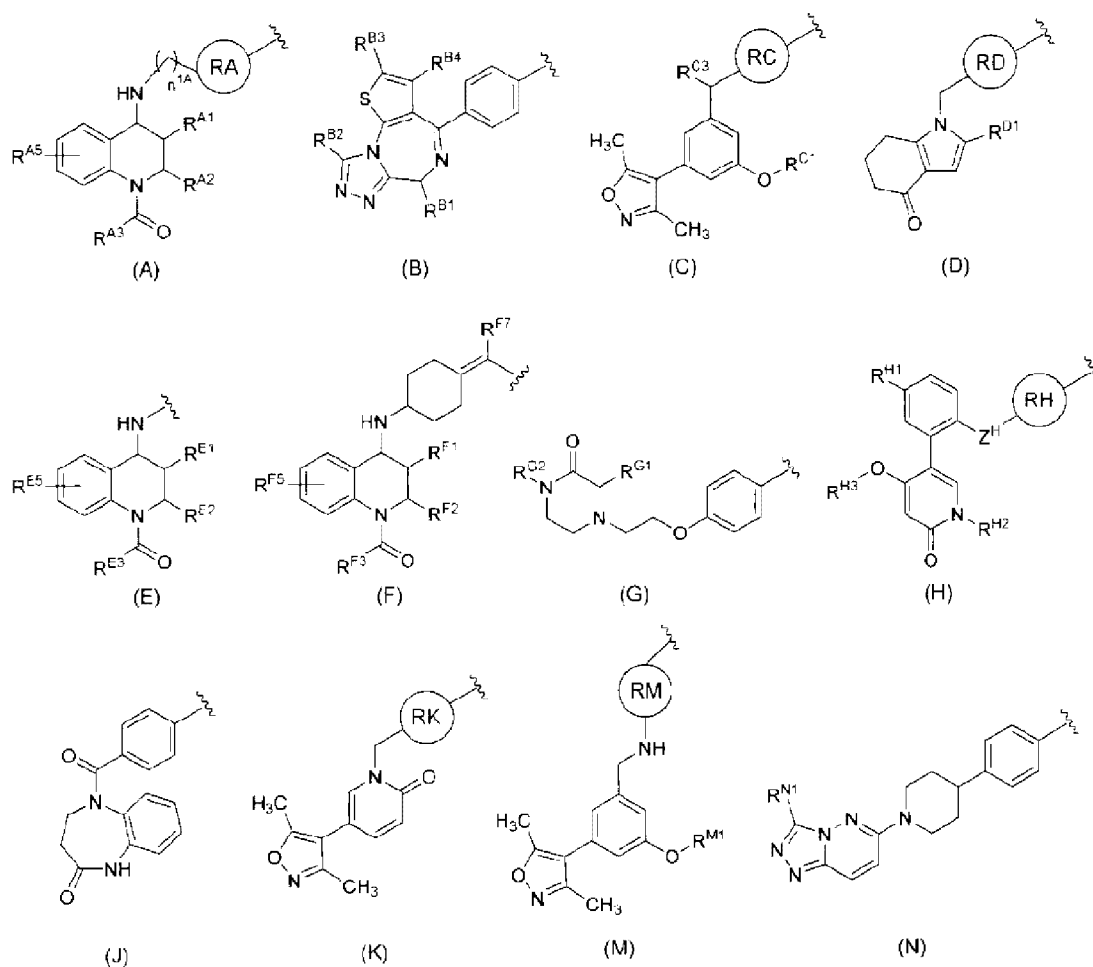
- 5 X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, except for the cases where (i) X^{1a} is -NH-SO₂- and X^{1b} is -SO₂-NH-, (ii) n^{1a} and n^{1b} are 0, X^{1a} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH- and X^{1b} is -NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a} is -O-
- 10

- C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- and X^{1b} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-,
- R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom or lower alkyl, or R^{1a} and R^{1b} together represent carbonyl,
- 5 X^{2a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,
- X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -CH₂-, except for the case where X^{2a} is -NH-SO₂- and X^{2b} is -SO₂-NH-,
- Z² represents CH or N, except for the cases where (i) Z² is N and X^{2b} is -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂- and (ii) Z² is CH and X^{2b} is -CH₂-,
- 10 n^{3a} and n^{3b} are the same or different and each represents 1 or 2,
- X³ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂-,
- Z³ represents CH or N, except for the cases where (i) Z³ is N and X³ is -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂- and (ii)
- 15 Z³ is N and n^{3a} or n^{3b} is 1,
- X^{5a} and X^{5b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-, except for the case where X^{5a} is -NH-SO₂- and X^{5b} is -SO₂-NH-,
- n⁶ represents 1 or 2,
- 20 Ar⁶ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl,
- X⁶ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -CH₂-NH- or -NH-C(=O)-NH-, except for the cases where (i) Ar⁶ is oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl and X⁶ is -NH-SO₂- and (ii) n⁶ is 1, Ar⁶ is pyrazolediyl or tetrahydropyridinediyl and X⁶ is -
- 25 C(=O)-NH-, -SO₂-NH-, -CH₂-NH-, or -NH-C(=O)-NH-,
- X⁷ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-C(=O)-NH-,
- n⁷ represents 1, 2, or 3,
- 30 Z⁷ represents S, SO, or SO₂,

- X^{8a} represents $-C(=O)-$, $-CH_2-$, or $-NH-C(=O)-$,
 X^{8b} represents a bond, $-C(=O)-$, $-CH_2-$, or $-CH(OH)-$,
 Ar^9 represents triazolediyl or oxazolediyl,
 Z^9 represents CH_2 or NH , except for the cases where (i) Ar^9 is
5 triazolediyl and Z^9 is NH and (ii) Ar^9 is oxazolediyl and Z^9 is CH_2 ,
 Z^{10} represents O or NH ,
 X^{11a} represents $-C(=O)-NH-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$,
 X^{11b} represents $-C(=O)-NH-$ or $-C(=O)-$,
 X^{12} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, or $-NH-C(=O)-$
10 $NH-$,
 Z^{12a} represents CH_2 or NH , except for the case where X^{12} is $-C(=O)-$
 $NH-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$ and Z^{12a} is NH ,
 Z^{12b} represents CH_2 or O , except for the case where Z^{12a} is NH and
 Z^{12b} is O ,
15 Z^{12c} represents a bond, CH_2 , or O , except for the cases where (i) Z^{12b}
is O and Z^{12c} is O and (ii) Z^{12a} is NH and Z^{12c} is CH_2 or O ,
 n^{13} represents 0, 1 or 2,
 n^{16} represents 1 or 2,
 Z^{16} represents a bond, CH_2 , or O ,
20 X^{16} represents $-CH_2-O-$, $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-C(=O)-$
 $NH-$, except for the case where Z^{16} is O and X^{16} is $-NH-C(=O)-$ or $-NH-$
 $C(=O)-NH-$,
 Ar^{16} represents triazolediyl, oxadiazolediyl or pyrazolediyl, except for
the cases where (i) X^{16} is $-CH_2-O-$ and Ar^{16} is oxadiazolediyl or pyrazolediyl
25 and (ii) n^{16} is 1, X^{16} is $-C(=O)-NH-$ or $-NH-C(=O)-NH-$ and Ar^{16} is
pyrazolediyl,
 n^{17} represents 1 or 2,
 X^{17} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-SO_2-$, or $-NH-C(=O)-$
 $NH-$, and
30 n^{18a} , n^{18b} , and n^{18c} are the same or different and each represents 1

or 2.

(3) The BET degrader according to (1) or (2), wherein L^1 and L^2 are the same or different and each is a group represented by a formula selected from the group consisting of the following formulas (A) to (H), (J), (K), (M) and (N):



wherein

the wavy lines each represents the bonding site to S,

R^{A1} , R^{A2} and R^{A3} are the same or different and each represents a hydrogen atom or lower alkyl,

R^{A5} represents a hydrogen atom, a halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted

tetrahydropyridinyl, optionally substituted dihydro-1H-pyrollyl, or optionally substituted tetrahydro-1H-azepinyl,

ring RA represents benzenediyl, cycloalkanediyl, pyridinediyl, piperidinediyl, azetidinediyl, pyrrolidinediyl, or homopiperidinediyl,

5 n^{1A} represents 0 or 1,

R^{B1} represents a hydrogen atom, optionally substituted lower alkoxy carbonylmethyl, optionally substituted cycloalkyloxycarbonylmethyl, or -CH₂CONR^{B5}R^{B6}, wherein R^{B5} and R^{B6} are the same or different and each represents a hydrogen atom or optionally substituted lower alkyl, or R^{B5} and

10 R^{B6} together with the adjacent nitrogen atom represent an optionally substituted nitrogen-containing aliphatic heterocyclic group,

R^{B2} represents optionally substituted lower alkyl,

R^{B3} and R^{B4} are the same or different and each represents a halogen or optionally substituted lower alkyl,

15 R^{C1} represents a hydrogen atom, lower alkyl, or lower alkanoyl,

R^{C3} represents a hydrogen atom or hydroxy,

ring RC represents benzenediyl, piperidinediyl, azetidinediyl, pyrrolidinediyl, homopiperidinediyl, piperazinediyl, or azaspiro[3.3]heptanediy,

20 R^{D1} represents optionally substituted lower alkyl or optionally substituted lower alkoxy carbonyl,

ring RD represents benzenediyl or cycloalkanediyl,

R^{E1} and R^{F1} each has the same definition as R^{A1}, and R^{E1} and R^{F1} may be the same or different,

25 R^{E2} and R^{F2} each has the same definition as R^{A2}, and R^{E2} and R^{F2} may be the same or different,

R^{E3} and R^{F3} each has the same definition as R^{A3}, and R^{E3} and R^{F3} may be the same or different,

R^{E5} and R^{F5} each has the same definition as R^{A5}, and R^{E5} and R^{F5} may

30 be the same or different,

- R^{F7} represents a hydrogen atom or a halogen,
 R^{G1} and R^{G2} are the same or different and each represents a hydrogen atom or lower alkyl,
 R^{H1} represents a hydrogen atom or lower alkyl sulfonamide,
5 R^{H2} and R^{H3} are the same or different and each represents lower alkyl,
 Z^H represents CH_2 or O,
ring RH represents benzenediyl, cycloalkanediyl, azetidinediyl, pyrrolidinediyl, piperidinediyl, or homopiperidinediyl,
10 ring RK represents benzenediyl or cycloalkanediyl,
 R^{M1} represents a hydrogen atom or lower alkyl,
ring RM represents cycloalkanediyl, and
 R^{N1} represents a hydrogen atom, a halogen, lower alkyl, or lower alkoxy.
- 15 (4) The BET degrader according to any one of (1) to (3), wherein L^1 represents a group represented by formula (A), (B), (C), (D), (F), or (G), L^2 represents a group represented by formula (A), (B), (C), (D), (H), (J), (K), or (M), and S is a group represented by formula (S1).
- (5) The BET degrader according to any one of (1) to (3), wherein L^1
20 represents a group represented by formula (A), L^2 represents a group represented by formula (A), and S is a group represented by formula (S2).
- (6) The BET degrader according to any one of (1) to (3), wherein L^1 represents a group represented by formula (A), (B), (C), (G), or (N), L^2 represents a group represented by formula (A) or (B), and S is a group
25 represented by formula (S3).
- (7) The BET degrader according to any one of (1) to (3), wherein L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (A), and S is a group represented by formula (S4) or (S5).
- 30 (8) The BET degrader according to any one of (1) to (3), wherein L^1

represents a group represented by formula (A), (B), (C), (D), (G), or (H),
L² represents a group represented by formula (A), (B), (C), or (D), and S
is a group represented by formula (S6).

5 (9) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A) or (B), L² represents a group
represented by formula (A), and S is a group represented by formula (S7).

(10) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A) or (B), L² represents a group
represented by formula (A), and S is a group represented by formula (S8).

10 (11) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A), L² represents a group
represented by formula (A), and S is a group represented by formula (S9).

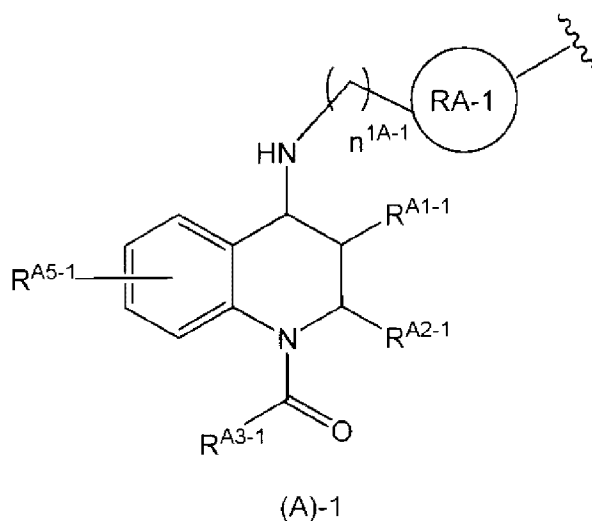
(12) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A) or (B), L² represents a group
15 represented by formula (A), and S represents a group represented by
formula (S10).

(13) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A) or (B), L² represents a group
represented by formula (A) or (B), and S represents a group represented
20 by formula (S11).

(14) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (A), L² represents a group
represented by formula (A), and S represents a group represented by
formula (S12), (S13), (S14), or (S15).

25 (15) The BET degrader according to any one of (1) to (3), wherein L¹
represents a group represented by formula (E), L² represents a group
represented by formula (A), and S represents a group represented by
formula (S16), (S17), or (S18).

(16) The BET degrader according to any one of (1) to (15), wherein
30 formula (A) is the following formula (A)-1:



wherein

the wavy line represents the bonding site to S,

R^{A1-1} represents a hydrogen atom,

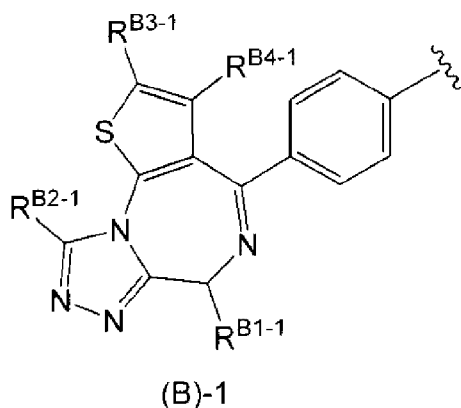
5 R^{A2-1} and R^{A3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms,

R^{A5-1} represents a hydrogen atom, a fluorine atom, optionally substituted alkyl having 1 to 5 carbon atoms, optionally substituted alkenyl having 2 to 6 carbon atoms, or optionally substituted tetrahydropyridinyl,

10 ring RA-1 represents benzenediyl, cycloalkanediyl, pyridinediyl, or piperidinediyl, and

n^{1A-1} represents 0 or 1.

(17) The BET degrader according to any one of (1) to (4), (6), (8) to (10), (12) and (13), wherein formula (B) is the following formula (B)-1:



wherein

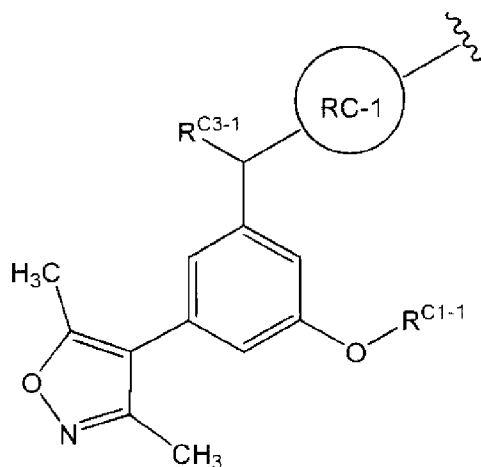
the wavy line represents the bonding site to S,

R^{B1-1} represents a hydrogen atom, optionally substituted
 5 alkoxycarbonylmethyl having 1 to 5 carbon atoms, optionally substituted
 cycloalkyloxycarbonylmethyl, or $-CH_2CONR^{B5-1}R^{B6-1}$, wherein, R^{B5-1} and R^{B6-1}
 ^{1} are the same or different and each represents a hydrogen atom or alkyl
 having 1 to 5 carbon atoms, or R^{B5-1} and R^{B6-1} together with the adjacent
 nitrogen atom represent an optionally substituted nitrogen-containing
 10 aliphatic heterocyclic group,

R^{B2-1} represents optionally substituted alkyl having 1 to 5 carbon
 atoms, and

R^{B3-1} and R^{B4-1} each represents optionally substituted alkyl having 1
 to 5 carbon atoms.

15 (18) The BET degrader according to any one of (1) to (4), (6) and (8),
 wherein formula (C) is the following formula (C)-1:



(C)-1

wherein

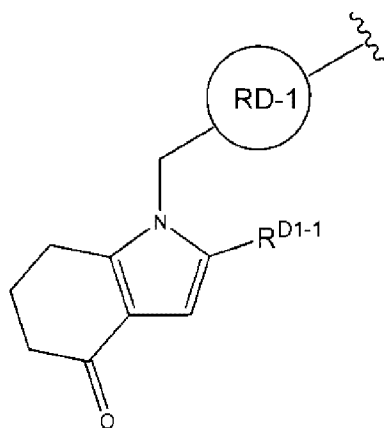
the wavy line represents the bonding site to S,

R^{C1-1} represents a hydrogen atom,

5 R^{C3-1} represents a hydrogen atom or hydroxy, and

ring RC-1 represents benzenediyl, piperidinediyl, piperadinediyl, or azaspiro[3.3]heptanediyl.

(19) The BET degrader according to any one of (1) to (4) and (8), wherein formula (D) is the following formula (D)-1:



(D)-1

wherein

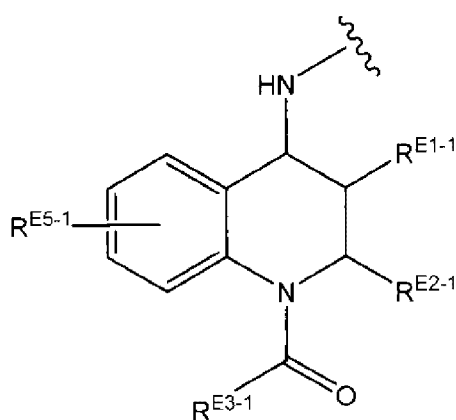
the wavy line represents the bonding site to S,

R^{D1-1} represents optionally substituted alkyl having 1 to 5 carbon atoms or optionally substituted alkoxy carbonyl having 1 to 5 carbon atoms,

5 and

ring RD-1 represents benzenediyl or cyclohexanediyl.

(20) The BET degrader according to any one of (1) to (3) and (15), wherein formula (E) is the following formula (E)-1:



(E)-1

10 wherein

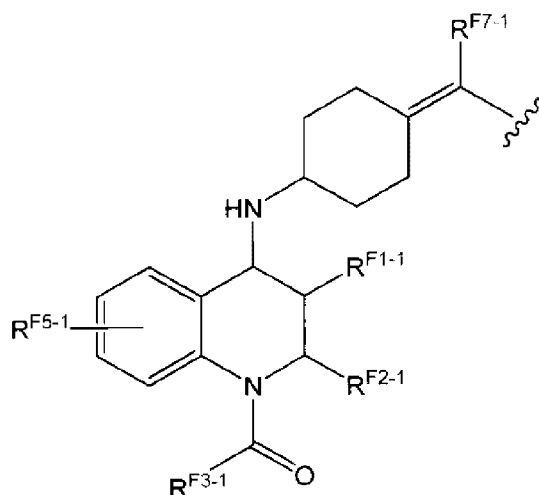
the wavy line represents the bonding site to S,

R^{E1-1} represents a hydrogen atom,

R^{E2-1} and R^{E3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms, and

15 R^{E5-1} represents a hydrogen atom.

(21) The BET degrader according to any one of (1) to (4), wherein formula (F) is the following formula (F)-1:



(F)-1

wherein

the wavy line represents the bonding site to S,

R^{F1-1} represents a hydrogen atom,

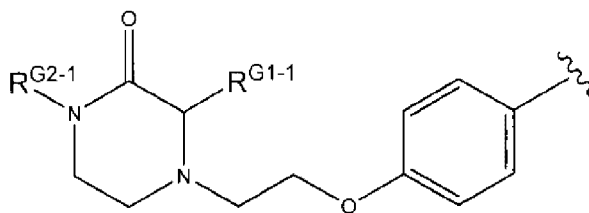
5 R^{F2-1} and R^{F3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms,

R^{F5-1} represents a hydrogen atom, and

R^{F7-1} represents a hydrogen atom or a fluorine atom.

(22) The BET degrader according to any one of (1) to (4), (6) and (8),

10 wherein formula (G) is the following formula (G)-1:



(G)-1

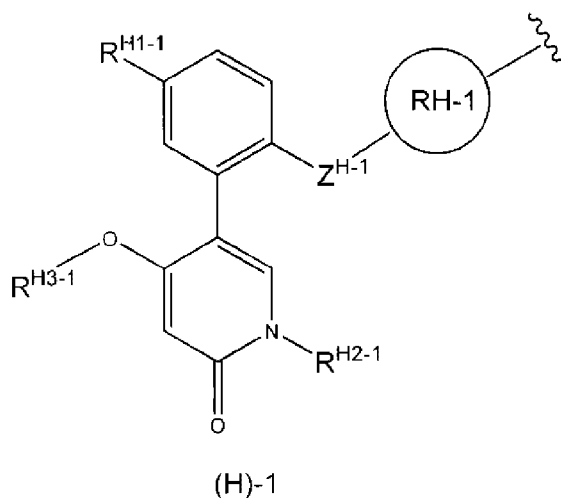
wherein

the wavy line represents the bonding site to S, and

R^{G1-1} and R^{G2-1} are the same or different and each represents alkyl

having 1 to 5 carbon atoms.

(23) The BET degrader according to any one of (1) to (4) and (8), wherein formula (H) is the following formula (H)-1:



5 wherein

the wavy line represents the bonding site to S,

R^{H1-1} represents a hydrogen atom or alkylsulfonamide having 1 to 5 carbon atoms,

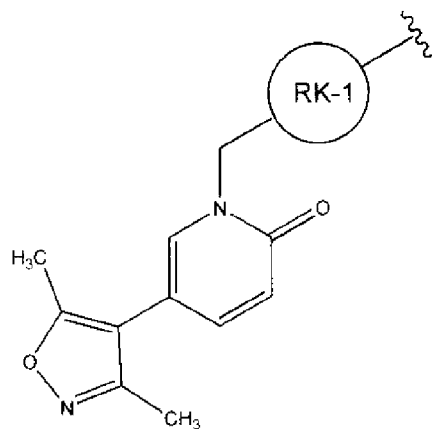
R^{H2-1} and R^{H3-1} are the same or different and each represents alkyl

10 having 1 to 5 carbon atoms,

Z^{H-1} represents CH_2 or O, and

ring RH-1 represents benzenediyl, cyclohexanediyl, or piperidinediyl.

(24) The BET degrader according to any one of (1) to (4), wherein formula (K) is the following formula (K)-1:



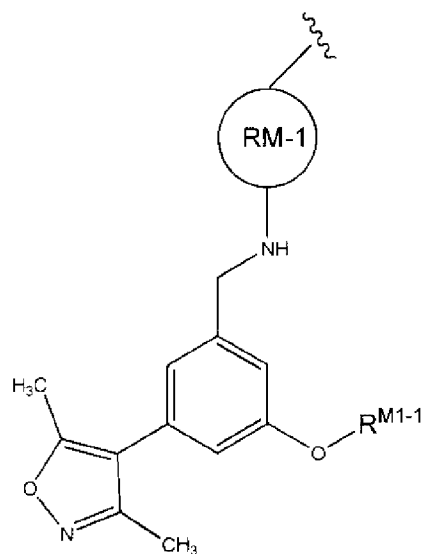
(K)-1

wherein

the wavy line represents the bonding site to S, and

ring RK-1 represents benzenediyl or cyclohexanediyl.

- 5 (25) The BET degrader according to any one of (1) to (4), wherein formula (M) is the following formula (M)-1:



(M)-1

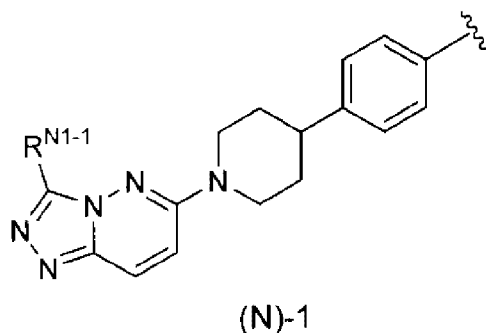
wherein

the wavy line represents the bonding site to S,

R^{M1-1} represents a hydrogen atom, and

ring RM-1 represents bicycloalkanediyl having 5 to 8 carbon atoms.

(26) The BET degrader according to any one of (1) to (3) and (6), wherein formula (N) is the following formula (N)-1:



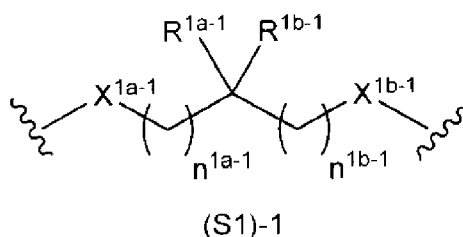
5

wherein

the wavy line represents the bonding site to S, and

R^{N-1} represents a halogen.

(27) The BET degrader according to any one of (1) to (4), wherein S is
10 the following formula (S1)-1:



wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

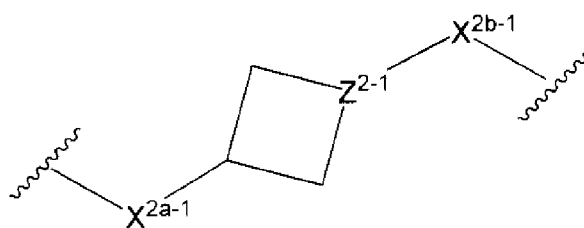
n^{1a-1} and n^{1b-1} are the same or different and each represents 0 or 1,

15 X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, except for the cases where (i) X^{1a-1} is -NH-SO₂- and X^{1b-1} is -SO₂-NH-, (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH- and X^{1b-1} is

-NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- and X^{1b-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and

R^{1a-1} represents a hydrogen atom and R^{1b-1} represents a hydrogen atom or alkyl having 1 to 5 carbon atoms, or R^{1a-1} and R^{1b-1} together represent carbonyl.

(28) The BET degrader according to any one of (1) to (3) and (5), wherein S is the following formula (S2)-1:



(S2)-1

wherein

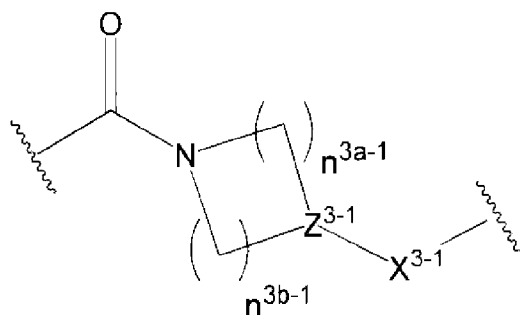
the wavy lines each represents the bonding site to L¹ or L²,

X^{2a-1} represents -C(=O)-NH- or -NH-C(=O)-,

X^{2b-1} represents -C(=O)-NH-, -NH-C(=O)-, or -CH₂-, and

Z²⁻¹ represents CH or N, except for the cases where (i) Z²⁻¹ is N and X^{2b-1} is -NH-C(=O)- and (ii) Z²⁻¹ is CH and X^{2b-1} is -CH₂-.

(29) The BET degrader according to any one of (1) to (3) and (6), wherein S is the following formula (S3)-1:



(S3)-1

wherein

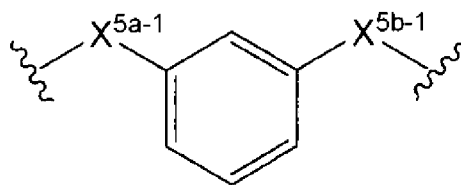
the wavy lines each represents the bonding site to L^1 or L^2 ,

n^{3a-1} and n^{3b-1} are the same or different and each represents 1 or 2,

5 X^{3-1} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-CH_2-$, and

Z^{3-1} represents CH or N, except for the cases where (i) Z^{3-1} is N and X^{3-1} is $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-CH_2-$ and (ii) Z^{3-1} is N and n^{3a-1} or n^{3b-1} is 1.

10 (30) The BET degrader according to any one of (1) to (3) and (7), wherein S is the following formula (S5)-1:



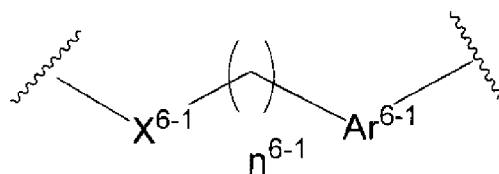
(S5)-1

wherein

the wavy lines each represents the bonding site to L^1 or L^2 and

15 X^{5a-1} and X^{5b-1} are the same or different and each represents $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-SO_2-$.

(31) The BET degrader according to any one of (1) to (3) and (8), wherein S is the following formula (S6)-1:



(S6)-1

wherein

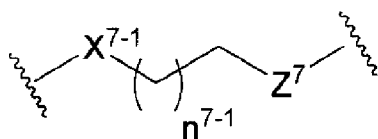
the wavy lines each represents the bonding site to L¹ or L²,

n⁶⁻¹ represents 1 or 2,

5 Ar⁶⁻¹ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl, and

X⁶⁻¹ represents -C(=O)-NH-, -NH-C(=O)-, or -CH₂-NH-, except for the case where n⁶⁻¹ is 1, Ar⁶⁻¹ is pyrazolediyl or tetrahydropyridinediyl and X⁶⁻¹ is -C(=O)-NH- or -CH₂-NH-.

10 (32) The BET degrader according to any one of (1) to (3) and (9), wherein S is the following formula (S7)-1:



(S7)-1

wherein

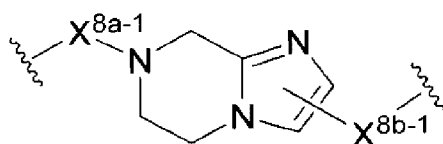
the wavy lines each represents the bonding site to L¹ or L²,

15 X⁷⁻¹ represents -C(=O)-NH- or -NH-C(=O)-,

n⁷⁻¹ represents 1, and

Z⁷⁻¹ represents S, SO, or SO₂.

(33) The BET degrader according to any one of (1) to (3) and (10), wherein S is the following formula (S8)-1:



(S8)-1

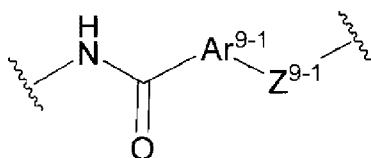
wherein

the wavy lines each represents the bonding site to L¹ or L²,

X^{8a-1} represents -C(=O)- or -CH₂-, and

5 X^{8b-1} represents a bond, -C(=O)-, -CH₂-, or -CH(OH)-.

(34) The BET degrader according to any one of (1) to (3) and (11),
wherein S is the following formula (S9)-1:



(S9)-1

wherein

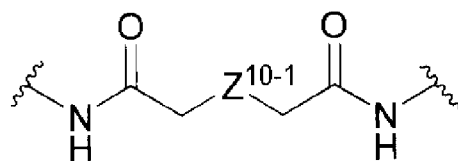
10 the wavy lines each represents the bonding site to L¹ or L²,

Ar⁹⁻¹ represents triazolediyl or oxazolediyl, and

Z⁹⁻¹ represents CH₂ or NH, except for the cases where (i) Ar⁹⁻¹ is triazolediyl and Z⁹⁻¹ is NH and (ii) Ar⁹⁻¹ is oxazolediyl and Z⁹⁻¹ is CH₂.

(35) The BET degrader according to any one of (1) to (3) and (12),

15 wherein S is the following formula (S10)-1:

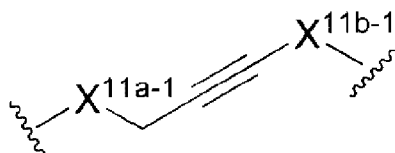


(S10)-1

wherein

the wavy lines each represents the bonding site to L^1 or L^2 and Z^{10-1} represents O or NH.

(36) The BET degrader according to any one of (1) to (3) and (13), wherein S is the following formula (S11)-1:



(S11)-1

5

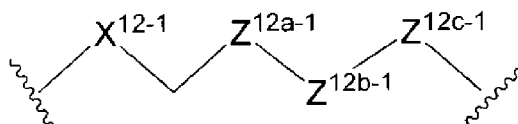
wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

X^{11a-1} represents $-C(=O)-NH-$, and

X^{11b-1} represents $-C(=O)-NH-$ or $-C(=O)-$.

10 (37) The BET degrader according to any one of (1) to (3) and (14), wherein S is the following formula (S12)-1:



(S12)-1

wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

15 X^{12-1} represents $-C(=O)-NH-$ or $-NH-C(=O)-$,

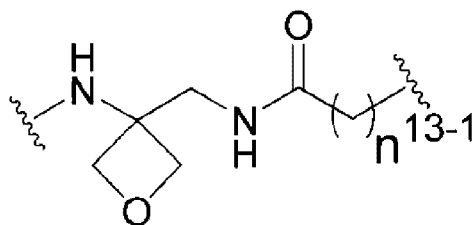
Z^{12a-1} represents CH_2 or NH , except for the case where X^{12-1} is $-C(=O)-NH-$ and Z^{12a-1} is NH ,

Z^{12b-1} represents CH_2 or O , except for the case where Z^{12a-1} is NH and Z^{12b-1} is O , and

20 Z^{12c-1} represents a bond or O , except for the cases where (i) Z^{12b-1} is

O and Z^{12c-1} is O and (ii) Z^{12a-1} is NH and Z^{12c-1} is O.

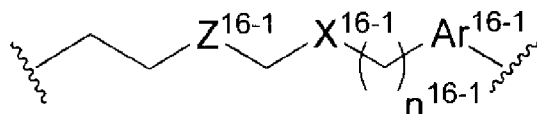
(38) The BET degrader according to any one of (1) to (3) and (14), wherein S is the following formula (S13)-1:



(S13)-1

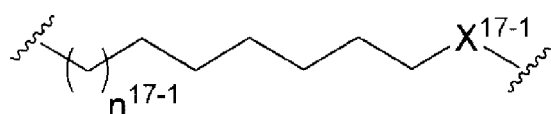
5 wherein
the wavy lines each represents the bonding site to L^1 or L^2 and
 n^{13-1} represents 0 or 2.

(39) The BET degrader according to any one of (1) to (3) and (15), wherein S is the following formula (S16)-1:



(S16)-1

10 wherein
the wavy lines each represents the bonding site to L^1 or L^2 ,
 n^{16-1} represents 1 or 2,
 Z^{16-1} represents a bond, CH_2 , or O,
15 X^{16-1} represents $-CH_2-O-$ or $-C(=O)-NH-$, and
 Ar^{16-1} represents triazolediyl, oxadiazolediyl, or pyrazolediyl, except
for the cases where (i) X^{16-1} is $-CH_2-O-$ and Ar^{16-1} is oxadiazolediyl or
pyrazolediyl and (ii) n^{16-1} is 1, X^{16-1} is $-C(=O)-NH-$ and Ar^{16-1} is pyrazolediyl.
(40) The BET degrader according to any one of (1) to (3) and (15),
20 wherein S is the following formula (S17)-1:



(S17)-1

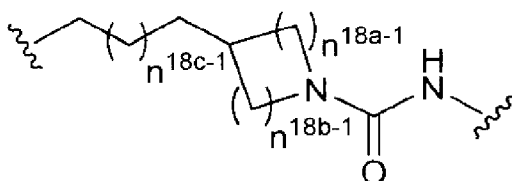
wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

n^{17-1} represents 1 or 2, and

5 X^{17-1} represents $-C(=O)-NH-$.

(41) The BET degrader according to any one of (1) to (3) and (15), wherein S is the following formula (S18)-1:



(S18)-1

wherein

10 the wavy lines each represents the bonding site to L^1 or L^2 ,

n^{18a-1} represents 2,

n^{18b-1} represents 2, and

n^{18c-1} represents 1.

(42) The BET degrader according to any one of (1) to (3), wherein L^1 and
15 L^2 each represents a group represented by formula (A) and S is a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A}
20 represents 0, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the

same or different and each represents -C(=O)-NH- or -NH-C(=O)- , R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(43) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S1), n^{1a} and n^{1b} each represents 0, X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH- , -NH-C(=O)- , or -NH-C(=O)-NH- , except for the case where X^{1a} is -C(=O)-NH- or -NH-C(=O)-NH- and X^{1b} is -NH-C(=O)- or -NH-C(=O)-NH- , R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(44) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or pyridinediyl, and n^{1A} represents 0, and

in formula (S1), n^{1a} and n^{1b} represent 1, X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH- or -NH-C(=O)- , R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(45) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S3), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms,

R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or

cycloalkanediyl, and n^{1A} represents 0, and

in formula (S3), n^{3a} and n^{3b} each represents 2, X^3 represents -C(=O)-NH-, and Z^3 represents N.

(46) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S3), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S3), n^{3a} and n^{3b} each represents 1, X^3 represents -C(=O)-NH-, and Z^3 represents CH.

(47) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S6), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0, and

in formula (S6), n^6 represents 1, Ar^6 represents oxadiazole-diyl, and X^6 represents -CH₂-NH-.

(48) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S6), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0, and

in formula (S6), n^6 represents 1, Ar^6 represents triazole-diyl, and X^6 represents -CH₂-NH-.

(49) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S6), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S6), n^6 represents 1, Ar^6 represents oxadiazole-diyl, and X^6 represents $-C(=O)-NH-$.

(50) The BET degrader according to any one of (1) to (3), wherein L^1 and L^2 each represents a group represented by formula (A) and S is a group represented by formula (S6), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S6), n^6 represents 2, Ar^6 represents triazole-diyl, and X^6 represents $-C(=O)-NH-$.

(51) The BET degrader according to any one of (1) to (3), wherein L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (H), and S represents a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

in formula (H), R^{H1} represents alkyl sulfonamide having 1 to 5 carbon atoms, R^{H2} and R^{H3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^H represents O, and ring RH represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(52) The BET degrader according to any one of (1) to (3), wherein L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (H), and S is a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

in formula (H), R^{H1} represents a hydrogen atom, R^{H2} and R^{H3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^H represents O, ring RH represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(53) A method for degrading BET, including administering to a subject the compound according to any one of (1) to (52) or a pharmaceutically acceptable salt thereof.

(54) A method for treating or preventing cancer, including administering to a subject the BET degrader according to any one of (1) to (52).

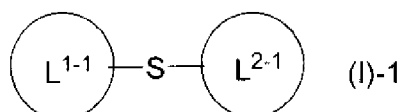
(55) The BET degrader according to any one of (1) to (52) for use as a medicament.

(56) A pharmaceutical composition, containing the BET degrader according to any one of (1) to (52).

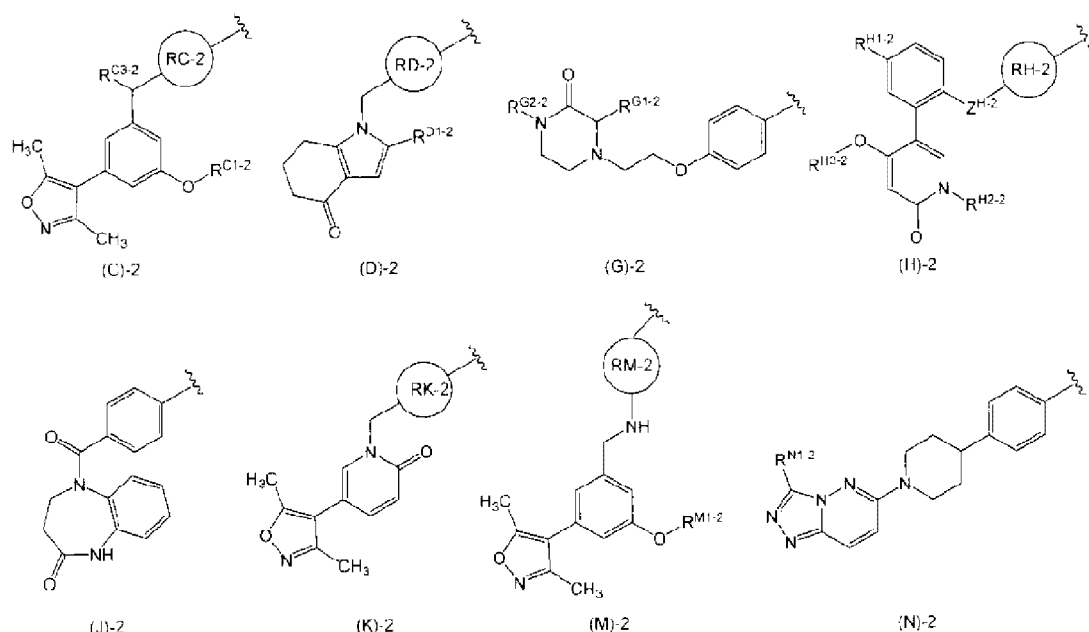
(57) The pharmaceutical composition according to (56), further containing a carrier.

(58) The pharmaceutical composition according to (56) or (57) for use in the treatment or prevention of cancer.

- (59) The BET degrader according to any one of (1) to (52) for use in the treatment or prevention of cancer.
- (60) Use of the compound according to any one of (1) to (52) or a pharmaceutically acceptable salt thereof for the manufacture of a drug for degrading BET protein.
- (61) Use of the BET degrader according to any one of (1) to (52) in the manufacture of a drug for the treatment or prevention of cancer.
- (62) Use of the BET degrader according to any one of (1) to (52) in the treatment or prevention of cancer.
- (63) A medicament, containing as an active ingredient the BET degrader according to any one of (1) to (52).
- (64) A prophylactic or therapeutic agent, containing as an active ingredient the BET degrader according to any one of (1) to (52).
- (65) A compound represented by the following formula (I)-1 or a pharmaceutically acceptable salt thereof:



- wherein one of L^{1-1} and L^{2-1} is a group represented by a formula selected from the group consisting of the following formulas (C)-2, (D)-2, (G)-2, (H)-2, (J)-2, (K)-2, (M)-2, and (N)-2, and the other of L^{1-1} and L^{2-1} is a group represented by a formula selected from the group consisting of formulas (A) to (H), (J), (K), (M), and (N) described in the above (3), and S is a group represented by a formula selected from the group consisting of formulas (S1) to (S18) described in the above (1) or (2):



wherein

the wavy lines each represents the bonding site to S,

R^{C1-2} represents a hydrogen atom, lower alkyl or lower alkanoyl,

5 R^{C3-2} represents a hydrogen atom or hydroxy,

ring RC-2 represents piperazinediyl or azaspiro[3.3]heptanediyl,

R^{D1-2} represents optionally substituted lower alkyl or optionally substituted lower alkoxy carbonyl,

ring RD-2 represents cycloalkanediyl,

10 R^{G1-2} and R^{G2-2} are the same or different and each represents a hydrogen atom or lower alkyl,

R^{H1-2} represents a hydrogen atom or lower alkyl sulfonamide,

R^{H2-2} and R^{H3-2} are the same or different and each represents lower alkyl,

15 Z^{H-2} represents CH₂ or O,

ring RH-2 represents benzenediyl, cycloalkanediyl, azetidinediyl, pyrrolidinediyl, piperidinediyl, or homopiperidinediyl,

ring RK-2 represents benzenediyl or cycloalkanediyl,

R^{M1-2} represents a hydrogen atom or lower alkyl,

ring $RM-2$ represents cycloalkanediyl, and

R^{N1-2} represents a hydrogen atom, a halogen, lower alkyl or lower alkoxy.

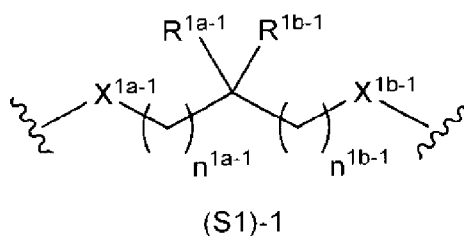
5 (66) The compound according to (65) or a pharmaceutically acceptable salt thereof, wherein L^{1-1} represents a group represented by formula (G)-2, L^{2-1} represents a group represented by formula (A), and S is a group represented by formula (S1).

(67) The compound according to (65) or a pharmaceutically acceptable
10 salt thereof, wherein L^{1-1} represents a group represented by formula (A), L^{2-1} represents a group represented by formula (C)-2, (D)-2, (H)-2, (J)-2, (K)-2, or (M)-2, and S is a group represented by formula (S1).

(68) The compound according to (65) or a pharmaceutically acceptable
15 salt thereof, wherein L^{1-1} represents a group represented by formula (G)-2 or (N)-2, L^{2-1} represents a group represented by formula (A), and S represents a group represented by formula (S3).

(69) The compound according to (65) or a pharmaceutically acceptable
20 salt thereof, wherein L^{1-1} represents a group represented by formula (C)-2, (G)-2, or (H)-2, L^{2-1} represents a group represented by formula (A), and S is a group represented by formula (S6).

(70) The compound according to any one of (65) to (67) or a pharmaceutically acceptable salt thereof, wherein S is the following formula (S1)-1:

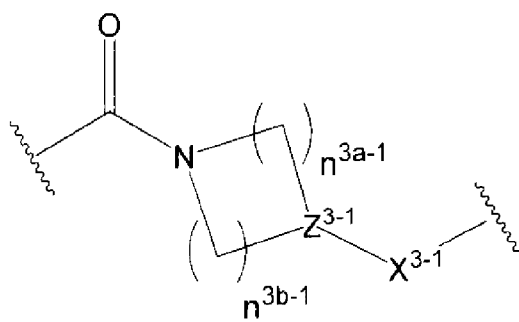


wherein

25 the wavy lines each represents the bonding site to L^{1-1} or L^{2-1} ,

n^{1a-1} and n^{1b-1} are the same or different and each represents 0 or 1,
 X^{1a-1} and X^{1b-1} are the same or different and each represents $-C(=O)-$
 $NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, $-NH-SO_2-$, $-O-C(=S)-NH-$, $-O-C(=O)-NH-$, $-$
 $NH-C(=O)-O-$, or $-NH-C(=O)-NH-$, except for the cases where (i) X^{1a-1} is $-$
 5 $NH-SO_2-$ and X^{1b-1} is $-SO_2-NH-$, (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is $-C(=O)-NH-$
 $, -SO_2-NH-$, $-O-C(=S)-NH-$, $-O-C(=O)-NH-$, or $-NH-C(=O)-NH-$, and X^{1b-1} is
 $-NH-C(=O)-$, $-NH-SO_2-$, $-NH-C(=O)-O-$, or $-NH-C(=O)-NH-$, and (iii) X^{1a-1} is
 $-O-C(=S)-NH-$, $-O-C(=O)-NH-$, $-NH-C(=O)-O-$, or $-NH-C(=O)-NH-$, and X^{1b-1}
 ^{1} is $-O-C(=S)-NH-$, $-O-C(=O)-NH-$, $-NH-C(=O)-O-$, or $-NH-C(=O)-NH-$, and
 10 R^{1a-1} represents a hydrogen atom and R^{1b-1} represents a hydrogen
 atom or alkyl having 1 to 5 carbon atoms, or R^{1a-1} and R^{1b-1} together
 represent carbonyl.

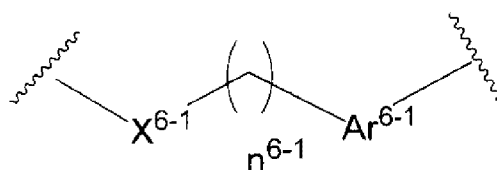
(71) The compound according to (65) or (68) or a pharmaceutically
 acceptable salt thereof, wherein S is the following formula (S3)-1:



(S3)-1

15 wherein
 the wavy lines each represents the bonding site to L^{1-1} or L^{2-1} ,
 n^{3a-1} and n^{3b-1} are the same or different and each represents 1 or 2,
 X^{3-1} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-$
 20 CH_2- , and
 Z^{3-1} represents CH or N, except for the cases where (i) Z^{3-1} is N and
 X^{3-1} is $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-CH_2-$, and (ii) Z^{3-1} is N and n^{3a-1}
 ^{1} or n^{3b-1} is 1.

(72) The compound according to (65) or (69) or a pharmaceutically acceptable salt thereof, wherein S is the following formula (S6)-1:



(S6)-1

wherein

5 the wavy lines each represents the bonding site to L¹⁻¹ or L²⁻¹,
n⁶⁻¹ represents 1 or 2,

Ar⁶⁻¹ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl, and

X⁶⁻¹ represents -C(=O)-NH-, -NH-C(=O)-, or -CH₂-NH-, except for
10 the case where (i) n⁶⁻¹ is 1, Ar⁶⁻¹ is pyrazolediyl or tetrahydropyridinediyl, and X⁶⁻¹ is -C(=O)-NH- or -CH₂-NH-.

(73) The compound according to (65) or a pharmaceutically acceptable salt thereof, wherein L¹⁻¹ represents a group represented by formula (A), L²⁻¹ represents a group represented by formula (H)-2, and S represents a
15 group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

20 in formula (H)-2, RH¹⁻² represents alkyl sulfonamide having 1 to 5 carbon atoms, R^{H2-2} and R^{H3-2} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^{H-2} represents O, and ring RH-2 represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the
25 same or different and each represents -C(=O)-NH- or -NH-C(=O)-, R^{1a}

represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(74) The compound according to (65) or a pharmaceutically acceptable salt thereof, wherein L^{1-1} represents a group represented by formula (A), L^{2-1} represents a group represented by formula (H)-2, and S represents a group represented by formula (S1), and wherein,

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

in formula (H)-2, R^{H1-2} represents a hydrogen atom, R^{H2-2} and R^{H3-2} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^{H-2} represents O, and ring RH-2 represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH- or -NH-C(=O)-, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

(75) A method for degrading BET, including administering to a subject the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.

(76) A method for treatment or prevention, including administering to a subject the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.

(77) The method according to (76) for treating or preventing cancer.

(78) The compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for use as a medicament.

(79) A pharmaceutical composition, containing the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.

(80) The pharmaceutical composition according to (79), further containing a carrier.

(81) The pharmaceutical composition according to (79) or (80) for use for the degradation of BET protein.

- (82) The pharmaceutical composition according to (79) or (80) for use in the treatment or prevention of cancer.
- (83) The compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for use for the degradation of BET protein.
- (84) The compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of cancer.
- (85) The compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for use in the manufacture of a drug for degrading BET protein.
- (86) Use of the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for the manufacture of a drug for the treatment or prevention of cancer.
- (87) Use of the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for the degradation of BET protein.
- (88) Use of the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof for the treatment or prevention of cancer.
- (89) A medicament, containing as an active ingredient the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.
- (90) A BET degrader, containing as an active ingredient the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.
- (91) A prophylactic or therapeutic agent, containing as an active ingredient the compound according to any one of (65) to (74) or a pharmaceutically acceptable salt thereof.

[0016]

- The BET degrader of the present invention or the compound of the

present invention or a pharmaceutically acceptable salt thereof includes two small molecular ligands for BET protein that are linked by a spacer having a specific structure as described in (1) to (91) above, and thus exhibits an action of degrading the target BET protein even at a low dose. The BET
5 degrader of the present invention or the compound of the present invention or a pharmaceutically acceptable salt thereof exhibits a potent anticancer activity.

BRIEF DESCRIPTION OF THE DRAWINGS

10 [0017]

FIG. 1 shows the results of changes in BRD4, BRD2 and BRD3 protein levels by a test compound (compound 1b, compound 1l or compound P3) in cells of a SU-DHL-4 cell line, detected by Western blotting. In the figure, "Control" is a lane in which a DMSO solution was added so that the final
15 concentration was 0.1 vol%, and the eluate obtained from the cells was electrophoresed. In the figure, "1b, 100 nM" is a lane in which a diluted solution of compound 1b was added so that the final concentration was 100 nmol/L, and the eluate obtained from the cells was electrophoresed. In the figure, "1l, 100 nM" is a lane in which a diluted solution of compound 1l was
20 added so that the final concentration was 100 nmol/L, and the eluate obtained from the cells was electrophoresed. In the figure, "P3, 100 nM" is a lane in which a diluted solution of compound P3 was added so that the final concentration was 100 nmol/L, and the eluate obtained from the cells was electrophoresed. In the figure, BRD2, BRD3, BRD4 and beta actin show
25 the protein amounts of BRD2, BRD3, BRD4 and beta actin, respectively. Compound P3 is a compound described as example 14 in Patent Document 2 (WO 2015/081284).

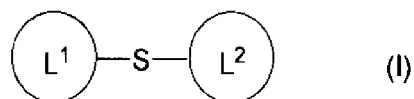
FIG. 2 shows the results of inhibition of BRD2, BRD3 and BRD4 degradation by a ubiquitination pathway inhibitor (MLN-4924), detected by
30 Western blotting. In the figure, "Control" is a lane in which a DMSO solution

was added so that the final concentration was 0.1 vol%, and the eluate obtained from the cells was electrophoresed. In the figure, "1b, 10 nM", "1b, 100 nM" and "1b, 1000 nM" each is a lane in which a diluted solution of compound 1b was added so that the final concentration was 10 nmol/L, 100 nmol/L and 1000 nmol/L, respectively, and the eluate obtained from the cells was electrophoresed. In the figure, "1l, 10 nM", "1l, 100 nM" and "1l, 1000 nM" each is a lane in which a diluted solution of compound 1l was added so that the final concentration was 10 nmol/L, 100 nmol/L and 1000 nmol/L, respectively, and the eluate obtained from the cells was electrophoresed. For the item shown as "MLN-4924 100 nM" in the figure, the condition with the addition of MLN-4924 with a final concentration of 100 nmol/L is indicated by "+", and the condition without the addition of MLN-4924 is indicated by "-". In the figure, BRD2, BRD3, BRD4 and beta actin represent the protein amounts of BRD2, BRD3, BRD4 and beta actin, respectively.

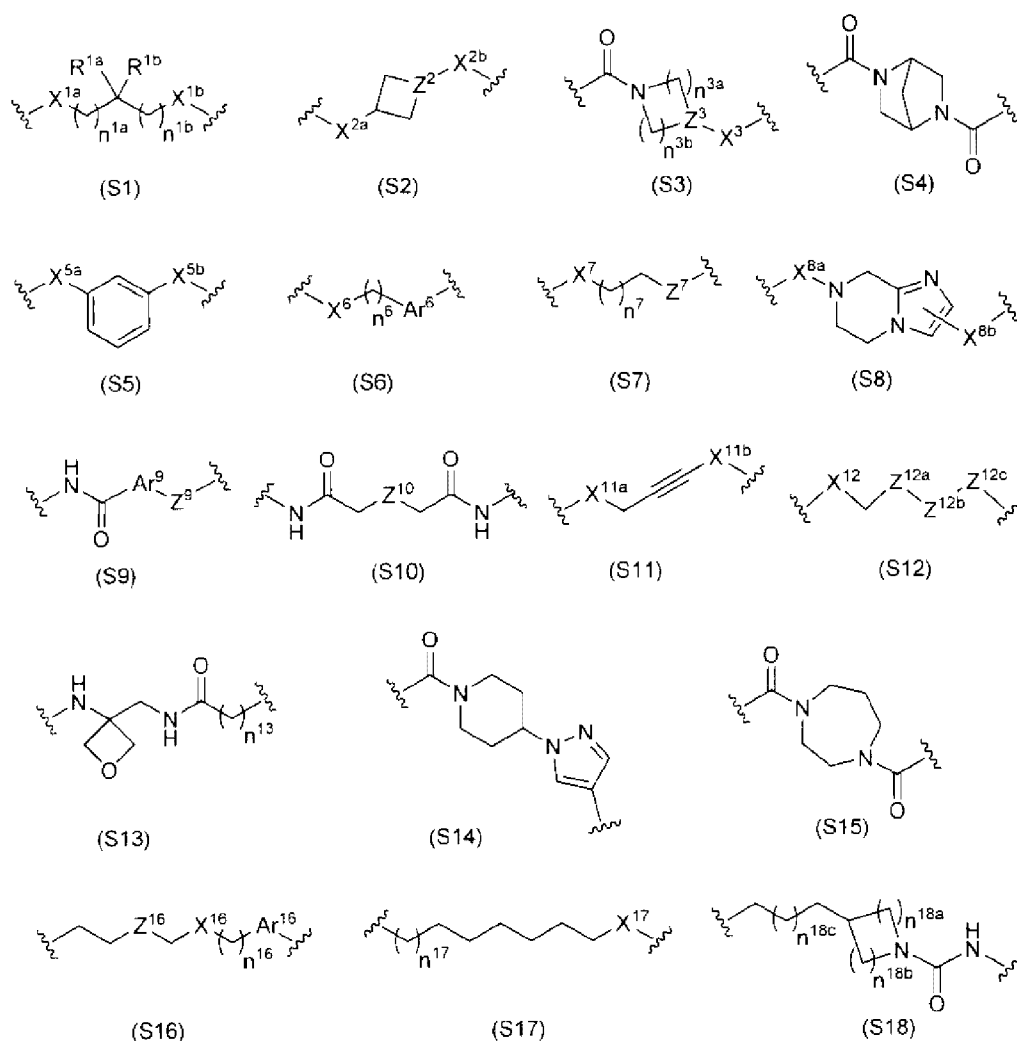
DETAILED DESCRIPTION OF THE INVENTION

[0018]

According to the present invention, there is provided a BET degrader containing as an active ingredient a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein, L^1 and L^2 are the same or different and each represents a small molecular ligand for BET protein, and S represents a group represented by a formula selected from the group consisting of the following formulas (S1) to (S18):



wherein

the wavy lines each represents the bonding site to L¹ or L²,

n^{1a} and n^{1b} are the same or different and each represents 0 or 1,

5 X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-,

R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom or lower alkyl, or R^{1a} and R^{1b} together represent carbonyl,

10 X^{2a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,

X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -

- CH₂-,
- Z² represents CH or N,
- n^{3a} and n^{3b} are the same or different and each represents 1 or 2,
- X³ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-
- 5 C(=O)-NH-, or -NH-CH₂-,
- Z³ represents CH or N,
- X^{5a} and X^{5b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,
- n⁶ represents 1 or 2,
- 10 Ar⁶ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl,
- X⁶ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -CH₂-NH-, -NH-CH₂-, or -NH-C(=O)-NH-,
- X⁷ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-C(=O)-
- 15 NH-,
- n⁷ represents 1, 2, or 3,
- Z⁷ represents S, SO, or SO₂,
- X^{8a} represents -C(=O)-, -CH₂-, or -NH-C(=O)-,
- X^{8b} represents a bond, -C(=O)-, -CH₂-, or -CH(OH)-,
- 20 Ar⁹ represents triazolediyl or oxazolediyl,
- Z⁹ represents CH₂ or NH,
- Z¹⁰ represents O or NH,
- X^{11a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,
- 25 X^{11b} represents -C(=O)-NH-, -NH-C(=O)-, or -C(=O)-,
- X¹² represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,
- Z^{12a} represents CH₂ or NH,
- Z^{12b} represents CH₂ or O,
- 30 Z^{12c} represents a bond, CH₂, or O,

n¹³ represents 0, 1, or 2,

n¹⁶ represents 1 or 2,

Z¹⁶ represents a bond, CH₂, or O,

X¹⁶ represents -CH₂-O-, -C(=O)-NH-, -NH-C(=O)-, or -NH-C(=O)-

5 NH-,

Ar¹⁶ represents triazolediyl, oxadiazolediyl, or pyrazolediyl,

n¹⁷ represents 1 or 2,

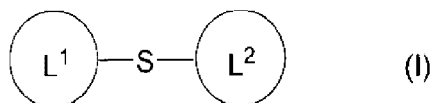
X¹⁷ represents -C(=O)-NH-, -NH-C(=O)-, -NH-SO₂-, or -NH-C(=O)-

NH-, and

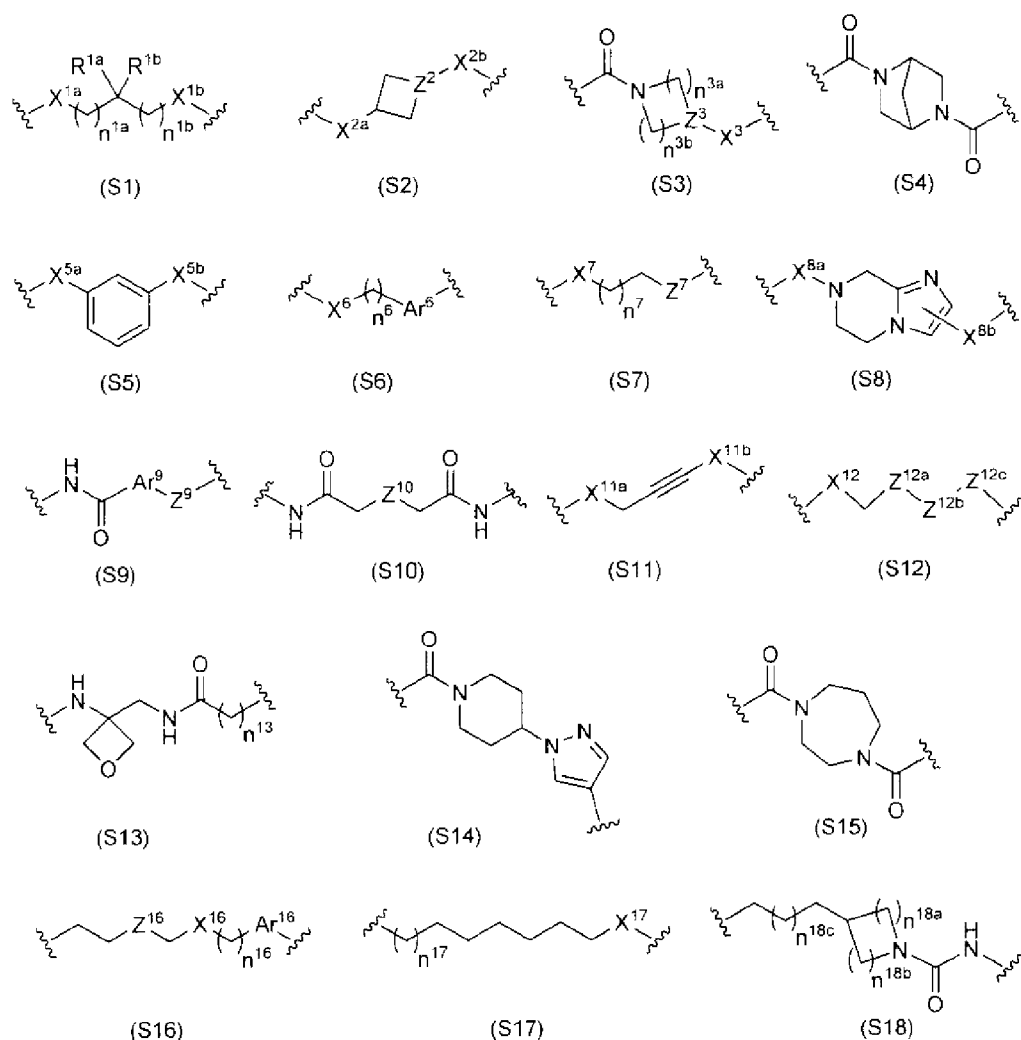
10 n^{18a}, n^{18b}, and n^{18c} are the same or different and each represents 1 or 2.

[0019]

According to a preferred embodiment of the present invention, there is provided a BET degrader containing as an active ingredient a compound
15 represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein, L¹ and L² are the same or different and each represents a small molecular ligand for BET protein, and S represents a group
20 represented by a formula selected from the group consisting of the following formulas (S1) to (S18):



wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

n^{1a} and n^{1b} are the same or different and each represents 0 or 1,

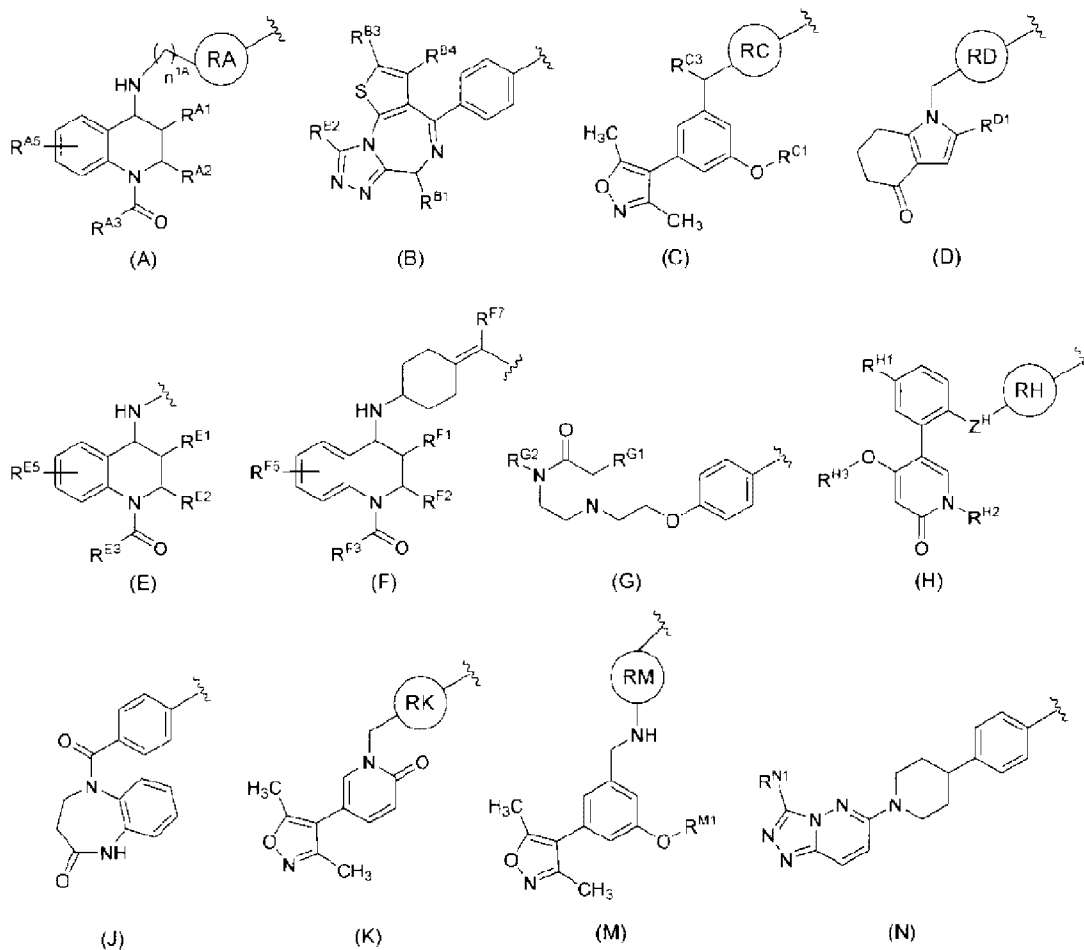
- 5 X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, except for the cases where (i) X^{1a} is -NH-SO₂- and X^{1b} is -SO₂-NH-, (ii) n^{1a} and n^{1b} are 0, X^{1a} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH- and X^{1b} is -NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- and X^{1b} is -
- 10

O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-,
 R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom or lower alkyl, or R^{1a} and R^{1b} together represent carbonyl,
 X^{2a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,
5 X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -CH₂-, except for the case where X^{2a} is -NH-SO₂- and X^{2b} is -SO₂-NH-,
 Z^2 represents CH or N, except for the cases where (i) Z^2 is N and X^{2b} is -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂- and (ii) Z^2 is CH and X^{2b} is -CH₂-,
 n^{3a} and n^{3b} are the same or different and each represents 1 or 2,
10 X^3 represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂-,
 Z^3 represents CH or N, except for the cases where (i) Z^3 is N and X^3 is -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂- and (ii) Z^3 is N and n^{3a} or n^{3b} is 1,
15 X^{5a} and X^{5b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-, except for the case where X^{5a} is -NH-SO₂- and X^{5b} is -SO₂-NH-,
 n^6 represents 1 or 2,
 Ar^6 represents triazolediyl, oxadiazolediyl, pyrazolediyl,
20 thiophenediyl, or tetrahydropyridinediyl,
 X^6 represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -CH₂-NH- or -NH-C(=O)-NH-, except for the cases where (i) Ar^6 is oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl and X^6 is -NH-SO₂- and (ii) n^6 is 1, Ar^6 is pyrazolediyl or tetrahydropyridinediyl and X^6 is -
25 C(=O)-NH-, -SO₂-NH-, -CH₂-NH-, or -NH-C(=O)-NH-,
 X^7 represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-C(=O)-NH-,
 n^7 represents 1, 2, or 3,
 Z^7 represents S, SO, or SO₂,
30 X^{8a} represents -C(=O)-, -CH₂-, or -NH-C(=O)-,

- X^{8b} represents a bond, $-C(=O)-$, $-CH_2-$, or $-CH(OH)-$,
 Ar^9 represents triazolediyl or oxazolediyl,
 Z^9 represents CH_2 or NH , except for the cases where (i) Ar^9 is triazolediyl and Z^9 is NH and (ii) Ar^9 is oxazolediyl and Z^9 is CH_2 ,
5 Z^{10} represents O or NH ,
 X^{11a} represents $-C(=O)-NH-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$,
 X^{11b} represents $-C(=O)-NH-$ or $-C(=O)-$,
 X^{12} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$,
10 Z^{12a} represents CH_2 or NH , except for the case where X^{12} is $-C(=O)-NH-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$ and Z^{12a} is NH ,
 Z^{12b} represents CH_2 or O , except for the case where Z^{12a} is NH and Z^{12b} is O ,
 Z^{12c} represents a bond, CH_2 , or O , except for the cases where (i) Z^{12b}
15 is O and Z^{12c} is O and (ii) Z^{12a} is NH and Z^{12c} is CH_2 or O ,
 n^{13} represents 0, 1 or 2,
 n^{16} represents 1 or 2,
 Z^{16} represents a bond, CH_2 , or O ,
 X^{16} represents $-CH_2-O-$, $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-C(=O)-NH-$, except for the case where Z^{16} is O and X^{16} is $-NH-C(=O)-$ or $-NH-C(=O)-NH-$,
20 Ar^{16} represents triazolediyl, oxadiazolediyl or pyrazolediyl, except for the cases where (i) X^{16} is $-CH_2-O-$ and Ar^{16} is oxadiazolediyl or pyrazolediyl and (ii) n^{16} is 1, X^{16} is $-C(=O)-NH-$ or $-NH-C(=O)-NH-$ and Ar^{16} is pyrazolediyl,
25 n^{17} represents 1 or 2,
 X^{17} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-SO_2-$, or $-NH-C(=O)-NH-$, and
 n^{18a} , n^{18b} , and n^{18c} are the same or different and each represents 1
30 or 2.

[0020]

According to a preferred embodiment of the present invention, there is provided a BET degrader containing as an active ingredient the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein L¹ and L² are the same or different and each is a group represented by a formula selected from the group consisting of the following formulas (A) to (H), (J), (K), (M), and (N):



wherein

the wavy lines each represents the bonding site to S,

R^{A1}, R^{A2} and R^{A3} are the same or different and each represents a hydrogen atom or lower alkyl,

R^{A5} represents a hydrogen atom, a halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted tetrahydropyridinyl, optionally substituted dihydro-1H-pyrrolyl, or optionally substituted tetrahydro-1H-azepinyl,

5 ring RA represents benzenediyl, cycloalkanediyl, pyridinediyl, piperidinediyl, azetidinediyl, pyrrolidinediyl, or homopiperidinediyl,

n^{1A} represents 0 or 1,

R^{B1} represents a hydrogen atom, optionally substituted lower alkoxy carbonylmethyl, optionally substituted cycloalkyloxy carbonylmethyl,

10 or $-CH_2CONR^{B5}R^{B6}$, wherein R^{B5} and R^{B6} are the same or different and each represents a hydrogen atom or optionally substituted lower alkyl, or R^{B5} and R^{B6} together with the adjacent nitrogen atom represent an optionally substituted nitrogen-containing aliphatic heterocyclic group,

R^{B2} represents optionally substituted lower alkyl,

15 R^{B3} and R^{B4} are the same or different and each represents a halogen or optionally substituted lower alkyl,

R^{C1} represents a hydrogen atom, lower alkyl, or lower alkanoyl,

R^{C3} represents a hydrogen atom or hydroxy,

20 ring RC represents benzenediyl, piperidinediyl, azetidinediyl, pyrrolidinediyl, homopiperidinediyl, piperazinediyl, or azaspiro[3.3]heptanediyl,

R^{D1} represents optionally substituted lower alkyl or optionally substituted lower alkoxy carbonyl,

25 ring RD represents benzenediyl or cycloalkanediyl,

R^{E1} and R^{F1} each has the same definition as R^{A1} , and R^{E1} and R^{F1} may be the same or different,

R^{E2} and R^{F2} each has the same definition as R^{A2} , and R^{E2} and R^{F2} may be the same or different,

30 R^{E3} and R^{F3} each has the same definition as R^{A3} , and R^{E3} and R^{F3} may be the same or different,

R^{E5} and R^{F5} each has the same definition as R^{A5} , and R^{E5} and R^{F5} may be the same or different,

R^{F7} represents a hydrogen atom or a halogen,

R^{G1} and R^{G2} are the same or different and each represents a
5 hydrogen atom or lower alkyl,

R^{H1} represents a hydrogen atom or lower alkyl sulfonamide,

R^{H2} and R^{H3} are the same or different and each represents lower
alkyl,

Z^H represents CH_2 or O ,

10 ring RH represents benzenediyl, cycloalkanediyl, azetidinediyl,
pyrrolidinediyl, piperidinediyl, or homopiperidinediyl,

ring RK represents benzenediyl or cycloalkanediyl,

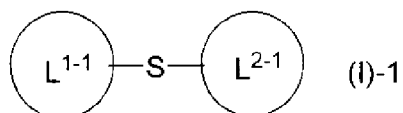
R^{M1} represents a hydrogen atom or lower alkyl,

ring RM represents cycloalkanediyl, and

15 R^{N1} represents a hydrogen atom, a halogen, lower alkyl, or lower
alkoxy.

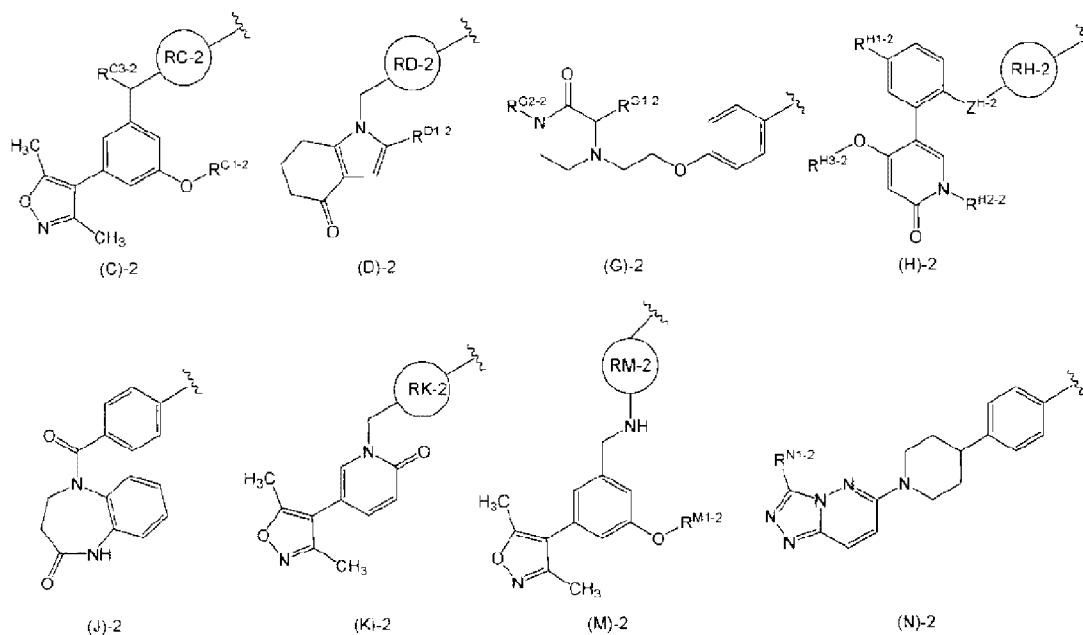
[0021]

According to another preferred embodiment of the present
invention, there is provided a compound represented by the following
20 formula (I)-1 or a pharmaceutically acceptable salt thereof:



wherein one of L^{1-1} and L^{2-1} is a group represented by a formula
selected from the group consisting of the following formulas (C)-2, (D)-2,
(G)-2, (H)-2, (J)-2, (K)-2, (M)-2, and (N)-2, and the other of L^{1-1} and L^{2-1}
25 is a group represented by a formula selected from the group consisting of
formulas (A) to (H), (J), (K), (M), and (N) described in the above (3), and
S is a group represented by a formula selected from the group consisting

of formulas (S1) to (S18) described in the above (1) or (2):



wherein

the wavy lines each represents the bonding site to S,

5 R^{C1-2} represents a hydrogen atom, lower alkyl or lower alkanoyl,

R^{C3-2} represents a hydrogen atom or hydroxy,

ring RC-2 represents piperazinediyl or azaspiro[3.3]heptanediyl,

R^{D1-2} represents optionally substituted lower alkyl or optionally substituted lower alkoxy carbonyl,

10 ring RD-2 represents cycloalkanediyl,

R^{G1-2} and R^{G2-2} are the same or different and each represents a hydrogen atom or lower alkyl,

R^{H1-2} represents a hydrogen atom or lower alkyl sulfonamide,

15 R^{H2-2} and R^{H3-2} are the same or different and each represents lower alkyl,

Z^{H-2} represents CH_2 or O,

ring RH-2 represents benzenediyl, cycloalkanediyl, azetidinediyl, pyrrolidinediyl, piperidinediyl, or homopiperidinediyl,

ring RK-2 represents benzenediyl or cycloalkanediyl,
R^{M1-2} represents a hydrogen atom or lower alkyl,
ring RM-2 represents cycloalkanediyl, and
R^{N1-2} represents a hydrogen atom, a halogen, lower alkyl or lower
5 alkoxy.

[0022]

Hereinafter, the compound represented by the general formula (I) is referred to as compound (I), and the compound represented by the general formula (I)-1 is referred to as compound (I)-1. The same applies to the
10 compounds having other formula numbers.

[0023]

In the present description, the small molecular ligand for the BET protein is not particularly limited as long as it is a ligand that acts on the BET protein, and includes more specifically, for example, the ligands known
15 in the followings: Journal of Medicinal Chemistry, 2013, vol.56, p.7501-7515 (Non-Patent Document 7), Proceedings of the National Academy of Sciences, 2013, vol.110, p.19754-19759 (Non-Patent Document 6), Oncotarget, 2015, vol.6, p.17698-17712 (Non-Patent Document 8), ACS Medicinal Chemistry Letters, 2013, vol.4, p.835-840, Journal of Medicinal
20 Chemistry, 2016, vol.59, p.1330-1339, Bioorganic & Medicinal Chemistry, 2012, vol.20, p.1878-1886, US2014/0256710A1, WO2014/128067, European Journal of Medicinal Chemistry, 2016, vol.121, p.294-299, Journal of Medicinal Chemistry, 2011, vol.54, p.6761-6770, Journal of Medicinal Chemistry, 2013, vol.56, p.3217-3227, Journal of Medicinal
25 Chemistry, 2012, vol.55, p.587-596, Bioorganic & Medicinal Chemistry, 2012, vol.22, p.2963-2967, Journal of Medicinal Chemistry, 2015, vol.58, p.4927-4939, WO2016/123709, WO2015/100282, WO2014/160873, WO2014/154760, WO2014/154762, US2015/0158873A1, WO2015/085925, WO2015/169962, WO2015/022332, WO2014/206150,
30 US2016/0129001A1, US2014/0349990A1, WO2015/075665,

WO2014/140076, Journal of Medicinal Chemistry, 2012, vol.55, p.576-586,
WO2015/074064, WO2015/004075, Journal of Medicinal Chemistry, 2012,
vol.55, p.9831-9837, Journal of Medicinal Chemistry, 2016, vol.59, p.1565-
1579, Journal of Medicinal Chemistry, 2016, vol.59, p.1518-1530, Journal
5 of Medicinal Chemistry, 2013, vol.56, p.3833-3851, Journal of Medicinal
Chemistry, 2018, vol.61, p.3037-3058, Journal of Medicinal Chemistry,
2016, vol.59, p.1565-1579, Journal of Medicinal Chemistry, 2017, vol.60,
p.4805-4817, Journal of Medicinal Chemistry, 2017, vol.60, p.9990-10012,
ACS Medicinal Chemistry Letters, 2018, vol.9, p.262-267, Journal of
10 Medicinal Chemistry, 2018, vol.61, P.462-481 and the like.

[0024]

According to a preferred embodiment of the present invention, the
BET degrader of the present invention or the compound of the present
invention or a pharmaceutically acceptable salt thereof acts on the BET
15 protein to promote interaction with DCAF16, which is one of E3 ubiquitin
ligases, and thus to promote ubiquitination of the target BET protein,
causing degradation by the proteasome to exhibit anticancer activity.
According to a more preferred embodiment of the present invention, there
is provided a BET degradation inducer containing as an active ingredient
20 the compound represented by formula (I) or a pharmaceutically acceptable
salt thereof.

[0025]

In the present specification, examples of the lower alkyl include
linear or branched alkyl having 1 to 10 carbon atoms, and more specifically
25 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-
butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, and
the like.

[0026]

In the present specification, examples of the lower
30 alkoxycarbonylmethyl include C₁₋₁₀ alkoxycarbonylmethyl, and more

specifically include methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, isobutoxycarbonylmethyl, sec-butoxycarbonylmethyl, tert-butoxycarbonylmethyl, 5 pentoxycarbonylmethyl, isopentoxycarbonylmethyl, neopentoxycarbonylmethyl, hexyloxycarbonylmethyl, heptoxycarbonylmethyl, octoxycarbonylmethyl, nonyloxycarbonylmethyl, decyloxycarbonylmethyl, and the like, wherein preferable is tert-butoxycarbonylmethyl.

10 [0027]

In the present specification, the halogen means each atom of fluorine, chlorine, bromine, and iodine.

[0028]

In the present specification, examples of the lower alkanoyl include 15 C₂₋₁₁ alkanoyl (alkanoyl having 2 to 11 carbon atoms).

[0029]

The lower alkyl in R^{A1}, R^{A2}, and R^{A3} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably methyl or ethyl.

20 [0030]

The lower alkyl in R^{A5} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably propyl.

[0031]

25 The lower alkenyl in R^{A5} is preferably alkenyl having 2 to 6 carbon atoms, more preferably alkenyl having 2 to 4 carbon atoms, and further preferably propenyl.

[0032]

The alkyl having 1 to 5 carbon atoms in R^{A2-1} and R^{A3-1} is preferably 30 alkyl having 1 to 3 carbon atoms and more preferably methyl or ethyl.

[0033]

The alkyl having 1 to 5 carbon atoms in R^{A5-1} is preferably alkyl having 1 to 3 carbon atoms and more preferably propyl.

[0034]

5 The alkenyl having 2 to 6 carbon atoms in R^{A5-1} is preferably alkenyl having 2 to 4 carbon atoms and more preferably propenyl.

[0035]

10 The cycloalkanediyl in ring RA and ring RA-1 is preferably cycloalkanediyl having 3 to 8 carbon atoms or bicycloalkanediyl having 3 to 8 carbon atoms, and more preferably cyclobutanediyl, cyclohexanediyl, bicyclo[1.1.1]pentanediyl, or bicyclo[2.2.2]octanediyl.

[0036]

15 The lower alkoxy carbonylmethyl in R^{B1} is preferably alkoxy carbonylmethyl having 1 to 10 carbon atoms and more preferably ethoxy carbonylmethyl, propoxy carbonylmethyl, or butoxy carbonylmethyl (preferably tert-butoxy carbonylmethyl).

[0037]

20 The cycloalkyloxy carbonylmethyl in R^{B1} and R^{B1-1} is preferably cycloalkyloxy carbonylmethyl having 3 to 8 carbon atoms and more preferably cyclohexyloxy carbonylmethyl.

[0038]

The alkoxy carbonylmethyl having 1 to 5 carbon atoms in R^{B1-1} is preferably ethoxy carbonylmethyl, propoxy carbonylmethyl, or butoxy carbonylmethyl (preferably tert-butoxy carbonylmethyl).

25 [0039]

The lower alkyl in R^{B5} and R^{B6} is preferably alkyl having 1 to 5 carbon atoms and more preferably ethyl.

[0040]

30 The alkyl having 1 to 5 carbon atoms in R^{B5-1} and R^{B6-1} is preferably ethyl.

[0041]

The nitrogen-containing aliphatic heterocyclic group in that R^{B5} and R^{B6} as well as R^{B5-1} and R^{B6-1} "together with the adjacent nitrogen atom representing an optionally substituted nitrogen-containing aliphatic heterocyclic group" is preferably a nitrogen-containing aliphatic heterocyclic group having 4 to 6 carbon atoms, more preferably azetidine, pyrrolidine, piperidine, piperazine, or morpholine, and further preferably piperazine.

[0042]

The lower alkyl in R^{B2} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably methyl.

[0043]

The alkyl having 1 to 5 carbon atoms in R^{B2-1} is preferably alkyl having 1 to 3 carbon atoms and more preferably methyl.

[0044]

The halogen in R^{B3} and R^{B4} is preferably a fluorine atom or a chlorine atom.

[0045]

The lower alkyl in R^{B3} and R^{B4} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably methyl.

[0046]

The alkyl having 1 to 5 carbon atoms in R^{B3-1} and R^{B4-1} is preferably alkyl having 1 to 3 carbon atoms and more preferably methyl.

[0047]

The lower alkyl in R^{C1} and R^{C1-2} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably methyl or ethyl.

[0048]

The lower alkanoyl in R^{C1} and R^{C1-2} is preferably alkanoyl having 2 to

11 carbon atoms, more preferably alkanoyl having 2 to 5 carbon atoms, and further preferably acetyl.

[0049]

The lower alkyl in R^{D1} and R^{D1-2} is preferably alkyl having 1 to 5
5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably ethyl.

[0050]

The alkyl having 1 to 5 carbon atoms in R^{D1-1} is more preferably alkyl having 1 to 3 carbon atoms and more preferably ethyl.

10 [0051]

The lower alkoxy carbonyl in R^{D1} and R^{D1-2} is preferably alkoxy carbonyl having 1 to 5 carbon atoms, more preferably alkoxy carbonyl having 1 to 3 carbon atoms, and further preferably ethoxy carbonyl or methoxy carbonyl.

15 [0052]

The alkoxy carbonyl having 1 to 5 carbon atoms in R^{D1-1} is preferably alkoxy carbonyl having 1 to 3 carbon atoms and more preferably ethoxy carbonyl or methoxy carbonyl.

[0053]

20 The cycloalkanediyl in ring RD and ring RD-2 is preferably cycloalkanediyl having 3 to 8 carbon atoms, and more preferably cyclohexanediyl.

[0054]

The halogen in R^{F7} is preferably a fluorine atom.

25 [0055]

The lower alkyl in R^{G1} and R^{G2} , and R^{G1-2} and R^{G2-2} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and even more preferably methyl.

[0056]

30 The lower alkyl sulfonamide in R^{H1} , R^{H1-1} and R^{H1-2} is preferably alkyl

sulfonamide having 1 to 3 carbon atoms, and more preferably ethyl sulfonamide.

[0057]

5 The lower alkyl in R^{H2} and R^{H3} , R^{H2-1} and R^{H3-1} , and R^{H2-2} and R^{H3-2} is preferably alkyl having 1 to 3 carbon atoms, and more preferably methyl.

[0058]

The cycloalkanediyl in ring RH and ring RH-2 is preferably cycloalkanediyl having 3 to 8 carbon atoms, and more preferably cyclohexanediyl.

10 [0059]

The cycloalkanediyl in ring RK, ring RK-1, and ring RK-2 is preferably cycloalkanediyl having 3 to 8 carbon atoms, and more preferably cyclohexanediyl.

[0060]

15 The lower alkyl in R^{M1} and R^{M1-2} is preferably alkyl having 1 to 3 carbon atoms, and more preferably methyl.

[0061]

20 The cycloalkanediyl in ring RM and ring RM-2 is preferably cycloalkanediyl having 3 to 8 carbon atoms, more preferably bicycloalkanediyl having 5 to 8 carbon atoms, and even more preferably bicyclo[1.1.1]pentanediyl or bicyclo[2.2.2]octanediyl.

[0062]

The bicycloalkanediyl having 5 to 8 carbon atoms in the ring RM-1 is preferably bicyclo[1.1.1]pentanediyl or bicyclo[2.2.2]octanediyl.

25 [0063]

The halogen in R^{N1} , R^{N1-1} and R^{N1-2} is preferably a chlorine atom.

[0064]

30 The lower alkyl in R^{N1} and R^{N1-2} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and even more preferably methyl.

[0065]

The lower alkoxy in R^{N1} and R^{N1-2} is preferably alkoxy having 1 to 5 carbon atoms, more preferably alkoxy having 1 to 3 carbon atoms, and further preferably methoxy.

5 [0066]

The lower alkyl in R^{1b} is preferably alkyl having 1 to 5 carbon atoms, more preferably alkyl having 1 to 3 carbon atoms, and further preferably methyl or propyl (preferably isopropyl).

[0067]

10 Examples of substituents in the "optionally substituted lower alkyl" and the "optionally substituted alkyl having 1 to 5 carbon atoms" of R^{A5} and R^{A5-1} include one or more substituents selected from the group consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino,
15 dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, wherein preferable
20 is amino.

[0068]

Examples of substituents in the "optionally substituted lower alkenyl" and the "optionally substituted alkenyl having 2 to 6 carbon atoms" of R^{A5} and R^{A5-1} include one or more substituents selected from the group
25 consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl,
30 pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl,

pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, wherein preferable is amino.

[0069]

Examples of substituents in the "optionally substituted tetrahydropyridinyl" of R^{A5} and R^{A5-1} include a halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and the like, but preferably the tetrahydropyridinyl is unsubstituted.

[0070]

Examples of substituents in the "optionally substituted dihydro-1H-pyrrolyl" of R^{A5} include a halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and the like, but preferably the dihydro-1H-pyrrolyl is unsubstituted.

[0071]

Examples of substituents in the "optionally substituted tetrahydro-1H-azepinyl" of R^{A5} include a halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and the like, but preferably the tetrahydro-1H-azepinyl is unsubstituted.

[0072]

Examples of substituents in the "optionally substituted lower alkoxycarbonylmethyl" and the "optionally substituted alkoxycarbonylmethyl having 1 to 5 carbon atoms" of R^{B1} and R^{B1-1} include one or more substituents selected from the group consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl,

ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, and pyrazinyl, wherein preferable is hydroxy, methoxy, or dimethylamino, and unsubstituted cases are also preferable.

[0073]

Examples of substituents in the "optionally substituted cycloalkyloxycarbonylmethyl" of R^{B1} and R^{B1-1} include one or more substituents selected from the group consisting of a halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and the like, wherein preferable is hydroxy.

[0074]

Examples of substituents in the "optionally substituted lower alkyl" of R^{B5} and R^{B6} include one or more substituents selected from the group consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, and the unsubstituted case is also preferable.

[0075]

Examples of substituents in R^{B5} and R^{B6} as well as R^{B5-1} and R^{B6-1} "together with the adjacent nitrogen atom representing an optionally

substituted nitrogen-containing aliphatic heterocyclic group" include one or more substituents selected from the group consisting of a halogen, methyl, ethyl, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, and the like, wherein preferable is hydroxyethyl.

[0076]

Examples of substituents in the "optionally substituted lower alkyl" and the "optionally substituted alkyl having 1 to 5 carbon atoms" of R^{B2} and R^{B2-1} include a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, but preferably the lower alkyl and the alkyl having 1 to 5 carbon atoms are unsubstituted.

[0077]

Examples of substituents in the "optionally substituted lower alkyl" and the "optionally substituted alkyl having 1 to 5 carbon atoms" of R^{B3} and R^{B4} as well as R^{B3-1} and R^{B4-1} include one or more substituents selected from the group consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, wherein preferable is a fluorine atom or cyano. Examples of the "optionally substituted lower

alkyl" and "optionally substituted alkyl having 1 to 5 carbon atoms" of R^{B3} and R^{B4} as well as R^{B3-1} and R^{B4-1} are particularly preferably unsubstituted lower alkyl and unsubstituted alkyl having 1 to 5 carbon atoms, respectively.

5 [0078]

Examples of substituents in the "optionally substituted lower alkyl" and "optionally substituted alkyl having 1 to 5 carbon atoms" of R^{D1} , R^{D1-1} and R^{D1-2} include a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, but preferably the lower alkyl and the alkyl having 1 to 5 carbon atoms are unsubstituted.

[0079]

Examples of substituents in the "optionally substituted lower alkoxy carbonyl" and "optionally substituted alkoxy carbonyl having 1 to 5 carbon atoms" of R^{D1} , R^{D1-1} and R^{D1-2} include one or more substituents selected from the group consisting of a halogen, hydroxy, methoxy, ethoxy, nitro, cyano, carboxy, methoxycarbonyl, ethoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, furyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like, wherein preferable is hydroxy or dimethylamino, and unsubstituted cases are also preferable.

[0080]

30 In formula (S1), X^{1a} and X^{1b} are the same or different and each

represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-,
 -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, preferably except for
 the cases where (i) X^{1a} is -NH-SO₂- and X^{1b} is -SO₂-NH-, (ii) n^{1a} and n^{1b} are
 0, X^{1a} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-
 5 C(=O)-NH-, and X^{1b} is -NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-
 C(=O)-NH-, and (iii) X^{1a} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-,
 or -NH-C(=O)-NH- and X^{1b} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-
 O-, or -NH-C(=O)-NH-.

Here, the left bonding hand of X^{1a} bonds to L¹ and the right bonding
 10 hand of X^{1b} bonds to L². For example, Compound No. 1a in the following
 Table 1 is a compound formed by bonding of L¹ and the left bonding hand
 of X^{1a} (-C(=O)-NH-) to become L¹-C(=O)-NH- and bonding of L² and the
 right bonding hand of X^{1b} (-NH-C(=O)-) to become -NH-C(=O)-L². The
 same applies to the following.

15 [0081]

In formula (S2), X^{2a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-
 , or -NH-SO₂- and X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -
 NH-SO₂-, or -CH₂-, preferably except for the case where X^{2a} is -NH-SO₂-
 and X^{2b} is -SO₂-NH-. Similar to the above, the left bonding hand of X^{2a}
 20 bonds to L¹ and the right bonding hand of X^{2b} bonds to L².

[0082]

In formula (S3), X³ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-
 , -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂-. Similar to the above, the right
 bonding hand of X³ bonds to L².

25 [0083]

In formula (S5), X^{5a} and X^{5b} are the same or different and each
 represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-, preferably
 except for the case where X^{5a} is -NH-SO₂- and X^{5b} is -SO₂-NH-. Similar to
 the above, the left bonding hand of X^{5a} bonds to L¹ and the right bonding
 30 hand of X^{5b} bonds to L².

[0084]

In formula (S6), X^6 is $-C(=O)-NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, $-NH-SO_2-$, $-CH_2-NH$, or $-NH-C(=O)-NH-$, preferably except for the cases where (i) Ar^6 is oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl and X^6 is $-NH-SO_2-$ and (ii) n^6 is 1, Ar^6 is pyrazolediyl or tetrahydropyridinediyl, and X^6 is $-C(=O)-NH-$, $-SO_2-NH-$, $-CH_2-NH-$, or $-NH-C(=O)-NH-$. Similar to the above, the left bonding hand of X^6 bonds to L^1 .

[0085]

In formula (S7), X^7 represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$. Similar to the above, the left bonding hand of X^7 bonds to L^1 .

[0086]

In formula (S8), X^{8a} represents $-C(=O)-$, $-CH_2-$, or $-NH-C(=O)-$ and X^{8b} is a bond, $-C(=O)-$, $-CH_2-$, or $-CH(OH)-$. Similar to the above, the left bonding hand of X^{8a} bonds to L^1 and the right bonding hand of X^{8b} bonds to L^2 .

[0087]

In formula (S11), X^{11a} represents $-C(=O)-NH-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$ and X^{11b} represents $-C(=O)-NH-$ or $-C(=O)-$. Similar to the above, the left bonding hand of X^{11a} bonds to L^1 and the right bonding hand of X^{11b} bonds to L^2 .

[0088]

In the above formula (S12), X^{12} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-SO_2-NH-$, or $-NH-C(=O)-NH-$. Similar to the above, the left bonding hand of X^{12} bonds to L^1 .

[0089]

In formula (S16), X^{16} represents $-CH_2-O-$, $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-C(=O)-NH-$, preferably except for the case where Z^{16} is O and X^{16} is $-NH-C(=O)-$ or $-NH-C(=O)-NH-$. Similar to the above, the left bonding

hand of X^{16} bonds to L^1 via Z^{16} or the like.

[0090]

In formula (S17), X^{17} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-SO_2-$, or $-NH-C(=O)-NH-$. Similar to the above, the right bonding hand of
5 X^{17} bonds to L^2 .

[0091]

In general formula (I), L^1 and L^2 are the same or different and each represents small molecular ligand for BET protein, preferably L^1 and L^2 are the same or different and each represents a group represented by a formula
10 selected from the group consisting of formulas (A) to (H), (J), (K), (M) and (N), more preferably at least one of L^1 and L^2 is a group represented by formula (A) or (B), and further preferably at least one of L^1 and L^2 is a group represented by formula (A).

[0092]

15 According to a preferred embodiment of the present invention, in general formula (I), when L^1 and L^2 are the same or different and each represents a group represented by formula (A), (B), (C), (D), (F), (G), (H), (J), (K), (M) or (N), S is preferably a group represented by a formula selected from the group consisting of formulas (S1) to (S15).

20 [0093]

According to a preferred embodiment of the present invention, in general formula (I), when L^1 or L^2 is a group represented by formula (E), S is preferably a group represented by formula (S16), (S17), or (S18).

[0094]

25 According to a preferred embodiment of the present invention, in general formula (I), when L^1 is a group represented by formula (F), S is preferably a group represented by any of the following:

a group represented by formula (S1), wherein X^{1a} is $-C(=O)-NH-$,
a group represented by formula (S2), wherein X^{2a} is $-C(=O)-NH-$,
30 a group represented by formula (S3),

a group represented by formula (S4),
a group represented by formula (S5), wherein X^{5a} is $-C(=O)-NH-$,
a group represented by formula (S6), wherein X^6 is $-C(=O)-NH-$,
a group represented by formula (S7), wherein X^7 is $-C(=O)-NH-$,
5 a group represented by formula (S8), wherein X^{8a} is $-C(=O)-$,
a group represented by formula (S11), wherein X^{11a} is $-C(=O)-NH-$,
a group represented by formula (S12), wherein X^{12} is $-C(=O)-NH-$,
a group represented by formula (S14), or
a group represented by formula (S15).

10 [0095]

According to another preferred embodiment of the present invention, in general formula (I), when L^2 is a group represented by formula (F), S is a group represented by any of the following:

a group represented by formula (S1), wherein X^{1b} is $-NH-C(=O)-$,
15 a group represented by formula (S2) wherein X^{2b} is $-NH-C(=O)-$,
a group represented by formula (S3), wherein X^3 is $-NH-C(=O)-$,
a group represented by formula (S4),
a group represented by formula (S5), wherein X^{5b} is $-NH-C(=O)-$,
a group represented by formula (S13), wherein n^{13} is 0,
20 a group represented by formula (S15), or
a group represented by formula (S17), wherein X^{17} is $-NH-C(=O)-$.

[0096]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the
25 compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A), (B), (C), (D), (F) or (G), L^2 represents a group represented by formula (A), (B), (C), (D), (H), (J), (K) or (M), and S is a group represented by formula (S1).

[0097]

30 According to a preferred embodiment of the present invention, there

is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A) (preferably formula (A1), formula (A5), or formula (A15)), L² represents a group represented by formula (A) (preferably formula (A1)), and S is a group represented by formula (S1).

[0098]

According to a preferred embodiment of the present invention, there is provided a BET degrader containing as an active ingredient a compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A), L² represents a group represented by formula (A), and S is a group represented by formula (S2).

[0099]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A), (B), (C), (G) or (N), L² represents a group represented by formula (A) or (B), and S is a group represented by formula (S3).

[0100]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A) (preferably formula (A1) or formula (A5)), L² represents a group represented by formula (A) (preferably formula (A1) or formula (A5)), and S is a group represented by formula (S3).

[0101]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the

compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (A), and S is a group represented by formula (S4) or (S5).

5 [0102]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A), (B), (C), (D), (G) or
10 (H), L^2 represents formula (A), (B), (C) or (D), and S is a group represented by formula (S6).

[0103]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the
15 compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A) (preferably formula (A1) or formula (A5)), L^2 represents a group represented by formula (A) (preferably a group represented by formula (A1) or formula (A5)), and S is a group represented by formula (S6).

20 [0104]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A) or (B), L^2 represents
25 a group represented by formula (A), and S is a group represented by formula (S7).

[0105]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the
30 compound or a pharmaceutically acceptable salt thereof, wherein in formula

(I), L¹ represents a group represented by formula (A) or (B), L² represents a group represented by formula (A), and S is a group represented by formula (S8).

[0106]

5 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A), L² represents a group represented by formula (A), and S is a group represented by formula (S9).

10 [0107]

 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A) or (B), L² represents a group represented by formula (A), and S is a group represented by formula (S10).

[0108]

 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A) or (B), L² represents a group represented by formula (A) or (B), and S is a group represented by formula (S11). According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A) or (B), L² represents a group represented by formula (A), and S is a group represented by formula (S11), wherein the group represented by formula (S11) is a group where X^{11b} is -C(=O)-, and the group represented by formula (A) in L² is a group where ring RA is piperidinediyl, azetidinediyl,

pyrrolidinediyl, or homopiperidinediyl.

[0109]

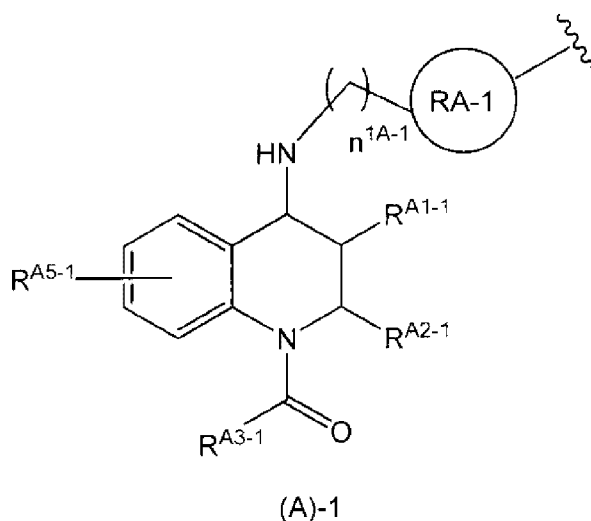
According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (A), L² represents a group represented by formula (A), and S is a group represented by formula (S12), (S13), (S14) or (S15).

[0110]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ represents a group represented by formula (E), L² represents a group represented by formula (A), and S is a group represented by formula (S16), (S17) or (S18).

[0111]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (A) is the following formula (A)-1:



wherein

the wavy line represents the bonding site to S,

R^{A1-1} represents a hydrogen atom,

5 R^{A2-1} and R^{A3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2-1} represents methyl and R^{A3-1} represents ethyl),

R^{A5-1} represents a hydrogen atom, a fluorine atom, optionally substituted alkyl having 1 to 5 carbon atoms (preferably alkyl having 1 to
10 3 carbon atoms which may be substituted with amino and more preferably propyl substituted with amino), optionally substituted alkenyl having 2 to 6 carbon atoms (preferably propenyl optionally substituted with amino and more preferably, propenyl substituted with amino), or optionally substituted tetrahydropyridinyl (preferably tetrahydropyridinyl),

15 ring RA-1 represents benzenediyl, cycloalkanediyl (preferably cyclobutanediyl, cyclohexanediyl, bicyclo[1.1.1]pentanediyl or bicyclo[2.2.2]octanediyl), pyridinediyl, or piperidinediyl, and

n^{1A-1} represents 0 or 1 (preferably 0).

[0112]

20 According to a more preferred embodiment of the present invention,

there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (A) is formula (A)-1, and wherein in formula (A)-1,

the wavy line represents the bonding site to S,

5 R^{A1-1} represents a hydrogen atom,

R^{A2-1} and R^{A3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2-1} represents methyl and R^{A3-1} represents ethyl),

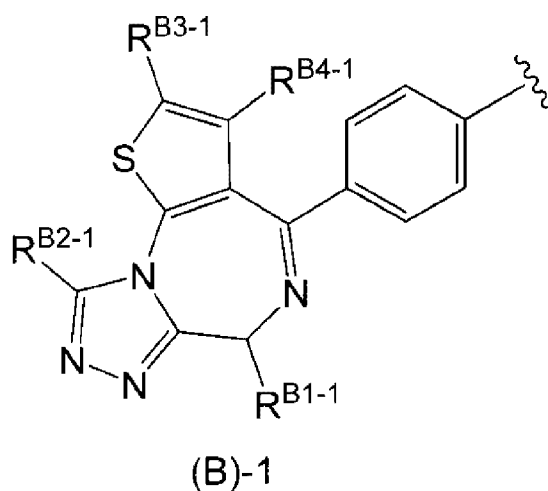
R^{A5-1} represents a hydrogen atom,

10 ring RA-1 represents benzenediyl, cyclohexanediyl, or pyridinediyl, and

n^{1A-1} represents 0 or 1 (preferably 0).

[0113]

According to a preferred embodiment of the present invention, there
15 is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (B) is the following formula (B)-1:



wherein

20 the wavy line represents the bonding site to S,

R^{B1-1} represents a hydrogen atom, optionally substituted

alkoxycarbonylmethyl having 1 to 5 carbon atoms (preferably optionally substituted ethoxycarbonylmethyl (more preferably hydroxy-substituted ethoxycarbonylmethyl, methoxy-substituted ethoxycarbonylmethyl, or dimethylamino-substituted ethoxycarbonylmethyl), optionally substituted propoxycarbonylmethyl (more preferably methoxy-substituted propoxycarbonylmethyl), or butoxycarbonylmethyl (more preferably tert-butoxycarbonylmethyl)), optionally substituted cycloalkyloxycarbonylmethyl (preferably optionally substituted cyclohexyloxycarbonylmethyl (more preferably hydroxy-substituted cyclohexylmethyl)), or $-\text{CH}_2\text{CONR}^{\text{B}5-1}\text{R}^{\text{B}6-1}$, wherein $\text{R}^{\text{B}5-1}$ and $\text{R}^{\text{B}6-1}$ are the same or different and each represents a hydrogen atom or alkyl having 1 to 5 carbon atoms (preferably, $\text{R}^{\text{B}5-1}$ represents a hydrogen atom and $\text{R}^{\text{B}5-1}$ represents ethyl), or $\text{R}^{\text{B}5-1}$ and $\text{R}^{\text{B}6-1}$ together with the adjacent nitrogen atom represent an optionally substituted nitrogen-containing aliphatic heterocyclic group (preferably piperazine),

$\text{R}^{\text{B}2-1}$ represents optionally substituted alkyl having 1 to 5 carbon atoms (preferably methyl), and

$\text{R}^{\text{B}3-1}$ and $\text{R}^{\text{B}4-1}$ represent optionally substituted alkyl having 1 to 5 carbon atoms (preferably methyl).

[0114]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (B) is formula (B)-1, and wherein in formula (B)-1,

the wavy line represents the bonding site to S,

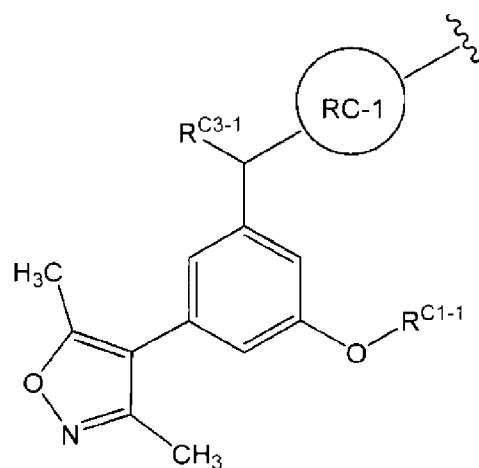
$\text{R}^{\text{B}1-1}$ represents tert-butoxycarbonylmethyl,

$\text{R}^{\text{B}2-1}$ represents optionally substituted alkyl having 1 to 5 carbon atoms (preferably methyl), and

$\text{R}^{\text{B}3-1}$ and $\text{R}^{\text{B}4-1}$ represent optionally substituted alkyl having 1 to 5 carbon atoms (preferably methyl).

[0115]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (C) is the following formula (C)-1:



(C)-1

wherein

the wavy line represents the bonding site to S,

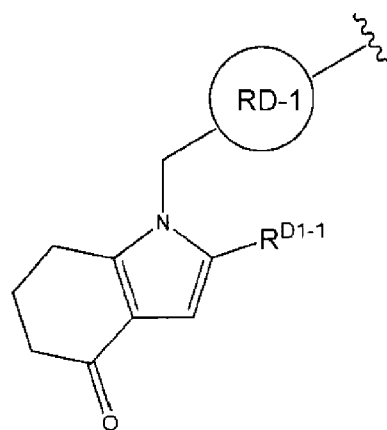
R^{C1-1} represents a hydrogen atom,

R^{C3-1} represents a hydrogen atom or hydroxy, and

ring RC-1 represents benzenediyl, piperidinediyl, piperadinediyl, or azaspiro[3.3]heptanediyl (when R^{C3-1} is a hydrogen atom, ring RC-1 is preferably piperidinediyl, piperadinediyl, or azaspiro[3.3]heptanediyl, and when R^{C3-1} is hydroxy, ring RC-1 is preferably benzenediyl).

[0116]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (D) is the following formula (D)-1:



(D)-1

wherein

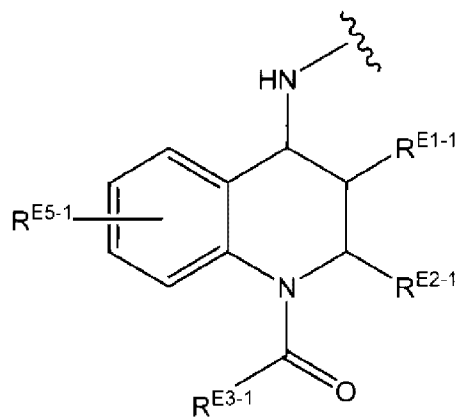
the wavy line represents the bonding site to S,

R^{D1-1} represents optionally substituted alkyl having 1 to 5 carbon
 5 atoms (preferably ethyl) or optionally substituted alkoxy carbonyl having 1
 to 5 carbon atoms (preferably hydroxyl-substituted ethoxy carbonyl,
 diethylamino-substituted ethoxy carbonyl, or unsubstituted
 methoxy carbonyl), and

ring RD-1 represents benzenediyl or cyclohexanediyl.

10 [0117]

According to a preferred embodiment of the present invention, there
 is provided the BET degrader containing as an active ingredient the
 compound or a pharmaceutically acceptable salt thereof, wherein in formula
 (I), formula (E) is the following formula (E)-1:



(E)-1

wherein

the wavy line represents the bonding site to S,

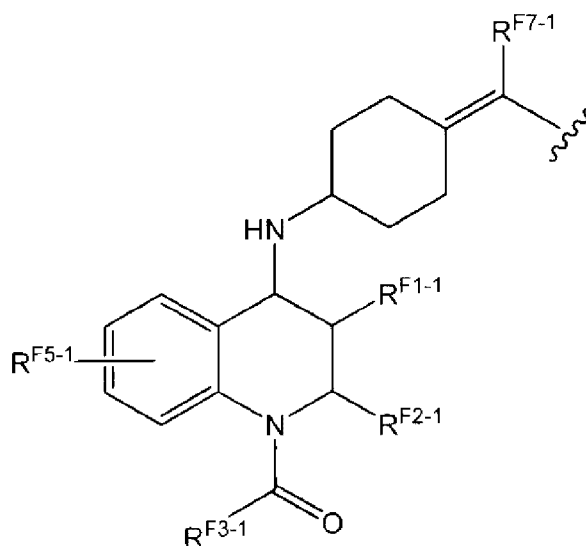
R^{E1-1} represents a hydrogen atom,

5 R^{E2-1} and R^{E3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{E2-1} represents methyl and R^{E3-1} represents ethyl), and

R^{E5-1} represents a hydrogen atom.

[0118]

10 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (F) is the following formula (F)-1:



(F)-1

wherein

the wavy line represents the bonding site to S,

R^{F1-1} represents a hydrogen atom,

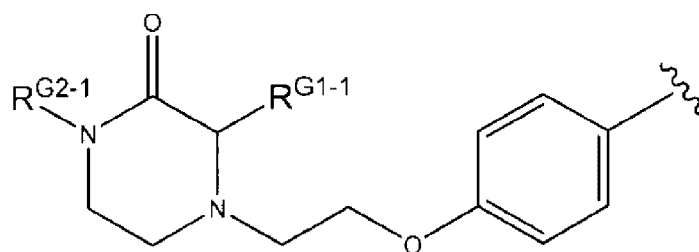
5 R^{F2-1} and R^{F3-1} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{F2-1} represents methyl and R^{F3-1} represents ethyl),

R^{F5-1} represents a hydrogen atom, and

R^{F7-1} represents a hydrogen atom or a fluorine atom.

10 [0119]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (G) is the following formula (G)-1:



(G)-1

wherein

the wavy line represents the bonding site to S, and

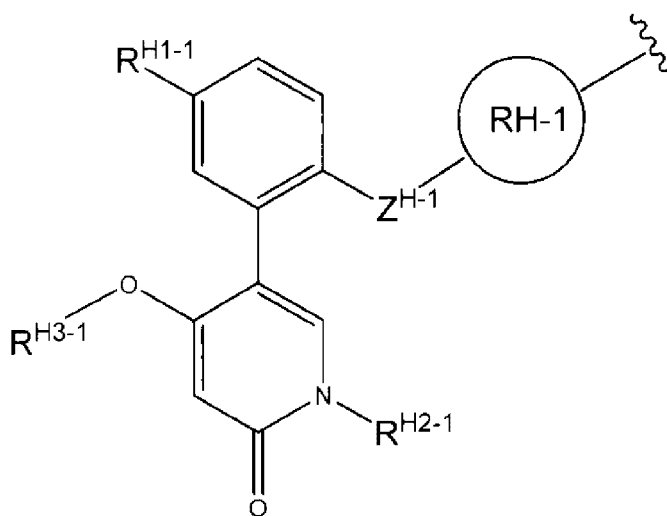
R^{G1-1} and R^{G2-1} are the same or different and each represents alkyl

5 having 1 to 5 carbon atoms (preferably methyl).

[0120]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula

10 (I), formula (H) is the following formula (H)-1:



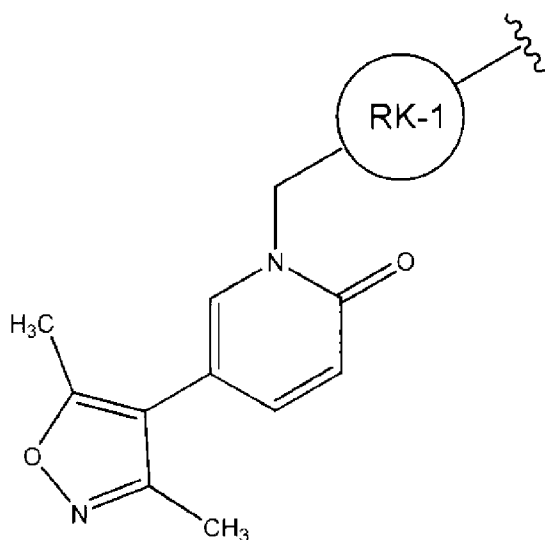
(H)-1

wherein

the wavy line represents the bonding site to S,
 R^{H1-1} represents a hydrogen atom or alkyl sulfonamide having 1 to 5
carbon atoms (preferably ethyl sulfonamide),
 R^{H2-1} and R^{H3-1} are the same or different and each represents alkyl
5 having 1 to 5 carbon atoms,
 Z^{H-1} represents CH_2 or O, and
ring RH-1 represents benzenediyl or piperidinediyl.

[0121]

According to a preferred embodiment of the present invention, there
10 is provided the BET degrader containing as an active ingredient the
compound or a pharmaceutically acceptable salt thereof, wherein in formula
(I), formula (K) is the following formula (K)-1:



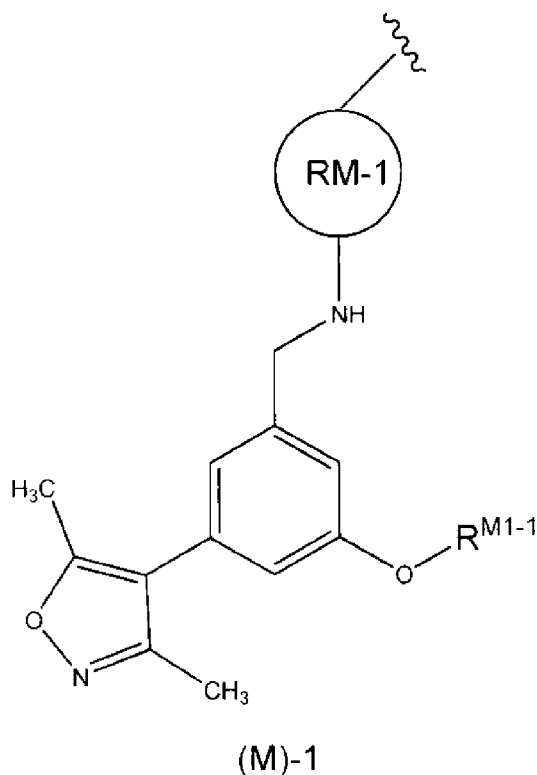
(K)-1

wherein
15 the wavy line represents the bonding site to S, and
ring RK-1 represents benzenediyl or cyclohexanediyl.

[0122]

According to a preferred embodiment of the present invention, there

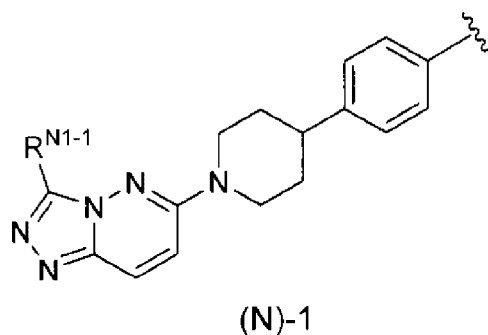
is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (M) is the following formula (M)-1:



5 wherein
 the wavy line represents the bonding site to S,
 R^{M1-1} represents a hydrogen atom, and
 ring RM-1 represents bicycloalkanediyl having 5 to 8 carbon atoms.

[0123]

10 According to a preferred embodiment of the present invention, there
 is provided the BET degrader containing as an active ingredient the
 compound or a pharmaceutically acceptable salt thereof, wherein in formula
 (I), formula (N) is the following formula (N)-1:



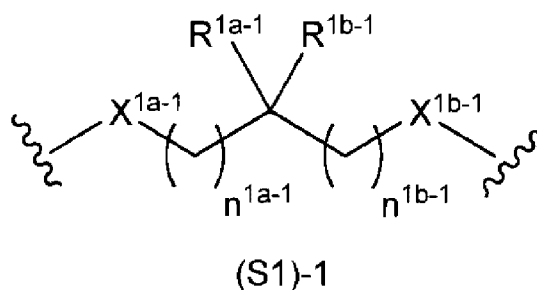
wherein

the wavy line represents the bonding site to S,

R^{N-1} represents a halogen (preferably a chlorine atom).

5 [0124]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), formula (S) is the following formula (S1)-1:



10

wherein

the wavy lines each represents the bonding site to L¹ or L²,

n^{1a-1} and n^{1b-1} are the same or different and each represents 0 or 1,

X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- (except for the cases where (i) X^{1a-1} is -NH-SO₂- and X^{1b-1} is -SO₂-NH-, (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH-, and X^{1b-1} is

15

-NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- and X^{1b-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-), wherein preferably X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, or -NH-C(=O)-NH- (except for the cases where (i) X^{1a-1} is -NH-C(=O)-NH- and X^{1b-1} is -NH-C(=O)-NH- and (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is -C(=O)-NH- or -NH-C(=O)-NH-, and X^{1b-1} is -NH-C(=O)-), and more preferably X^{1a-1} represents -NH-C(=O)- or -NH-C(=O)-NH- and X^{1b-1} represents -C(=O)-NH-, and

10 R^{1a-1} represents a hydrogen atom, R^{1b-1} represents a hydrogen atom or alkyl having 1 to 5 carbon atoms (preferably methyl or isopropyl), or R^{1a-1} and R^{1b-1} together represent carbonyl.

[0125]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is formula (S1)-1, wherein in formula (S1)-1,

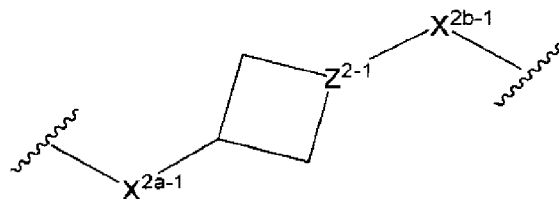
the wavy lines each represents the bonding site to L¹ or L², n^{1a-1} and n^{1b-1} are the same or different and each represents 0 or 1, X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- (except for the cases where (i) X^{1a-1} is -NH-SO₂- and X^{1b-1} is -SO₂-NH-, (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH-, and X^{1b-1} is -NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH- and X^{1b-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-), wherein preferably X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, or -NH-C(=O)-NH- (except for the cases where (i) X^{1a-1} is -NH-C(=O)-NH- and X^{1b-1} is -NH-C(=O)-NH- and (ii)

n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is $-C(=O)-NH-$ or $-NH-C(=O)-NH-$, and X^{1b-1} is $-NH-C(=O)-$, and more preferably X^{1a-1} represents $-NH-C(=O)-$ or $-NH-C(=O)-NH-$ and X^{1b-1} represents $-C(=O)-NH-$, and

R^{1a-1} represents a hydrogen atom and R^{1b-1} represents a hydrogen atom.

[0126]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S2)-1:



(S2)-1

wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

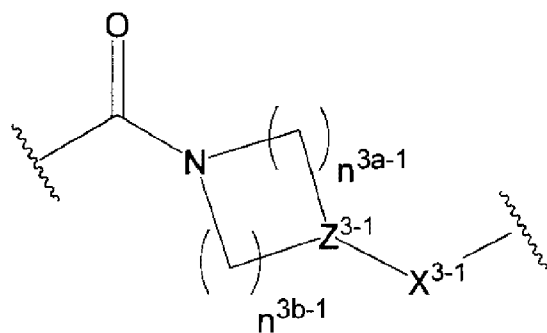
X^{2a-1} represents $-C(=O)-NH-$ or $-NH-C(=O)-$,

X^{2b-1} represents $-C(=O)-NH-$, $-NH-C(=O)-$, or $-CH_2-$, and

Z^{2-1} represents CH or N (except for the cases where (i) Z^{2-1} is N and X^{2b-1} is $-NH-C(=O)-$ and (ii) Z^{2-1} is CH and X^{2b-1} is $-CH_2-$).

[0127]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S3)-1:



(S3)-1

wherein

the wavy lines each represents the bonding site to L¹ or L²,

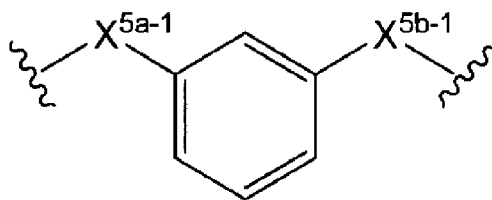
n^{3a-1} and n^{3b-1} are the same or different and each represents 1 or 2,

5 X³⁻¹ represents -C(=O)-NH-, -NH-C(=O)-, -NH-C(=O)-NH-, or -NH-CH₂- (preferably -C(=O)-NH-), and

Z³⁻¹ represents CH or N (except for the cases where (i) Z³⁻¹ is N and X³⁻¹ is -NH-C(=O)-, -NH-C(=O)-NH-, or -NH-CH₂- and (ii) Z³⁻¹ is N and n^{3a-1} or n^{3b-1} is 1).

10 [0128]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S5)-1:



(S5)-1

15

wherein

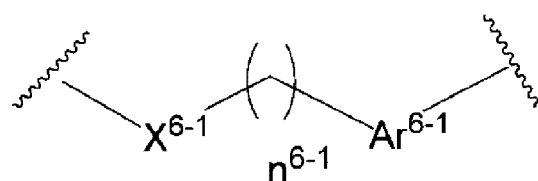
the wavy lines each represents the bonding site to L¹ or L², and

X^{5a-1} and X^{5b-1} are the same or different and each represents -C(=O)-

NH-, -NH-C(=O)-, or -NH-SO₂- (preferably, X^{5a-1} is -C(=O)-NH- or -NH-SO₂- and X^{5b-1} represents -C(=O)-NH- or -NH-C(=O)-).

[0129]

According to a preferred embodiment of the present invention, there
 5 is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S6)-1:



(S6)-1

wherein

10 the wavy lines each represents the bonding site to L¹ or L²,

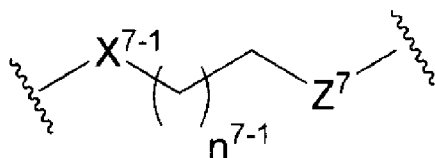
n⁶⁻¹ represents 1 or 2,

Ar⁶⁻¹ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl, and

X⁶⁻¹ represents -C(=O)-NH-, -NH-C(=O)-, or -CH₂-NH- (except for
 15 the case where (i) n⁶⁻¹ is 1, Ar⁶⁻¹ is pyrazolediyl or tetrahydropyridinediyl, and X⁶⁻¹ is -C(=O)-NH- or -CH₂-NH-).

[0130]

According to a preferred embodiment of the present invention, there
 is provided the BET degrader containing as an active ingredient the
 20 compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S7)-1:



(S7)-1

wherein

the wavy lines each represents the bonding site to L¹ or L²,

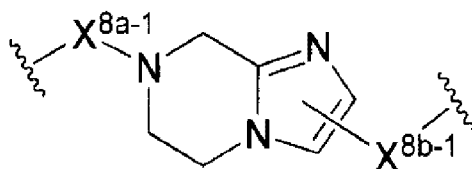
X⁷⁻¹ represents -C(=O)-NH- or -NH-C(=O)-,

5 n⁷⁻¹ represents 1, and

Z⁷⁻¹ represents S, SO, or SO₂.

[0131]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula
10 (I), S is the following formula (S8)-1:



(S8)-1

wherein

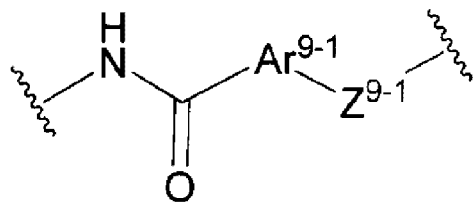
the wavy lines each represents the bonding site to L¹ or L²,

15 X^{8a-1} represents -C(=O)- or -CH₂-, and

X^{8b-1} represents a bond, -C(=O)-, -CH₂-, or -CH(OH)-.

[0132]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula
20 (I), S is the following formula (S9)-1:



(S9)-1

wherein

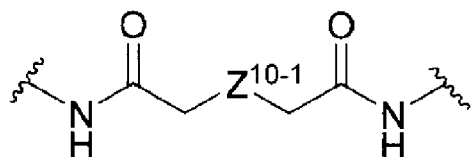
the wavy lines each represents the bonding site to L¹ or L²,

Ar⁹⁻¹ represents triazolediyl or oxazolediyl, and

5 Z⁹⁻¹ represents CH₂ or NH (except for the cases where (i) Ar⁹⁻¹ is triazolediyl and Z⁹⁻¹ is NH and (ii) Ar⁹⁻¹ is oxazolediyl and Z⁹⁻¹ is CH₂).

[0133]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula
10 (I), S is the following formula (S10)-1:



(S10)-1

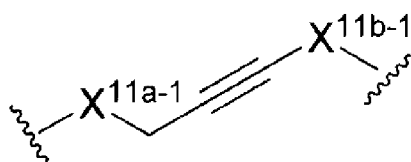
wherein

the wavy lines each represents the bonding site to L¹ or L², and

15 Z¹⁰⁻¹ represents O or NH.

[0134]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula
20 (I), S is the following formula (S11)-1:



(S11)-1

wherein

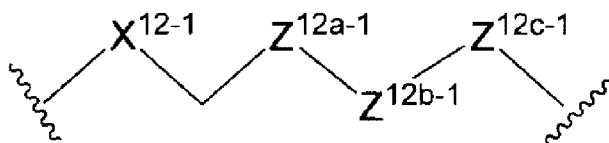
the wavy lines each represents the bonding site to L¹ or L²,

X^{11a-1} represents -C(=O)-NH-, and

5 X^{11b-1} represents -C(=O)-NH- or -C(=O)-.

[0135]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula
10 (I), S is the following formula (S12)-1:



(S12)-1

wherein

the wavy lines each represents the bonding site to L¹ or L²,

X¹²⁻¹ represents -C(=O)-NH- or -NH-C(=O)-,

15 Z^{12a-1} represents CH₂ or NH (except for the case where X¹²⁻¹ is -C(=O)-NH- and Z^{12a-1} is NH),

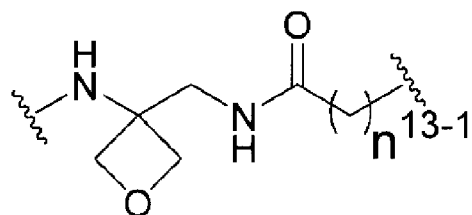
Z^{12b-1} represents CH₂ or O (except for the case where Z^{12a-1} is NH and Z^{12b-1} is O), and

20 Z^{12c-1} represents a bond or O (except for the cases where (i) Z^{12b-1} is O and Z^{12c-1} is O and (ii) Z^{12a-1} is NH and Z^{12c-1} is O).

[0136]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula

5 (I), S is the following formula (S13)-1:



(S13)-1

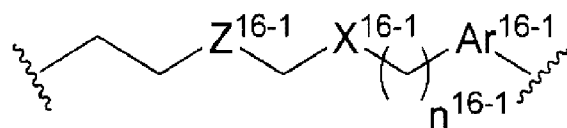
wherein

the wavy lines each represents the bonding site to L¹ or L², and

n¹³⁻¹ represents 0 or 2.

10 [0137]

According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S16)-1:



(S16)-1

15

wherein

the wavy lines each represents the bonding site to L¹ or L²,

n¹⁶⁻¹ represents 1 or 2,

Z¹⁶⁻¹ represents a bond, CH₂, or O,

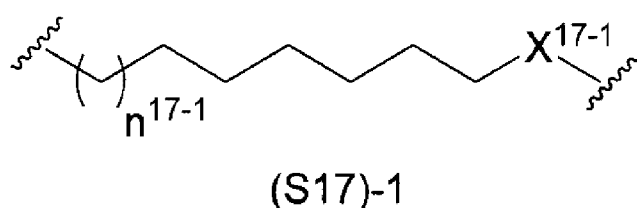
20 X¹⁶⁻¹ represents -CH₂-O- or -C(=O)-NH-, and

Ar¹⁶⁻¹ represents triazolediyl, oxadiazolediyl, or pyrazolediyl (except

for the cases where (i) X^{16-1} is $-\text{CH}_2\text{-O}-$ and Ar^{16-1} is oxadiazolediyl or pyrazolediyl and (ii) n^{16-1} is 1, X^{16-1} is $-\text{C}(=\text{O})\text{-NH}-$, and Ar^{16-1} is pyrazolediyl).

[0138]

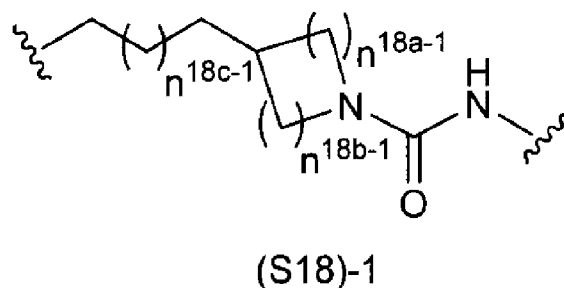
- 5 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S17)-1:



- 10 wherein
the wavy lines each represents the bonding site to L^1 or L^2 ,
 n^{17-1} represents 1 or 2, and
 X^{17-1} represents $-\text{C}(=\text{O})\text{-NH}-$.

[0139]

- 15 According to a preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), S is the following formula (S18)-1:



- 20 wherein
the wavy lines each represents the bonding site to L^1 or L^2 , and

n^{18a-1} represents 2, n^{18b-1} represents 2, and n^{18c-1} represents 1.

[0140]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 and L^2 each represents a group represented by formula (A) (preferably formula (A1)) and S is a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

[0141]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 and L^2 each represents a group represented by formula (A) (preferably formula (A1) or (A5)) and S is a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S1), n^{1a} and n^{1b} each represents 0, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-$

C(=O)-NH- (preferably -NH-C(=O)- or -NH-C(=O)-NH-) (except for the case where X^{1a} is -C(=O)-NH- or -NH-C(=O)-NH- and X^{1b} is -NH-C(=O)- or -NH-C(=O)-NH-), R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom.

5 [0142]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ and L² each represents a group represented by formula (A)
10 (preferably formula (A1) or (A15)) and S is a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents
15 a hydrogen atom, ring RA represents benzenediyl or pyridinediyl, and n^{1A} represents 0, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents -C(=O)-NH- or -NH-C(=O)-, R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom.

20 [0143]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ and L² each represents a group represented by formula (A)
25 (preferably formula (A1) or (A5)) and S is a group represented by formula (S3), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents
30 a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and

n^{1A} represents 0, and

in formula (S3), n^{3a} and n^{3b} each represents 2, X^3 represents -C(=O)-NH-, and Z^3 represents N.

[0144]

5 According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 and L^2 each represents a group represented by formula (A) (preferably formula (A1) or (A5)) and S is a group represented by formula
10 (S3), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and
15 n^{1A} represents 0, and

in formula (S3), n^{3a} and n^{3b} each represents 1, X^3 represents -C(=O)-NH-, and Z^3 represents CH.

[0145]

According to a more preferred embodiment of the present invention,
20 there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 and L^2 each represents a group represented by formula (A) (preferably formula (A1)) and S is a group represented by formula (S6), and wherein

25 in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0, and

30 in formula (S6), n^6 represents 1, Ar^6 represents oxadiazolediyl, and

X⁶ represents -CH₂-NH-.

[0146]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ and L² each represents a group represented by formula (A) (preferably formula (A1)) and S is a group represented by formula (S6), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0, and

in formula (S6), n⁶ represents 1, Ar⁶ represents triazolediyl, and X⁶ represents -CH₂-NH-.

[0147]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L¹ and L² each represents a group represented by formula (A) (preferably formula (A1) or (A5)) and S is a group represented by formula (S6), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S6), n⁶ represents 1, Ar⁶ represents oxadiazolediyl, and X⁶ represents -C(=O)-NH-.

[0148]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 and L^2 each represents a group represented by formula (A) (preferably formula (A1) or (A5)) and S is a group represented by formula (S6), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms (preferably, R^{A2} represents methyl and R^{A3} represents ethyl), R^{A5} represents a hydrogen atom, ring RA represents benzenediyl or cycloalkanediyl, and n^{1A} represents 0, and

in formula (S6), n^6 represents 2, Ar^6 represents triazolediyl, and X^6 represents $-C(=O)-NH-$.

[0149]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (H), and S represents a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

in formula (H), R^{H1} represents alkyl sulfonamide having 1 to 5 carbon atoms, R^{H2} and R^{H3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^H represents O, and ring RH represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a}

represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

[0150]

According to a more preferred embodiment of the present invention, there is provided the BET degrader containing as an active ingredient the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I), L^1 represents a group represented by formula (A), L^2 represents a group represented by formula (H), and S represents a group represented by formula (S1), and wherein

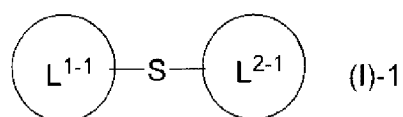
in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents 0,

in formula (H), R^{H1} represents a hydrogen atom, R^{H2} and R^{H3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^H represents O, ring RH represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

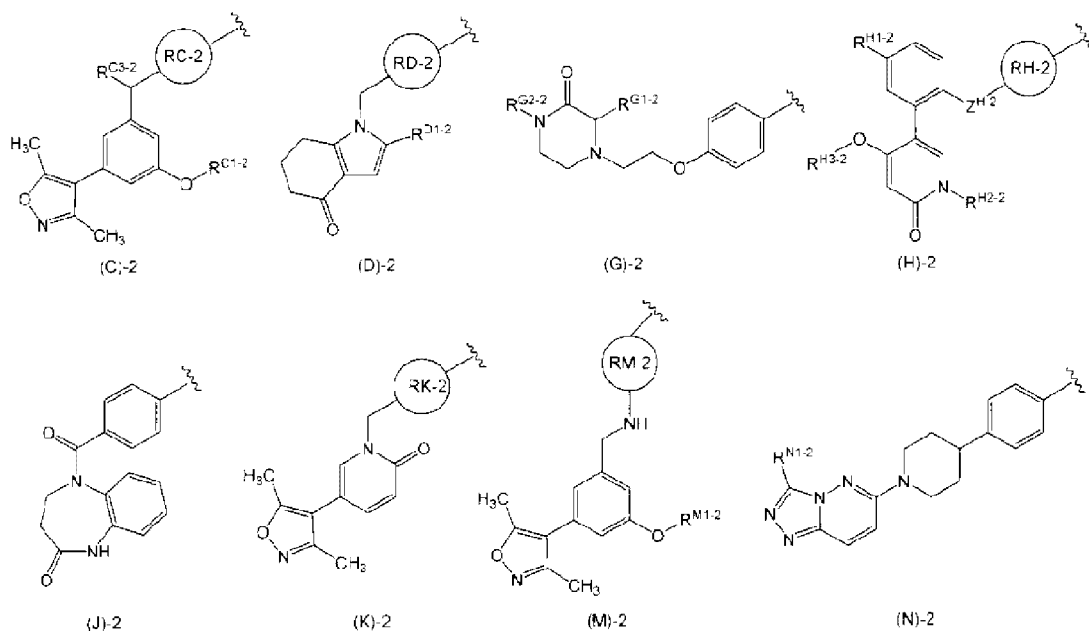
[0151]

According to another aspect of the present invention, there is provided a compound represented by the following formula (I)-1 or a pharmaceutically acceptable salt thereof:



wherein one of L^{1-1} and L^{2-1} is a group represented by a formula selected from the group consisting of the following formula (C)-2, (D)-2, (G)-2, (H)-2, (J)-2, (K)-2, (M)-2, and (N)-2, and the other of L^{1-1} and L^{2-1} is a group represented by a formula selected from the group consisting of the above formulas (A) to (H), (J), (K), (M), and (N) in formula (I), and S

is a group represented by a formula selected from the group consisting of the above formulas (S1) to (S18) in formula (I):



5

wherein

the wavy lines each represents the bonding site to S,

RC1-2 represents a hydrogen atom, lower alkyl or lower alkanoyl (preferably a hydrogen atom),

10 RC3-2 represents a hydrogen atom or hydroxy (preferably a hydrogen atom),

ring RC-2 represents piperazinediyl or azaspiro[3.3]heptanediyl,

RD1-2 represents optionally substituted lower alkyl (preferably ethyl) or optionally substituted lower alkoxy carbonyl,

ring RD-2 represents cycloalkanediyl (preferably cyclohexanediyl),

15 RG1-2 and RG2-2 are the same or different and each represents a hydrogen atom or lower alkyl (preferably methyl),

RH1-2 represents a hydrogen atom or lower alkyl sulfonamide (preferably ethyl sulfonamide),

R^{H2-2} and R^{H3-2} are the same or different and each represents lower alky (preferably methyl),

Z^{H-2} represents CH_2 or O,

ring $RH-2$ represents benzenediyl, cycloalkanediyl, azetidinediyl, pyrrolidinediyl, piperidinediyl, or homopiperidinediyl (preferably benzenediyl, cyclohexanediyl, or piperidinediyl),

ring $RK-2$ represents benzenediyl or cycloalkanediyl (preferably cyclohexanediyl),

R^{M1-2} represents a hydrogen atom or lower alkyl,

ring $RM-2$ represents cycloalkanediyl (preferably bicycloalkanediyl having 5 to 8 carbon atoms, more preferably bicyclo[1.1.1]pentanediyl or bicyclo[2.2.2]octanediyl), and

R^{N1-2} represents a hydrogen atom, a halogen, lower alkyl, or lower alkoxy (preferably a halogen).

[0152]

According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, L^{1-1} represents a group represented by formula (G)-2, L^{2-1} represents a group represented by formula (A), and S is a group represented by formula (S1).

[0153]

According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, L^{1-1} represents a group represented by formula (A), L^{2-1} represents a group represented by formula (C)-2, (D)-2, (H)-2, (J)-2, (K)-2, or (M)-2, and S is a group represented by formula (S1).

[0154]

According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable

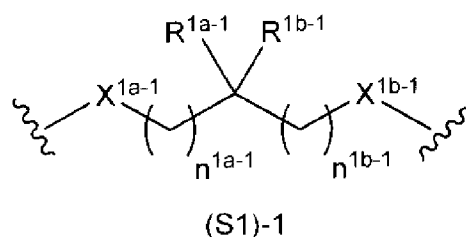
salt thereof, wherein in formula (I)-1, L^{1-1} represents a group represented by formula (G)-2 or (N)-2, L^{2-1} represents a group represented by formula (A), and S represents a group represented by formula (S3).

[0155]

5 According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, L^{1-1} represents a group represented by formula (C)-2, (G)-2, or (H)-2, L^{2-1} represents a group represented by formula (A), and S is a group represented by formula (S6).

10 [0156]

According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, S is the following formula (S1)-1:



15 wherein

the wavy lines each represents the bonding site to L^{1-1} or L^{2-1} ,

n^{1a-1} and n^{1b-1} are the same or different and each represents 0 or 1,

X^{1a-1} and X^{1b-1} are the same or different and each represents -C(=O)-

NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -O-C(=S)-NH-, -O-C(=O)-NH-, -
 20 NH-C(=O)-O-, or -NH-C(=O)-NH- (except for the cases where (i) X^{1a-1} is -NH-SO₂- and X^{1b-1} is -SO₂-NH-, (ii) n^{1a-1} and n^{1b-1} are 0, X^{1a-1} is -C(=O)-NH-, -SO₂-NH-, -O-C(=S)-NH-, -O-C(=O)-NH-, or -NH-C(=O)-NH-, and X^{1b-1} is -NH-C(=O)-, -NH-SO₂-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and (iii) X^{1a-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-, and X^{1b-1} is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-),
 25 ¹ is -O-C(=S)-NH-, -O-C(=O)-NH-, -NH-C(=O)-O-, or -NH-C(=O)-NH-),

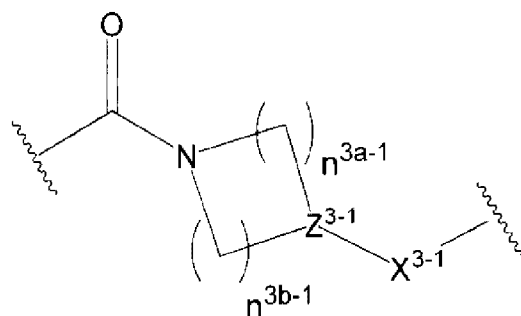
and

R^{1a-1} represents a hydrogen atom and R^{1b-1} represents a hydrogen atom or alkyl having 1 to 5 carbon atoms, or R^{1a-1} and R^{1b-1} together represent carbonyl.

5 When S is the above formula (S1)-1, preferred embodiments in formula (I)-1 may be the same as the above preferred embodiments in formula (I).

[0157]

10 According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, S is the following formula (S3)-1:



(S3)-1

wherein

the wavy lines each represents the bonding site to L^{1-1} or L^{2-1} ,

15 n^{3a-1} and n^{3b-1} are the same or different and each represents 1 or 2,

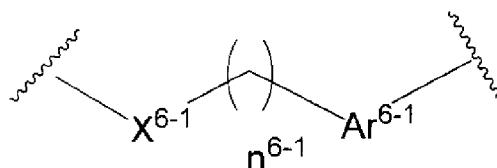
X^{3-1} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-CH_2-$, and

Z^{3-1} represents CH or N (except for the cases where (i) Z^{3-1} is N and X^{3-1} is $-NH-C(=O)-$, $-NH-C(=O)-NH-$, or $-NH-CH_2-$, and (ii) Z^{3-1} is N and n^{3a-1} or n^{3b-1} is 1).

20 When S is the above formula (S3)-1, preferred embodiments in formula (I)-1 may be the same as the above preferred embodiments in formula (I).

[0158]

According to another preferred embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, S is the following formula (S6)-1:



(S6)-1

5

wherein

the wavy lines each represents the bonding site to L¹⁻¹ or L²⁻¹,

n⁶⁻¹ represents 1 or 2,

Ar⁶⁻¹ represents triazolediyl, oxadiazolediyl, pyrazolediyl,

10 thiophenediyl, or tetrahydropyridinediyl, and

X⁶⁻¹ represents -C(=O)-NH-, -NH-C(=O)- or -CH₂-NH- (except for the cases where (i) n⁶⁻¹ is 1, Ar⁶⁻¹ is pyrazolediyl or tetrahydropyridinediyl, and X⁶⁻¹ is -C(=O)-NH- or -CH₂-NH-).

When S is the above formula (S6)-1, preferred embodiments in
15 formula (I)-1 may be the same as the above preferred embodiments in formula (I).

[0159]

According to a more preferable embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable
20 salt thereof, wherein in formula (I)-1, L¹⁻¹ represents a group represented by formula (A), L²⁻¹ represents a group represented by formula (H)-2, and S is a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms,
25 R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A}

represents O,

in formula (H)-2, R^{H1-2} represents alkyl sulfonamide having 1 to 5 carbon atoms, R^{H2-2} and R^{H3-2} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^{H-2} represents O, and ring RH-2 represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

[0160]

According to a more preferable embodiment of the present invention, there is provided the compound or a pharmaceutically acceptable salt thereof, wherein in formula (I)-1, L^{1-1} represents a group represented by formula (A), L^{2-1} represents a group represented by formula (H)-2, and S is a group represented by formula (S1), and wherein

in formula (A), R^{A1} represents a hydrogen atom, R^{A2} and R^{A3} are the same or different and each represents alkyl having 1 to 5 carbon atoms, R^{A5} represents a hydrogen atom, ring RA represents benzenediyl, and n^{1A} represents O,

in formula (H)-2, R^{H1-2} represents a hydrogen atom, R^{H2-2} and R^{H3-2} are the same or different and each represents alkyl having 1 to 5 carbon atoms, Z^{H-2} represents O, and ring RH-2 represents benzenediyl, and

in formula (S1), n^{1a} and n^{1b} each represents 1, X^{1a} and X^{1b} are the same or different and each represents $-C(=O)-NH-$ or $-NH-C(=O)-$, R^{1a} represents a hydrogen atom, and R^{1b} represents a hydrogen atom.

[0161]

The pharmaceutically acceptable salt of compound (I) or compound (I)-1 includes, for example, pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, and the like. Examples of the pharmaceutically acceptable acid addition salt of compound (I) or compound (I)-1 include inorganic acid salt

such as hydrochloride, hydrobromide, nitrate, sulfate, phosphate, and the like; and organic acid salt such as acetate, oxalate, maleate, fumarate, citrate, benzoate, methanesulfonate, and the like; and the like. Examples of the pharmaceutically acceptable metal salt include alkali metal salt such as sodium salt, potassium salt, and the like; alkaline earth metal salt such as magnesium salt, calcium salt, and the like; aluminum salt; zinc salt; and the like. Examples of the pharmaceutically acceptable ammonium salt include salt of such as ammonium, tetramethylammonium, and the like. Examples of the pharmaceutically acceptable organic amine addition salt include addition salt of such as morpholine, piperidine, and the like, and examples of the pharmaceutically acceptable amino acid addition salts include addition salts of such as lysine, glycine, phenylalanine, aspartic acid, glutamic acid, and the like.

[0162]

The compound of the present invention means a compound that has desirable properties for one or more of various evaluation items required of a pharmaceutical composition or a therapeutic or prophylactic agent for cancer, the properties including not only pharmacological activity but also physical stability, stability under physiological conditions, safety for living body, and the like.

[0163]

Method for the manufacture of compound (I)

Next, the method for the manufacture of compound (I) or compound (I)-1 will be described.

Incidentally, in the manufacturing method described below, when the defined groups react under the conditions of the manufacturing method or are not appropriate to implement the manufacturing method, the target compounds can be manufactured by using a method of introducing and removing a protecting group commonly used in organic synthetic chemistry [e.g., a method described in Protective Groups in Organic Synthesis, 3rd

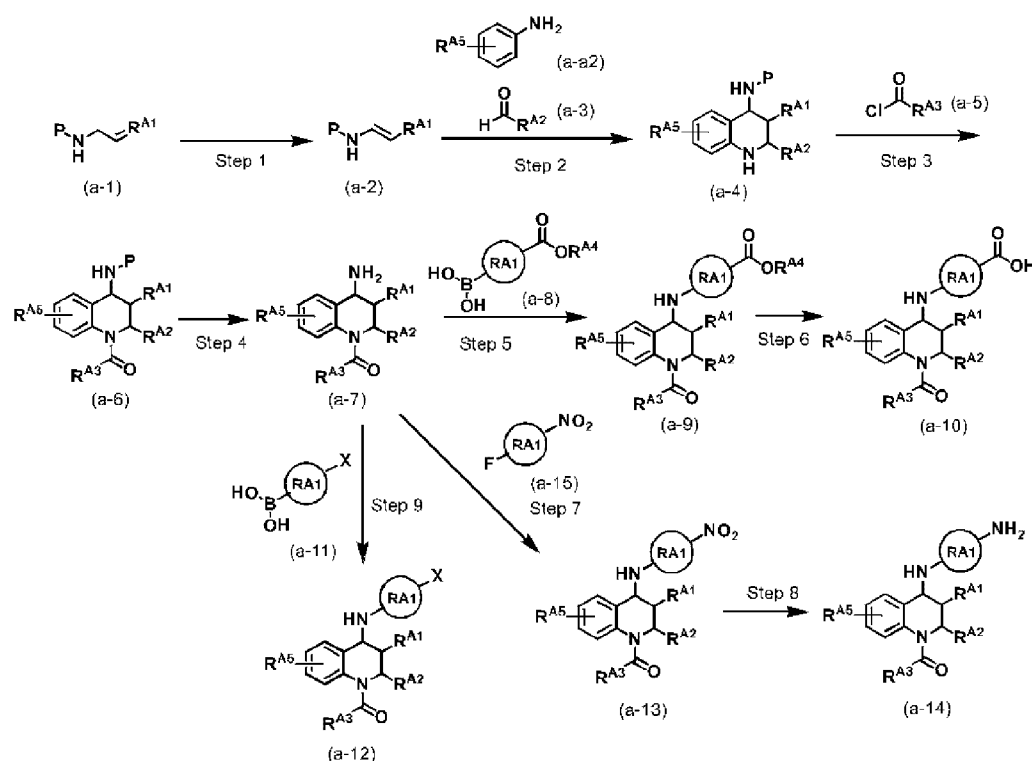
Edition by T. W. Greene, John Wiley & Sons Inc. (1999) and the like]. Furthermore, as necessary, the order of reaction steps such as introduction of substituents and the like can also be changed.

First, the method for the manufacture of a compound having a chemical structure of L¹ or L² moiety corresponding to a ligand in compound (I) will be described. The same applied to L¹⁻¹ and L²⁻¹ moieties in compound (I)-1.

[0164]

[Manufacturing method 1]

Among compounds having a chemical structure represented by formula (A), the following compounds in which ring RA is ring RA1 and n^{1A} is 0: (i) compound (a-10) in which carboxy is bonded to the wavy line portion, (ii) compound (a-14) in which amino is bonded to the wavy line portion, and (iii) compound (a-12) in which a halogen is bonded to the wavy line portion can be manufactured according to the following steps:



wherein R^{A1} , R^{A2} , R^{A3} , and R^{A5} are as defined above, X represents a halogen, R^{A4} represents lower alkyl, ring RA1 represents benzenediyl or pyridinediyl, and P represents an amine protecting group such as, for
5 example, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), p-methoxybenzyl (PMB), and the like.

[0165]

(Step 1)

Compound (a-2) can be manufactured by reacting compound (a-1)
10 and 0.001 equivalent to 0.5 equivalent of rhodium catalyst in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

Examples of the rhodium catalyst include tris(triphenylphosphine)carbonyl rhodium hydride and the like.

15 [0166]

Examples of the solvent include tetrahydrofuran (THF), acetonitrile, and the like, and these can be used alone or as a mixture.

[0167]

Compound (a-1) can be obtained as a commercially available
20 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.118, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0168]

(Step 2)

25 Compound (a-4) can be manufactured by reacting compound (a-a2), 1 equivalent to 5 equivalents of compound (a-2), and 1 equivalent to 5 equivalents of compound (a-3) in the presence of a catalytic amount of bismuth(III) chloride in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

30 [0169]

Examples of the solvent include THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0170]

Compound (a-3) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

Compound (a-a2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0171]

(Step 3)

Compound (a-6) can be manufactured by reacting compound (a-4) and 1 equivalent to 5 equivalents of compound (a-5) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0172]

Examples of the base include sodium hydride, potassium hydride, lithium diisopropylamide (LDA), lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

[0173]

Examples of the solvent include chloroform, dichloromethane, dimethylformamide (DMF), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), dimethylsulfoxide (DMSO), THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0174]

Compound (a-5) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.101, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

5 [0175]

(Step 4)

When P in compound (a-6) is, for example, Boc, compound (a-7) can be manufactured by reacting compound (a-6) in the presence of 1 equivalent to a large excess of acid in a solvent at a temperature between
10 -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

Examples of the acid include hydrochloric acid, sulfuric acid, trifluoroacetic acid, trifluoromethanesulfonic acid, bis(trifluoromethanesulfonyl)imide, and the like.

[0176]

15 Examples of the solvent include chloroform, dichloromethane, toluene, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0177]

Further, when P in compound (a-6) is, for example, Cbz, compound
20 (a-7) can be manufactured by reacting compound (a-6) in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst under a hydrogen atmosphere in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0178]

25 Examples of the palladium catalyst include palladium on carbon, palladium hydroxide, and the like.

[0179]

Examples of the solvent include methanol, ethanol, ethyl acetate, THF, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

30 [0180]

Further, when P in compound (a-6) is, for example, PMB, compound (a-7) can be manufactured by reacting compound (a-6) in the presence of 1 equivalent to 5 equivalents of an oxidizing agent in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours. Compound (a-7) can also be manufactured by the same method as when P is Boc or Cbz.

[0181]

Examples of the oxidizing agent include 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), ammonium cerium(IV) nitrate (CAN), and the like.

10 [0182]

Examples of the solvent include chloroform, dichloromethane, dichloroethane, and the like, and these can be used alone or as a mixture.

[0183]

(Step 5)

15 Compound (a-9) can be manufactured by reacting compound (a-7), 1 equivalent to 5 equivalents of compound (a-8), and 0.001 equivalent to 2 equivalents of copper(II) catalyst in the presence of 1 equivalent to a large excess of base under an oxygen atmosphere in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

20 [0184]

Examples of the copper catalyst include copper(II) acetate, copper(II) chloride, copper(II) oxide, and copper sulfate pentahydrate, and the like.

25 [0185]

Examples of the base include pyridine, 4-dimethylaminopyridine, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0186]

30 Examples of the solvent include chloroform, dichloromethane, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0187]

Compound (a-8) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.97, Maruzen Co., Ltd. (2004)

5 and the like] or methods based thereon.

[0188]

(Step 6)

Compound (a-10) can be manufactured by reacting compound (a-9) in the presence of 1 equivalent to a large excess of base in a solvent at a
10 temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0189]

Examples of the base include sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate,
15 cesium carbonate, potassium phosphate, and the like.

[0190]

Examples of the solvent include methanol, ethanol, DMF, DMA, NMP, DMSO, THF, acetonitrile, water, and the like, and these can be used alone or as a mixture.

20 [0191]

(Step 7)

Compound (a-13) can be manufactured by reacting compound (a-7) and 1 equivalent to 5 equivalents of compound (a-15) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between
25 -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0192]

Examples of the base include sodium hydride, potassium hydride, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide,
30 potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-

diisopropylethylamine, and the like.

[0193]

Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

5 [0194]

Compound (a-15) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 17, p.396, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

10 [0195]

(Step 8)

Compound (a-14) can be manufactured by reacting compound (a-13) in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst under a hydrogen atmosphere in a solvent at a temperature
15 between -20°C and the boiling point of the solvent used for 5 minute to 120 hours.

[0196]

Examples of the palladium catalyst include palladium on carbon, palladium hydroxide, and the like.

20 [0197]

Examples of the solvent include methanol, ethanol, ethyl acetate, THF, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

[0198]

(Step 9)

25 Compound (a-12) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-11) in the same manner as in step 5 of manufacturing method 1.

[0199]

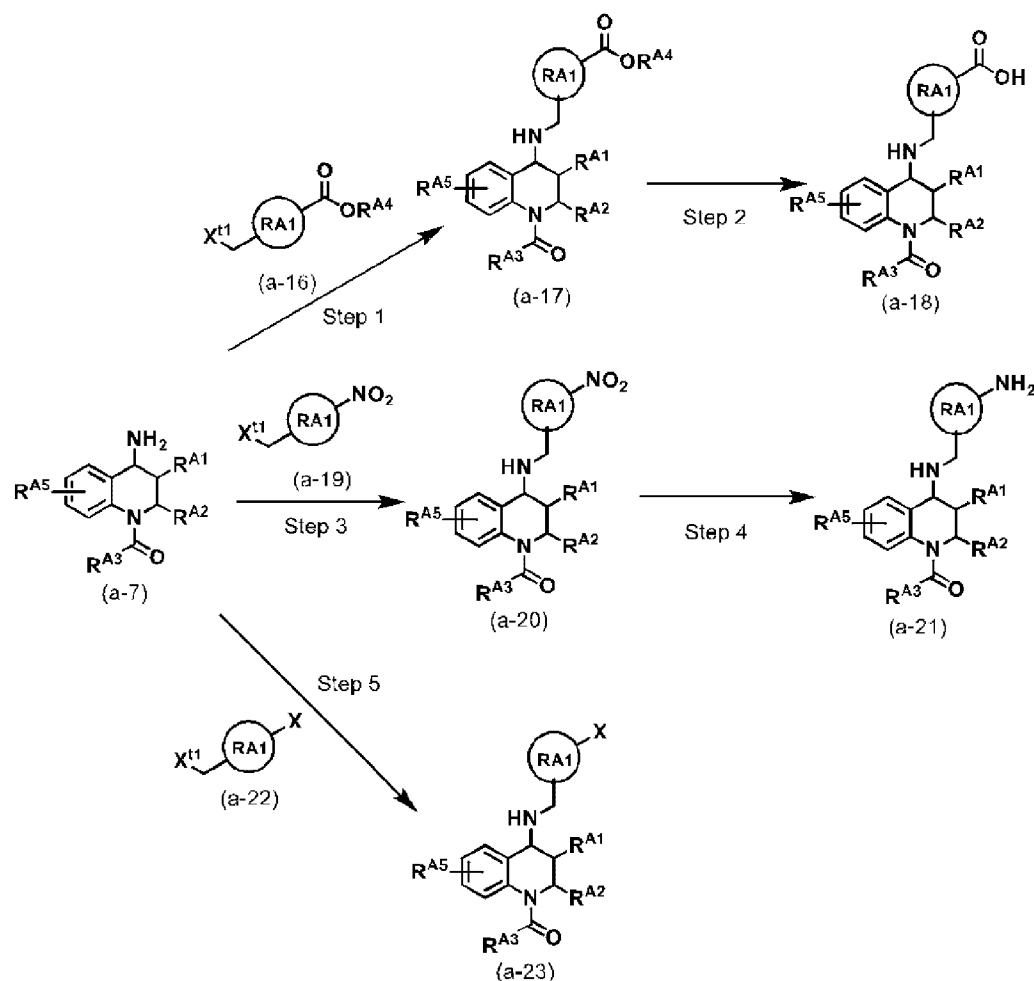
30 Compound (a-11) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental

Chemistry Lecture, 5th Edition, Volume 18, p.97, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0200]

[Manufacturing method 1-2]

- 5 Among compounds having a chemical structure represented by
formula (A), the following compounds in which ring RA is ring RA1 and n1^A
is 1: (i) compound (a-18) in which carboxy is bonded to the wavy line
portion, (ii) compound (a-21) in which amino is bonded to the wavy line
portion, and (iii) compound (a-23) in which a halogen is bonded to the wavy
10 portion can be manufactured according to the following steps:



wherein R^{A1} , R^{A2} , R^{A3} , and R^{A5} are as defined above, R^{A4} represents lower alkyl, X^{t1} represents a halogen, and ring RA1 represents benzenediyl or pyridinediyl.

[0201]

5 (Step 1)

Compound (a-17) can be manufactured by reacting compound (a-7) and 1 equivalent to 5 equivalents of compound (a-16) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

10 [0202]

Examples of the base include sodium hydride, potassium hydride, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0203]

Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, dichloromethane, chloroform, and the like, and these can be used alone or as a mixture.

20 Compound (a-16) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.377, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0204]

25 (Step 2)

Compound (a-18) can be manufactured by using compound (a-17) in the same manner as in step 6 of manufacturing method 1.

[0205]

(Step 3)

30 Compound (a-20) can be manufactured by using compound (a-7)

and 1 equivalent to 5 equivalents of compound (a-19) in the same manner as in step 1 of manufacturing method 1-2.

Compound (a-19) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
5 Chemistry Lecture, 5th Edition, Volume 13, p.377, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0206]

(Step 4)

Compound (a-21) can be manufactured by using compound (a-20)
10 in the same manner as in step 8 of manufacturing method 1.

[0207]

(Step 5)

Compound (a-23) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-22) in the same manner
15 as in step 1 of manufacturing method 1-2.

[0208]

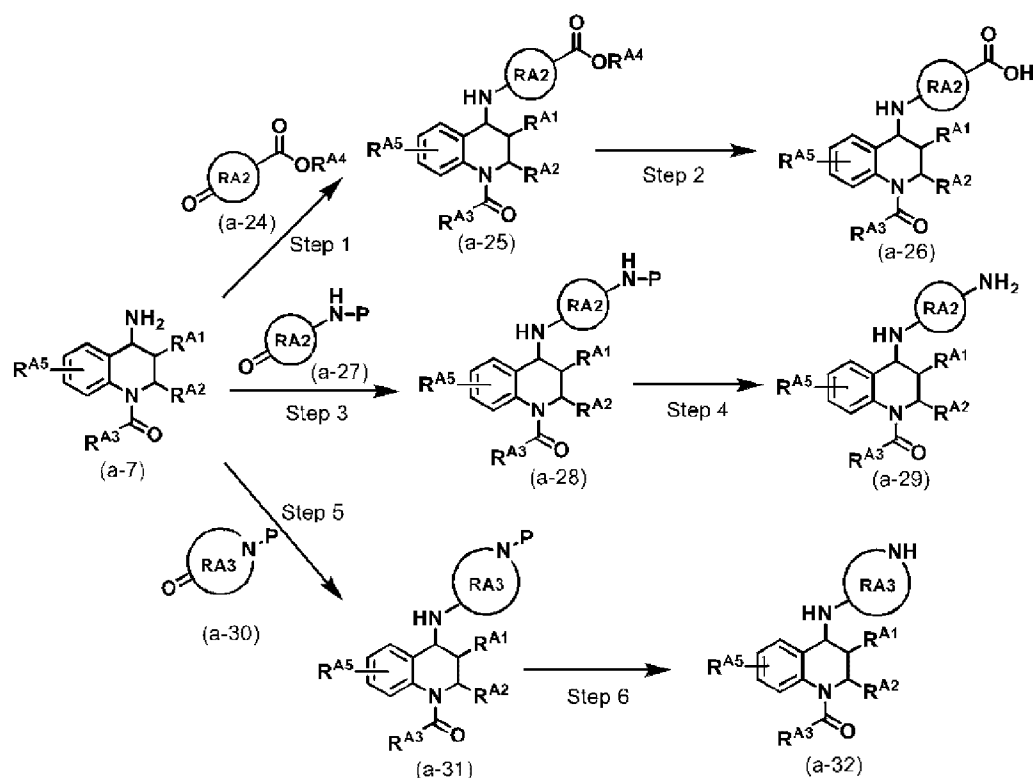
Compound (a-22) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 13, p.377, Maruzen Co., Ltd. (2004)
20 and the like] or methods based thereon.

[0209]

[Manufacturing method 1-3]

Among compounds having a chemical structure represented by formula (A), the following compounds in which ring RA is ring RA2 and n1^A
25 is 0: (i) compound (a-26) in which carboxy is bonded to the wavy line portion and (ii) compound (a-29) in which amino is bonded to the wavy line portion; and among compounds having a chemical structure represented by formula (A), compound (a-32) in which ring RA is ring RA3 can be manufactured respectively according to the following steps:

30



wherein R^{A1} , R^{A2} , R^{A3} , R^{A5} , and P are as defined above, R^{A4} represents lower alkyl, ring RA2 represents cycloalkanediyl, and ring RA3 represents piperidinediyl, azetidinediyl, pyrrolidinediyl, or homopiperidinediyl.

[0210]

(Step 1)

Compound (a-25) can be manufactured by reacting compound (a-7) and 1 equivalent to 5 equivalents of compound (a-24) in the presence of 1 equivalent to 5 equivalents of reducing agent and 1 equivalent to 5 equivalents of acid in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0211]

Examples of the reducing agent include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, and the like.

[0212]

Examples of the acid include hydrochloric acid, trifluoroacetic acid,

acetic acid, and the like.

[0213]

Examples of the solvent include methanol, ethanol, and the like, and these can be used alone or as a mixture.

5 [0214]

Compound (a-24) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.153, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

10 [0215]

(Step 2)

Compound (a-26) can be manufactured by using compound (a-25) in the same manner as in step 6 of manufacturing method 1.

[0216]

15 (Step 3)

Compound (a-28) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-27) in the same manner as in step 1 of manufacturing method 1-3.

[0217]

20 Compound (a-27) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.153, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0218]

25 (Step 4)

Compound (a-29) can be manufactured by using compound (a-28) in the same manner as in step 4 of manufacturing method 1.

[0219]

(Step 5)

30 Compound (a-31) can be manufactured by using compound (a-7)

and 1 equivalent to 5 equivalents of compound (a-30) in the same manner as in step 1 of manufacturing method 1-3.

[0220]

Compound (a-30) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.153, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0221]

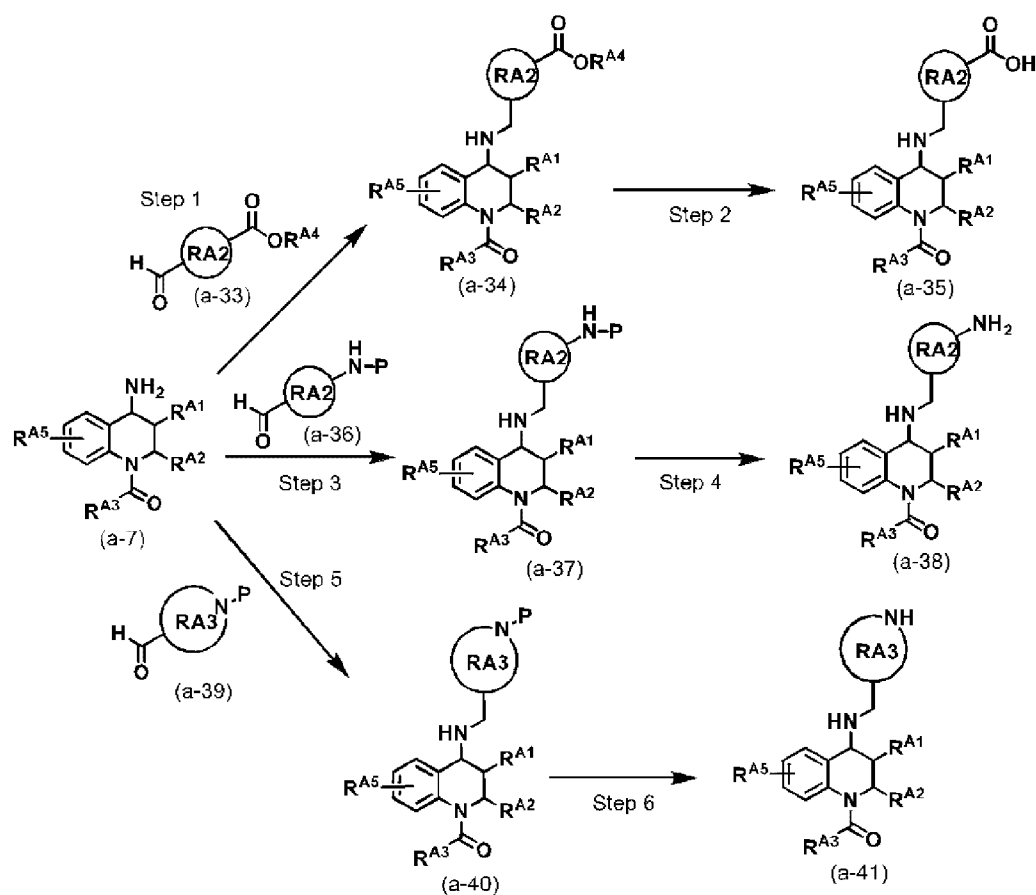
(Step 6)

Compound (a-32) can be manufactured by using compound (a-31) in the same manner as in step 4 of manufacturing method 1.

[0222]

[Manufacturing method 1-4]

Among compounds having a chemical structure represented by formula (A), the following compounds in which ring RA is ring RA2 and n^{1A} is 1: (i) compound (a-35) in which carboxy is bonded to the wavy line portion and (ii) compound (a-38) in which amino is bonded to the wavy line portion; and among compounds having a chemical structure represented by formula (A), compound (a-41) in which n^{1A} is 1 and ring RA is ring RA3 can be manufactured respectively according to the following steps:



wherein R^{A1} , R^{A2} , R^{A3} , R^{A5} , and P are as defined above, R^{A4} represents lower alkyl, ring RA2 represents cycloalkanediyl, and ring RA3 represents

5 piperidinediyl, azetidinediyl, pyrrolidinediyl, or homopiperidinediyl.

[0223]

(Step 1)

Compound (a-34) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-33) in the same manner

10 as in step 1 of manufacturing method 1-3.

[0224]

Compound (a-33) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.1, Maruzen Co., Ltd. (2004)

15 and the like] or methods based thereon.

[0225]

(Step 2)

Compound (a-35) can be manufactured by using compound (a-34) in the same manner as in step 6 of manufacturing method 1.

5 [0226]

(Step 3)

Compound (a-37) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-36) in the same manner as in step 1 of manufacturing method 1-3.

10 [0227]

Compound (a-36) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

15 [0228]

(Step 4)

Compound (a-38) can be manufactured by using compound (a-37) in the same manner as in step 4 of manufacturing method 1.

[0229]

20 (Step 5)

Compound (a-40) can be manufactured by using compound (a-7) and 1 equivalent to 5 equivalents of compound (a-39) in the same manner as in step 1 of manufacturing method 1-3.

[0230]

25 Compound (a-39) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0231]

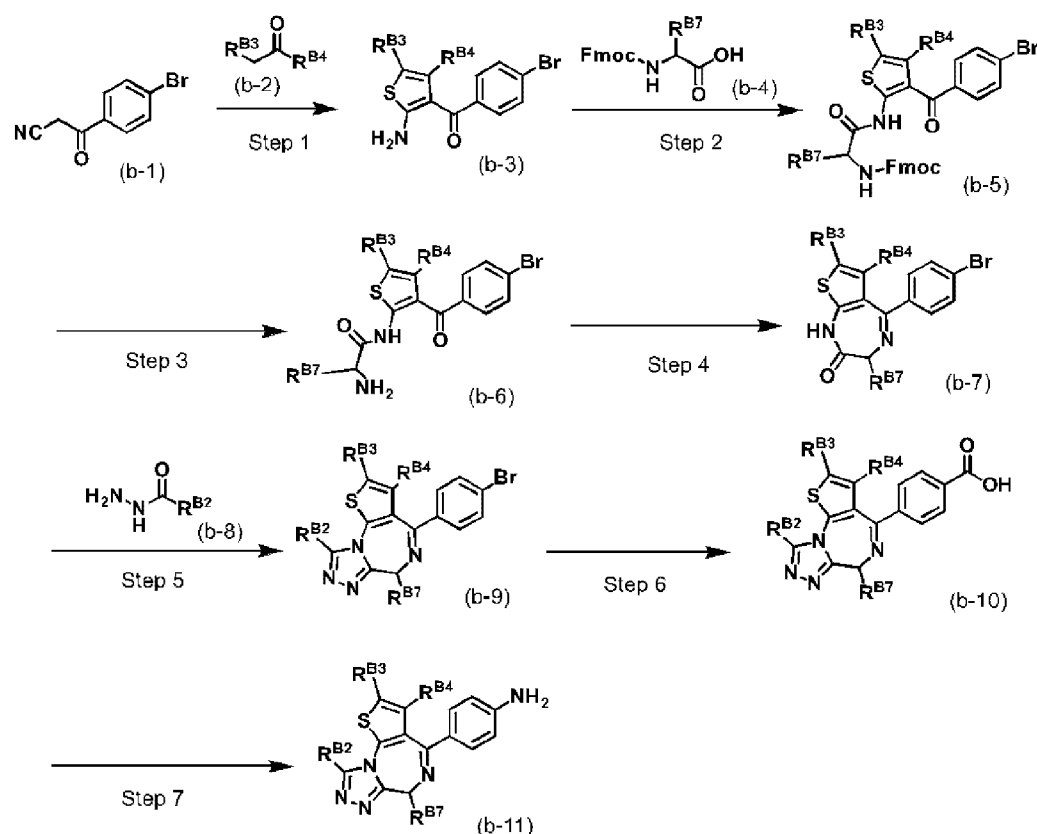
30 (Step 6)

Compound (a-41) can be manufactured by using compound (a-40) in the same manner as in step 4 of manufacturing method 1.

[0232]

[Manufacturing method 2]

- 5 Among compounds having a chemical structure represented by formula (B), the following compounds in which R^{B1} is R^{B7} : (i) compound (b-9) in which bromine is bonded to the wavy portion, (ii) compound (b-10) in which carboxy is bonded to the wavy portion, and (iii) compound (b-11) in which amino is bonded to the wavy portion can be manufactured
- 10 respectively according to the following steps:



- wherein R^{B2} , R^{B3} , and R^{B4} are as defined above, R^{B7} represents a
- 15 hydrogen atom and tert-butoxycarbonylmethyl, and Fmoc represents 9-fluorenylmethyloxycarbonyl.

[0233]

(Step 1)

The compound (b-3) can be manufactured by reacting compound (b-1) and 1 equivalent to 5 equivalents of compound (b-2) in the presence of
5 1 equivalent to 5 equivalents of sulfur and 0.25 to 5 equivalents of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0234]

Examples of the base include pyrrolidine, piperidine, morpholine,
10 and the like.

[0235]

Examples of the solvent include methanol, ethanol, DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

15 [0236]

The compound (b-1) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.517, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

20 [0237]

Compound (b-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 15, p.153, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

25 [0238]

(Step 2)

Compound (b-5) can be manufactured by reacting compound (b-3) and 1 equivalent to 5 equivalents of compound (b-4) in the presence of 1 equivalent to a large excess of condensing agent and, according to
30 necessity, in the presence of 1 equivalent to a large excess of additive in a

solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0239]

Examples of the condensing agent include dicyclohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), (1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), and the like.

10 [0240]

Examples of the additive include 1-hydroxybenzotriazole monohydrate (HOBt), triethylamine, N,N-diisopropylethylamine, and the like.

[0241]

15 Examples of the solvent include chloroform, dichloromethane, DMF, DMA, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0242]

Compound (b-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.175, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0243]

(Step 3)

25 Compound (b-6) can be manufactured by reacting compound (b-5) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0244]

30 Examples of the base include pyrrolidine, piperidine, morpholine,

and the like.

[0245]

Examples of the solvent include methanol, ethanol, DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a
5 mixture.

[0246]

(Step 4)

Compound (b-7) can be manufactured by reacting compound (b-6) in the presence of 1 equivalent to a large excess of acid in a solvent at a
10 temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0247]

Examples of the acid include acetic acid, formic acid, hydrochloric acid, magnesium sulfate, and the like.

15 [0248]

Examples of the solvent include methanol, ethanol, toluene and the like, and these can be used alone or as a mixture.

[0249]

(Step 5)

20 Compound (b-9) can be manufactured by reacting compound (b-7) and 1 equivalent to 5 equivalents of compound (b-8) in the presence of 1 equivalent to a large excess of base and 1 equivalent to 5 equivalents of phosphoric ester in a solvent at a temperature between -78°C and the boiling point of the solvent used for 5 minutes to 120 hours.

25 [0250]

Examples of the base include sodium hydride, potassium hydride, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-
30 diisopropylethylamine, and the like.

[0251]

Examples of the phosphoric acid ester include diethyl chlorophosphate, dimethyl chlorophosphate, and the like.

[0252]

5 Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0253]

Compound (b-8) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 14, p.406, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0254]

(Step 6)

Compound (b-10) can be manufactured by reacting compound (b-9)
15 in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst, 0.001 equivalent to 0.5 equivalent of phosphorus ligand, and 1 equivalent to a large excess of base under a carbon monoxide atmosphere in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

20 [0255]

Examples of the palladium catalyst include palladium acetate, palladium chloride, tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$), bis(triphenylphosphine)palladium dichloride, [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride ($\text{Pd}(\text{dppf})\text{Cl}_2$),
25 tris(dibenzylideneacetone)dipalladium ($\text{Pd}_2(\text{dba})_3$), and the like.

[0256]

Examples of the phosphorus ligand include triphenylphosphine, tributylphosphine, bis(diphenylphosphino)propane, bis(diphenylphosphino)butane, bis(diphenylphosphino)ferrocene, and the
30 like.

[0257]

Examples of the base include sodium hydride, potassium hydride, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0258]

Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, toluene, water, and the like, and these can be used alone or as a mixture.

[0259]

(Step 7)

Compound (b-11) can be manufactured by reacting compound (b-10) in the presence of 1 equivalent to 5 equivalents of diphenylphosphoryl azide and 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0260]

Examples of the base include potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate, sodium hydroxide, potassium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0261]

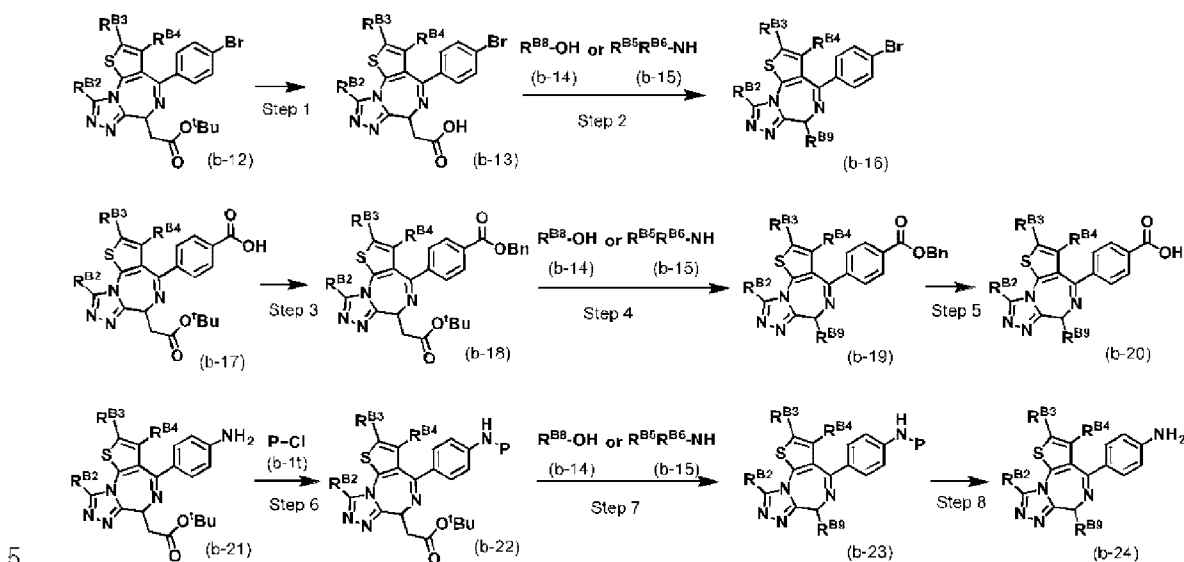
Examples of the solvent include THF, acetonitrile, 1,4-dioxane, toluene, water, and the like, and these can be used alone or as a mixture.

[0262]

[Manufacturing method T2]

Among compounds having a chemical structure represented by formula (B), the following compounds in which R^{B1} is R^{B9} : (i) compound (b-16) in which bromine is bonded to the wavy portion, (ii) compound (b-20)

in which carboxy is bonded to the wavy portion, and (iii) compound (b-24) in which amino is bonded to the wavy portion can be manufactured respectively according to the following steps.



wherein R^{B2} , R^{B3} , R^{B4} , R^{B5} , and R^{B6} are as defined above, R^{B8} represents optionally substituted lower alkyl or optionally substituted cycloalkyl, R^{B9} represents optionally substituted lower alkoxycarbonylmethyl, optionally substituted cycloalkyloxycarbonylmethyl, or $-\text{CH}_2\text{CONR}^{\text{B5}}\text{R}^{\text{B6}}$, tBu represents tert-butyl, Bn represents benzyl, and P represents an amine protecting group such as Cbz, Fmoc, and the like.

[0263]

(Step 1)

15 Compound (b-13) can be manufactured by reacting compound (b-12) in the presence of 1 equivalent to a large excess of acid without solvent or in a solvent at a temperature between 0°C and 150°C for 5 minutes to 120 hours.

20 Compound (b-12) is, among compound (b-9) obtained in step 5 of manufacturing method 2, a compound in which R^{B7} is tert-butoxycarbonylmethyl.

[0264]

Examples of the acid include hydrochloric acid, sulfuric acid, formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, titanium tetrachloride, boron trifluoride, and the like, and these are used alone or as a mixture.

[0265]

Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, 1,2-dimethoxyethane (DME), 1,4-dioxane, DMF, DMA, NMP, and the like, and these are used alone or as a mixture.

[0266]

(Step 2)

Compound (b-16) can be manufactured by using compound (b-13) and 1 equivalent to 10 equivalents of compound (b-14) or compound (b-15) in the same manner as in step 2 of manufacturing method 2.

[0267]

Compound (b-14) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0268]

Compound (b-15) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0269]

(Step 3)

Compound (b-18) can be manufactured by reacting compound (b-17) and 1 equivalent to 10 equivalents of benzyl bromide in the presence of 1 equivalent to 10 equivalents of base without solvent or in a solvent at

a temperature between -20°C and 150°C for 5 minutes to 120 hours.

[0270]

Compound (b-17) is, among compound (b-10) obtained in step 6 of manufacturing method 2, a compound in which R^{B7} is tert-butoxycarbonylmethyl.

[0271]

Examples of the base include potassium carbonate, potassium hydroxide, sodium hydroxide, sodium methoxide, potassium tert-butoxide, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, pyridine, DBU, and the like.

[0272]

Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, THF, DME, 1,4-dioxane, DMF, DMA, NMP, pyridine, and the like, and these are used alone or as a mixture.

[0273]

(Step 4)

Compound (b-19) can be manufactured by using compound (b-18) and 1 equivalent to 10 equivalents of compound (b-14) or compound (b-15) in the same manner as in step 1 and step 2.

[0274]

(Step 5)

Compound (b-20) can be manufactured by reacting compound (b-19) in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst under a hydrogen atmosphere in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0275]

Examples of the palladium catalyst include palladium on carbon, palladium hydroxide, and the like.

[0276]

Examples of the solvent include methanol, ethanol, ethyl acetate, THF, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

[0277]

5 (Step 6)

Compound (b-22) can be manufactured by reacting compound (b-21) and 1 equivalent to 10 equivalents of compound (b-1t) in the presence of 1 equivalent to 10 equivalents of base without solvent or in a solvent at a temperature between -20°C and 150°C for 5 minutes to 120 hours.

10 [0278]

Compound (b-1t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 3, p. 167 (1955) and the like] or methods based thereon.

[0279]

15 Compound (b-21) is, among compound (b-11) obtained in step 7 of manufacturing method 2, a compound in which R^{B7} is tert-butoxycarbonylmethyl.

[0280]

20 Examples of the base include potassium carbonate, potassium hydroxide, sodium hydroxide, potassium tert-butoxide, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, pyridine, DBU, 4-dimethylaminopyridine, and the like.

[0281]

25 Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, 1,4-dioxane, DMF, DMA, NMP, pyridine, water, and the like, and these are used alone or as a mixture.

[0282]

(Step 7)

30 Compound (b-23) can be manufactured by using compound (b-22)

and 1 equivalent to 10 equivalents of compound (b-14) or compound (b-15) in the same manner as in step 1 and step 2.

[0283]

(Step 8)

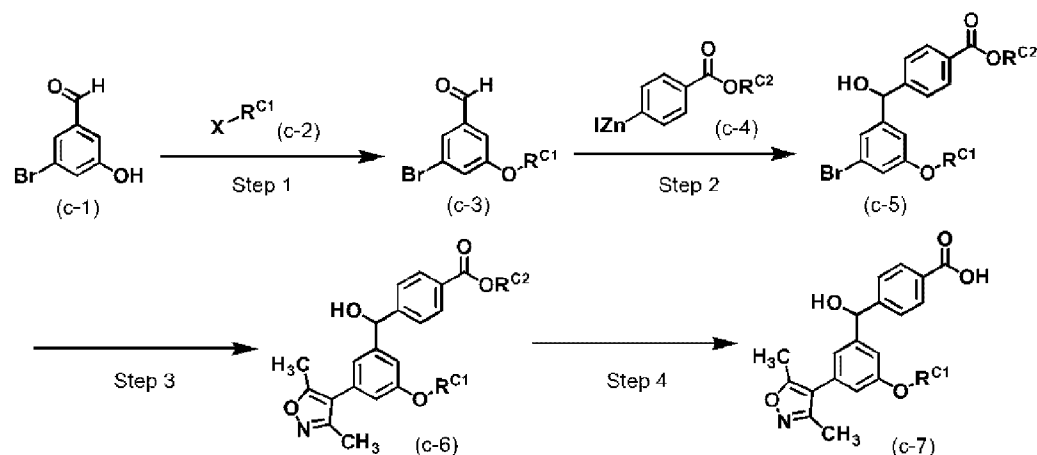
- 5 Compound (b-24) can be manufactured in the same manner as in step 5 when P in compound (b-23) is, for example, Cbz, and can be manufactured in the same manner as in step 3 of manufacturing method 2 when P in compound (b-23) is, for example, Fmoc.

[0284]

- 10 [Manufacturing method 3]

Among compounds having a chemical structure represented by formula (C), compound (c-7) in which R^{C3} is hydroxy, ring RC is benzenediyl, and carboxy is bonded to the wavy portion can be manufactured according to the following steps:

15



wherein R^{C1} is as defined above, X represents a halogen, and R^{C2} represents lower alkyl.

- 20 [0285]

(Step 1)

Compound (c-3) can be manufactured by reacting compound (c-1) and 1 equivalent to 5 equivalents of compound (c-2) in the presence of 1

equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.
[0286]

Examples of the base include sodium hydride, potassium hydride,
5 butyllithium, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0287]

10 Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0288]

Compound (c-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
15 Chemistry Lecture, 5th Edition, Volume 13, p.341, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0289]

(Step 2)

Compound (c-5) can be manufactured by reacting compound (c-3)
20 and 1 equivalent to 5 equivalents of compound (c-4) in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0290]

Examples of the solvent include THF, 1,4-dioxane, diethyl ether,
25 toluene, and the like, and these can be used alone or as a mixture.

[0291]

Compound (c-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 18, p.78, Maruzen Co., Ltd. (2004)
30 and the like] or methods based thereon.

[0292]

(Step 3)

The compound (c-6) can be manufactured by reacting compound (c-5) and 1 equivalent to 5 equivalents of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)isoxazole in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst and 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0293]

Examples of the palladium catalyst include palladium acetate, palladium chloride, Pd(PPh₃)₄, bis(triphenylphosphine)palladium dichloride, Pd(dppf)Cl₂, Pd₂(dba)₃, and the like.

[0294]

Examples of the base include potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate, sodium hydroxide, potassium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0295]

Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, toluene, water, and the like, and these can be used alone or as a mixture.

[0296]

(Step 4)

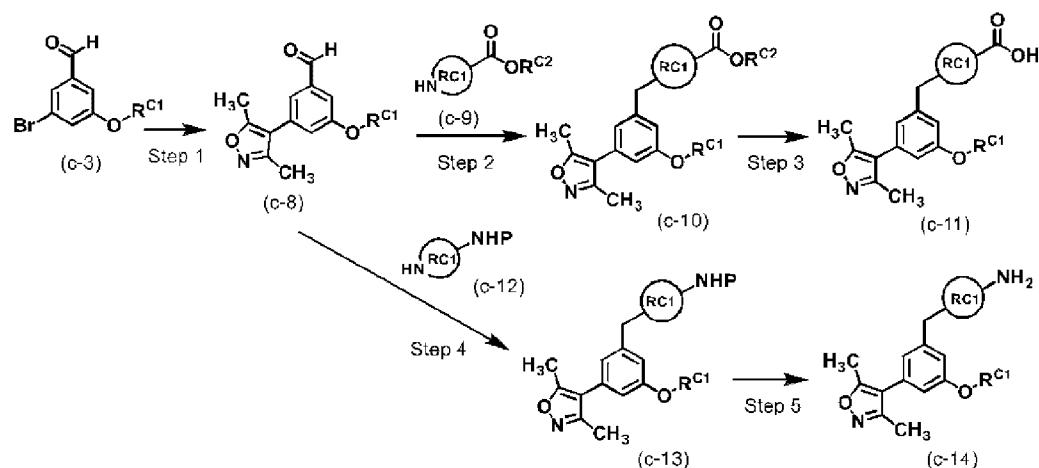
Compound (c-7) can be manufactured by using compound (c-6) in the same manner as in step 6 of manufacturing method 1.

[0297]

[Manufacturing method Y4]

Among compounds having a chemical structure represented by formula (C), the following compounds in which R^{C3} is a hydrogen atom and ring RC is ring RC1: (i) compound (c-11) in which carboxy is bonded to the

wavy portion and (ii) compound (c-14) in which amino is bonded to the wavy portion can be manufactured respectively according to the following steps:



5

wherein R^{C1} and R^{C2} are as defined above, P represents an amine protecting group such as Boc, Cbz, PMB, and the like, and ring RC1 represents piperidinediyl, azetidinediyl, pyrrolidinediyl, homopiperidinediyl, piperazinediyl, or azaspiro[3.3]heptanedyl. Incidentally, one secondary amine constituting the ring RC1 becomes a reaction point with compound (c-8).

[0298]

(Step 1)

Compound (c-8) can be manufactured by using compound (c-3) in the same manner as in step 3 of manufacturing method 3.

[0299]

(Step 2)

Compound (c-10) can be manufactured by using compound (c-8) and 1 equivalent to 5 equivalents of (c-9) in the same manner as in step 1 of manufacturing method 1-3.

[0300]

Compound (c-9) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

5 [0301]

(Step 3)

Compound (c-11) can be manufactured by using compound (c-10) in the same manner as in step 6 of manufacturing method 1.

[0302]

10 (Step 4)

Compound (c-13) can be manufactured by using compound (c-8) and 1 equivalent to 5 equivalents of compound (c-12) in the same manner as in step 1 of manufacturing method 1-3.

[0303]

15 Compound (c-12) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0304]

20 (Step 5)

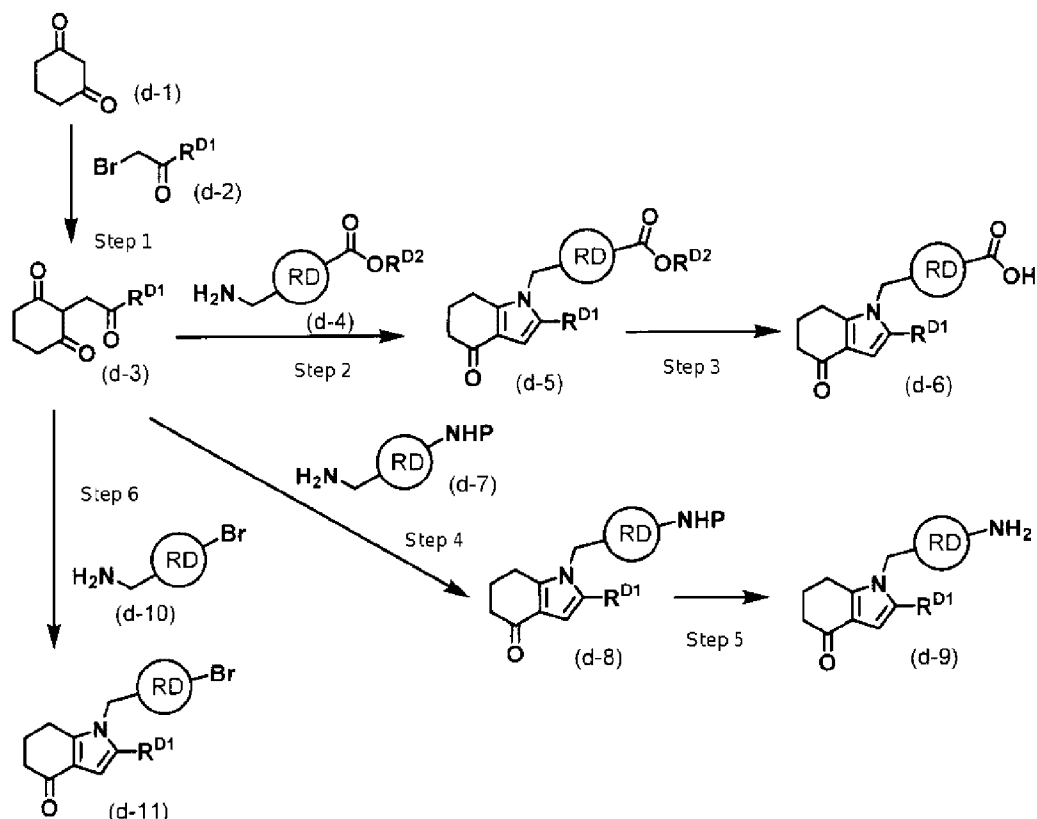
Compound (c-14) can be manufactured by using compound (c-13) in the same manner as in step 4 of manufacturing method 1.

[0305]

[Manufacturing method 4]

25 Among compounds having a chemical structure represented by formula (D), (i) compound (d-6) in which carboxy is bonded to the wavy portion, (ii) compound (d-9) in which amino is bonded to the wavy portion, and (iii) compound (d-11) in which bromine is bonded to the wavy portion can be manufactured respectively according to the following steps:

30



wherein R^{D1} and ring RD are as defined above, R^{D2} represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0306]

(Step 1)

Compound (d-3) can be manufactured by reacting cyclohexane-1,3-dione and 1 equivalent to 5 equivalents of compound (d-2) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0307]

Examples of the base include sodium hydride, potassium hydride, LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide,

sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0308]

5 Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0309]

 Compound (d-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0310]

(Step 2)

 Compound (d-5) can be manufactured by reacting compound (d-3)
15 and 1 equivalent to 5 equivalents of compound (d-4) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0311]

 Examples of the base include sodium hydride, potassium hydride,
20 LDA, lithium bis[trimethylsilyl]amide, sodium bis[trimethylsilyl]amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, and the like.

[0312]

25 Examples of the solvent include toluene, DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0313]

 Compound (d-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
30 Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)

and the like] or methods based thereon.

[0314]

(Step 3)

Compound (d-6) can be manufactured by using compound (d-5) in
5 the same manner as in step 6 of manufacturing method 1.

[0315]

(Step 4)

Compound (d-8) can be manufactured by using compound (d-3) and
1 equivalent to 5 equivalents of compound (d-7) in the same manner as in
10 step 2.

[0316]

Compound (d-7) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)
15 and the like] or methods based thereon.

[0317]

(Step 5)

Compound (d-9) can be manufactured by using compound (d-8) in
the same manner as in step 4 of manufacturing method 1.

20 (Step 6)

Compound (d-11) can be manufactured by using compound (d-3)
and 1 equivalent to 5 equivalents of compound (d-10) in the same manner
as in step 2.

[0318]

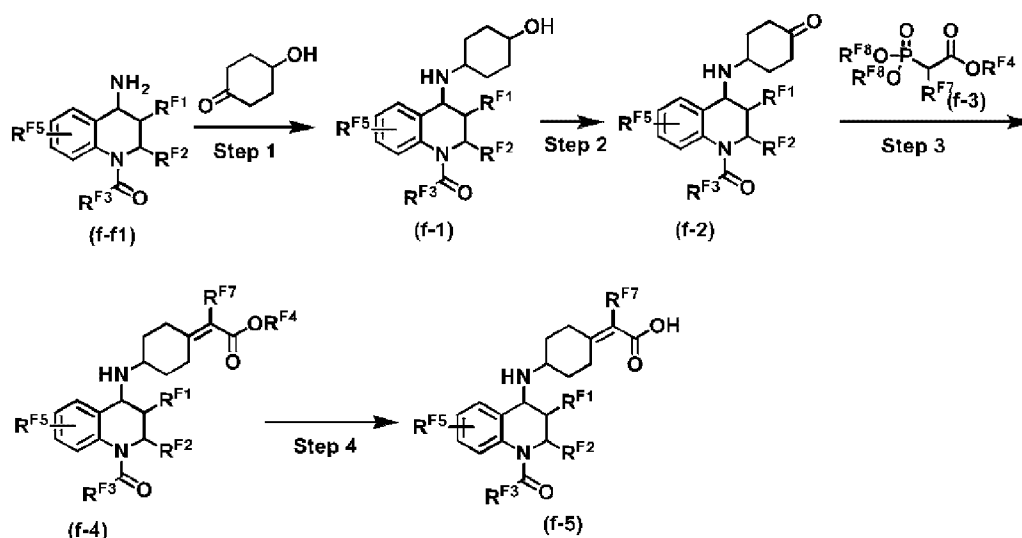
25 Compound (d-10) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0319]

30 [Manufacturing method Y5]

Compound (e-1) having a chemical structure represented by formula (E) and having a hydrogen atom bonded to the wavy portion can be obtained in the same manner as in step 4 of manufacturing method 1.
[manufacturing method Y6]

5 Compound (f-5) having a chemical structure represented by formula (F) and having carboxy bonded to the wavy portion can be manufactured according to the following steps:



10 wherein R^{F1} , R^{F2} , R^{F3} , R^{F5} , and R^{F7} are as defined above, and R^{F4} and R^{F8} each represent lower alkyl.

[0320]

(Step 1)

15 Compound (f-1) can be manufactured by using compound (f-f1) and 1 equivalent to 10 equivalents of 4-hydroxycyclohexan-1-one in the same manner as in step 1 of manufacturing method 1-3.

Compound (f-f1) can be obtained in the same manner as in step 4 of manufacturing method 1.

20 [0321]

(Step 2)

Compound (f-2) can be manufactured by reacting compound (f-1) in the presence of 1 equivalent to 5 equivalents of oxidizing agent in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

5 [0322]

Examples of the oxidizing agent include Dess-Martin periodinane (DMP), DMSO/oxalyl chloride, sulfur trioxide-pyridine, and the like.

[0323]

10 Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DME, 1,4-dioxane, DMF, DMA, NMP, DMSO, and the like, and these can be used alone or as a mixture.

[0324]

(Step 3)

15 Compound (f-4) can be manufactured by reacting 1 equivalent to 5 equivalents of compound (f-3) and 1 equivalent to 5 equivalents of base in a solvent at a temperature between -78°C and the boiling point of the solvent used for 5 minutes to 30 minutes and, subsequently, by adding compound (f-2) to the reaction mixture and reacting the mixture at a
20 temperature between -78°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0325]

Examples of the base include sodium hydride, potassium tert-butoxide, LDA, lithium bis[trimethylsilyl]amide, sodium
25 bis[trimethylsilyl]amide, DBU, and the like.

[0326]

Examples of the solvent include THF, DME, hexamethylphosphoric triamide (HMPA), and the like, and these can be used alone or as a mixture.

[0327]

30 Compound (f-3) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 4th Edition, Volume 24, p.243, Maruzen Co., Ltd. (1994) and the like] or methods based thereon.

[0328]

5 (Step 4)

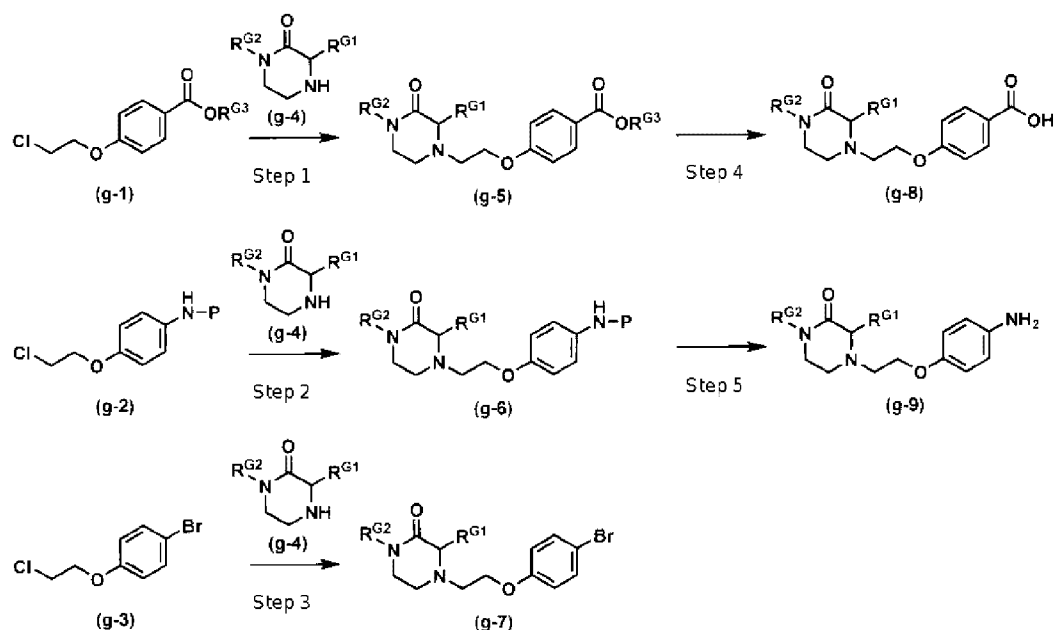
Compound (f-5) can be manufactured by using compound (f-4) in the same manner as in step 6 of manufacturing method 1.

[0329]

[Manufacturing method Y7]

10 Among compounds having a chemical structure represented by formula (G), (i) compound (g-8) in which carboxy is bonded to the wavy line portion, (ii) compound (g-9) in which amino is bonded to the wavy line portion, and (iii) compound (g-7) in which a bromine atom is bonded to the wavy line portion can be manufactured according to the following steps:

15



wherein R^{G1} and R^{G2} are as defined above, R^{G3} represents a lower

alkyl group, and P represents an amine protecting group such as Boc, Cbz, PMB and the like.

[0330]

(Step 1)

5 Compound (g-5) can be manufactured by reacting compound (g-1) and 1 equivalent to 5 equivalents of compound (g-4) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

 Examples of the base include sodium hydride, potassium hydride,
10 butyl lithium, LDA, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine and the like.

[0331]

15 Examples of the solvent include DMF, DMA, NMP, DMSO, THF, acetonitrile and the like, and these can be used alone or as a mixture.

[0332]

 Compound (g-1) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
20 Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

 Compound (g-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)
25 and the like] or methods based thereon.

[0333]

(Step 2)

 Compound (g-6) can be manufactured by using compound (g-2) in the same manner as in step 1 of manufacturing method Y7.

30 Compound (g-2) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0334]

5 (Step 3)

Compound (g-7) can be manufactured by using compound (g-3) in the same manner as in step 1 of manufacturing method Y7.

Compound (g-3) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0335]

(Step 4)

Compound (g-8) can be manufactured by using compound (g-5) in
15 the same manner as in step 6 of manufacturing method 1.

[0336]

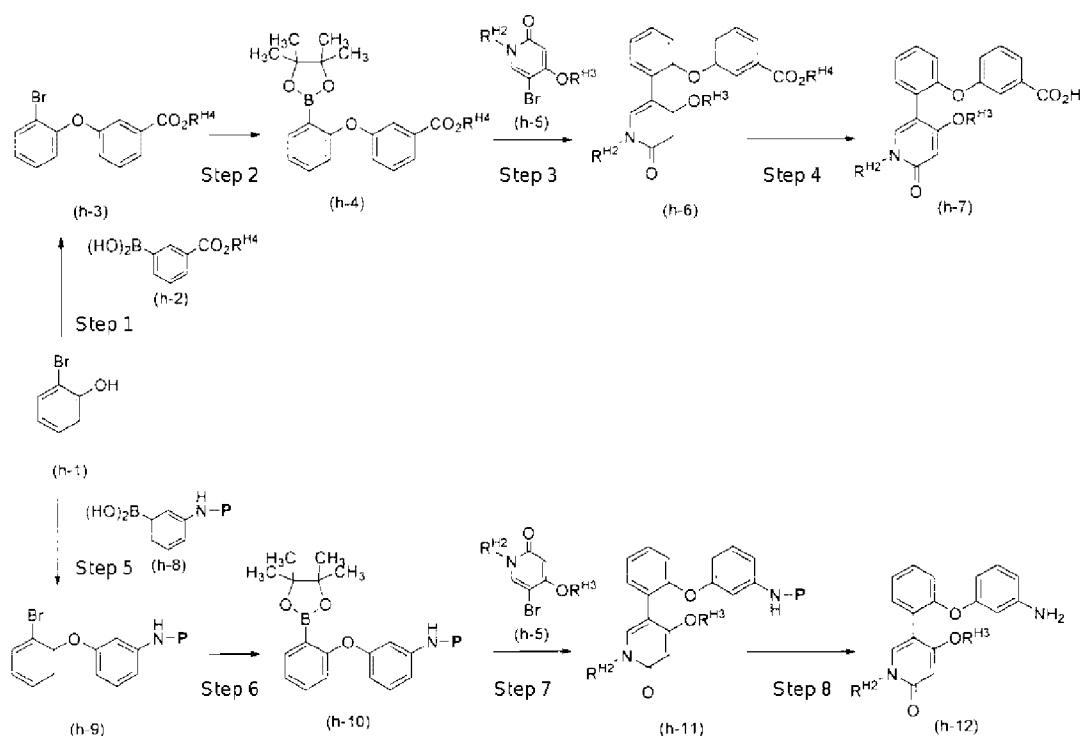
(Step 5)

Compound (g-9) can be manufactured by using compound (g-6) in the same manner as in step 4 of manufacturing method 1.

20 [0337]

[Manufacturing method Y8-1]

Among compounds having a chemical structure represented by formula (H), the following compounds in which R^{H1} is a hydrogen atom, ring RH is benzenediyl, and Z^H is an oxygen atom: (i) compound (h-7) in which
25 carboxy is bonded to the wavy line portion and (ii) compound (h-12) in which amino is bonded to the wavy line portion can be manufactured according to the following steps:



wherein R^{H2} and R^{H3} are as defined above, R^{H4} represents a lower alkyl group, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0338]

(Step 1)

Compound (h-3) can be manufactured in the same manner as in step 5 of manufacturing method 1 using 2-bromophenol (h-1) and 1 equivalent to 5 equivalents of compound (h-2).

Compound (h-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0339]

(Step 2)

Compound (h-4) can be manufactured by reacting compound (h-3) in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst, 1 equivalent to 5 equivalents of bis(pinacolato)diboron, and 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0340]

Examples of the palladium catalyst include palladium acetate, palladium chloride, Pd(PPh₃)₄, bis(triphenylphosphine)palladium dichloride, Pd(dppf)Cl₂, Pd₂(dba)₃ and the like.

[0341]

Examples of the base include potassium carbonate, potassium phosphate, potassium acetate, potassium phenoxide and the like.

[0342]

Examples of the solvent include 1,2-dichloroethane, toluene, THF, DMF and the like, and these can be used alone or as a mixture.

[0343]

(Step 3)

Compound (h-6) can be manufactured in the same manner as in step 3 of manufacturing method 3 by using compound (h-4) and 1 equivalent to 5 equivalents of compound (h-5).

Compound (h-5) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Journal of Medicinal Chemistry Vol.60, p.3828 (2017) and the like] or methods based thereon.

[0344]

(Step 4)

Compound (h-7) can be manufactured by using compound (h-6) in the same manner as in step 6 of manufacturing method 1.

[0345]

(Step 5)

Compound (h-9) can be manufactured in the same manner as in step

5 of manufacturing method 1 using 2-bromophenol (h-1) and 1 equivalent to 5 equivalents of compound (h-8).

Compound (h-8) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
5 Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0346]

(Step 6)

Compound (h-10) can be manufactured in the same manner as in
10 step 2 of manufacturing method Y8-1 using compound (h-9) and 1 equivalent to 5 equivalents of bis(pinacolato)diboron.

[0347]

(Step 7)

Compound (h-11) can be manufactured by using compound (h-10)
15 in the same manner as in step 3 of manufacturing method Y8-1.

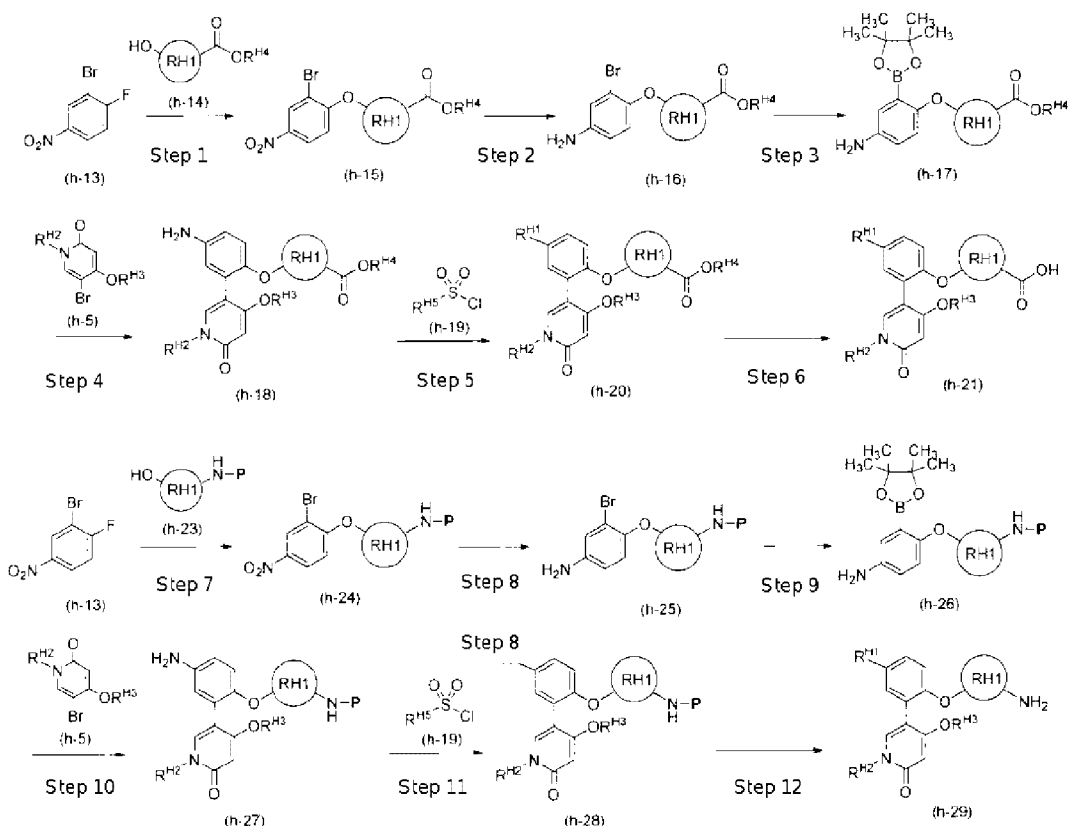
[0348]

(Step 8)

Compound (h-12) can be manufactured by using compound (h-11)
in the same manner as in step 4 of manufacturing method 1.

20 [Manufacturing method Y8-2]

Among compounds having a chemical structure represented by
formula (H), the following compounds in which R^{H1} is lower alkyl
sulfonamide, ring RH is ring RH1, and Z^H is an oxygen atom: (i) compound
(h-21) in which carboxy is bonded to the wavy line portion and (ii)
25 compound (h-29) in which amino is bonded to the wavy line portion can be
manufactured according to the following steps:



wherein R^{H2} and R^{H3} are as defined above, R^{H4} represents lower alkyl, R^{H5} represents a lower alkyl moiety in the lower alkyl sulfonamide of R^{H1} ,
 5 ring RH1 represents cycloalkanediyl or benzenediyl, P represents an amine protecting group such as Boc, Cbz, PMB and the like.

[0349]

(Step 1)

Compound (h-15) can be manufactured by reacting 2-bromo-1-fluoro-4-nitrobenzene (h-13) and 1 equivalent to 5 equivalents of compound (h-14) in the presence of 1 equivalent to a large excess of base
 10 in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0350]

15 Examples of the base include sodium hydride, potassium hydride,

LDA, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, cesium carbonate, DBU, triethylamine and the like.

5 [0351]

Examples of the solvent include acetonitrile, THF, DME, dioxane, DMF, DMA, NMP and the like, and these can be used alone or as a mixture.

[0352]

Compound (h-14) can be obtained as a commercially available
10 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0353]

(Step 2)

15 Compound (h-16) can be manufactured by using compound (h-15) in the same manner as in step 8 of manufacturing method 1.

[0354]

(Step 3)

Compound (h-17) can be manufactured by using compound (h-16)
20 in the same manner as in step 2 of manufacturing method Y8-1.

[0355]

(Step 4)

Compound (h-18) can be manufactured by using compound (h-17)
in the same manner as in step 3 of manufacturing method Y8-1.

25 [0356]

(Step 5)

Compound (h-20) can be manufactured by reacting compound (h-18) and 1 equivalent to 5 equivalents of compound (h-19) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature
30 between -20°C and the boiling point of the solvent used for 5 minutes to

120 hours.

[0357]

Examples of the base include sodium hydride, potassium hydride, sodium methoxide, potassium ethoxide, potassium tert-butoxide, potassium carbonate, sodium hydroxide, cesium carbonate, DBU, triethylamine, pyridine, 4-dimethylaminopyridine and the like.

[0358]

Examples of the solvent include pyridine, THF, DME, dioxane, dichloromethane and the like, and these can be used alone or as a mixture.

10 [0359]

Compound (h-19) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Synthesis Vol.24, p.4131 (2006) and the like] or methods based thereon.

[0360]

15 (Step 6)

Compound (h-21) can be manufactured by using compound (h-20) in the same manner as in step 6 of manufacturing method 1.

[0361]

(Step 7)

20 Compound (h-24) can be manufactured in the same manner as in step 1 of manufacturing method Y8-2 using 2-bromo-1-fluoro-4-nitrobenzene (h-13) and 1 equivalent to 5 equivalents of compound (h-23).

Compound (h-23) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

25 [0362]

(Step 8)

Compound (h-25) can be manufactured by using compound (h-24) in the same manner as in step 2 of manufacturing method Y8-2.

30

[0363]

(Step 9)

Compound (h-26) can be manufactured by using compound (h-25) in the same manner as in step 3 of manufacturing method Y8-2.

5 [0364]

(Step 10)

Compound (h-27) can be manufactured by using compound (h-26) in the same manner as in step 4 of manufacturing method Y8-2.

[0365]

10 (Step 11)

Compound (h-28) can be manufactured by using compound (h-27) in the same manner as in step 5 of manufacturing method Y8-2.

[0366]

(Step 12)

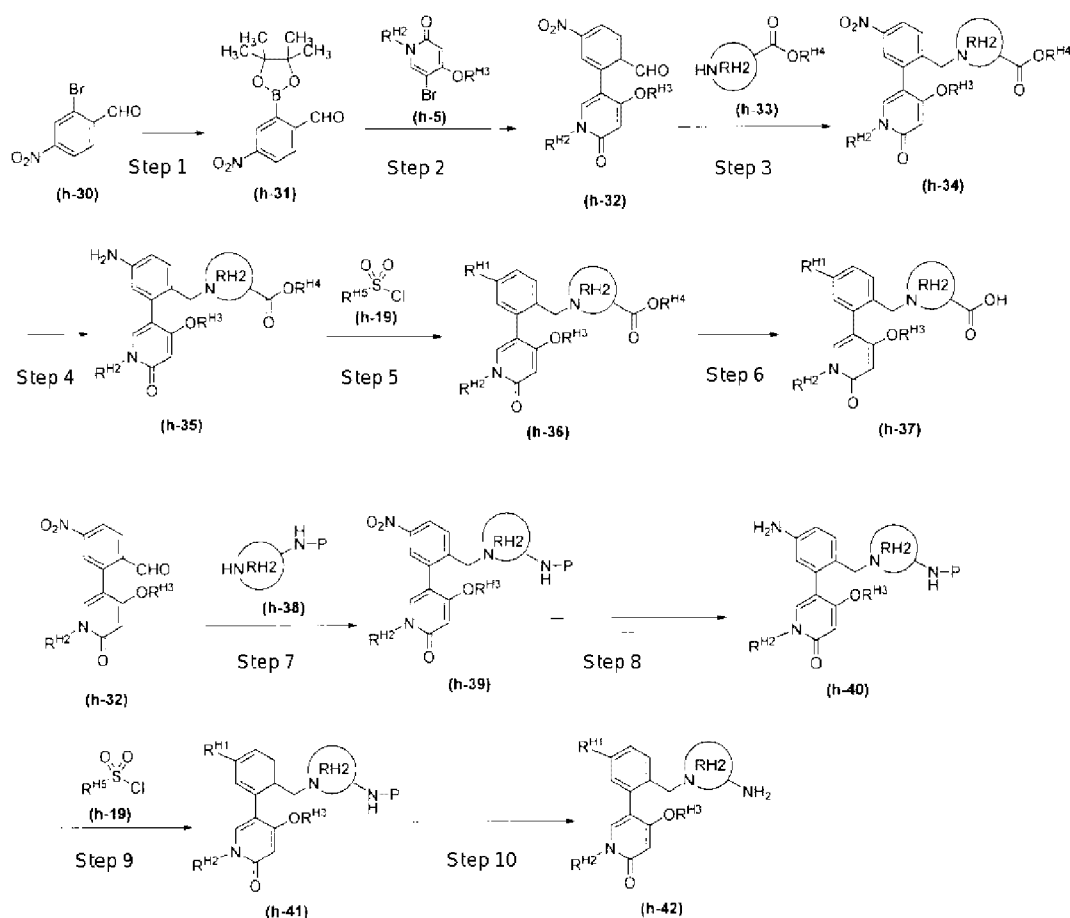
15 Compound (h-29) can be manufactured by using compound (h-28) in the same manner as in step 4 of manufacturing method 1.

[0367]

[Manufacturing method Y8-3]

Among compounds having a chemical structure represented by
20 formula (H), the following compounds in which R^{H1} is lower alkyl sulfonamide, ring RH is ring RH2, and Z^H is methylene: (i) compound (h-37) in which carboxy is bonded to the wavy line portion and (ii) compound (h-42) in which amino is bonded to the wavy line portion can be manufactured according to the following steps:

25



wherein R^{H2} and R^{H3} are as defined above, R^{H4} represents lower alkyl, R^{H5} represents a lower alkyl moiety in the lower alkyl sulfonamide of R^{H1} , P represents an amine protecting group such as Boc, Cbz, PMB and the like, ring RH2 represents azetidinediyl, pyrrolidinediyl, piperidinediyl or homopiperidinediyl.

[0368]

(Step 1)

Compound (h-31) can be manufactured by using 2-bromo-4-nitrobenzaldehyde (h-30) in the same manner as in step 2 of manufacturing method Y8-1.

[0369]

(Step 2)

Compound (h-32) can be manufactured by using compound (h-31) in the same manner as in step 3 of manufacturing method Y8-1.

[0370]

(Step 3)

- 5 Compound (h-34) can be manufactured in the same manner as in step 1 of manufacturing method 1-3 using compound (h-32) and 1 equivalent to 5 equivalents of compound (h-33).

 Compound (h-33) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon. Incidentally, one secondary amine constituting the ring RH2 becomes a reaction point with compound (h-32).

[0371]

(Step 4)

- 15 Compound (h-35) can be manufactured by using compound (h-34) in the same manner as in step 8 of manufacturing method 1.

[0372]

(Step 5)

- Compound (h-36) can be manufactured by using compound (h-35)
20 in the same manner as in step 5 of manufacturing method Y8-2.

[0373]

(Step 6)

 Compound (h-37) can be manufactured by using compound (h-36) in the same manner as in step 6 of manufacturing method 1.

- 25 [0374]

(Step 7)

 Compound (h-39) can be manufactured in the same manner as in step 1 of manufacturing method 1-3 using compound (h-32) and 1 equivalent to 5 equivalents of compound (h-38).

- 30 Compound (h-38) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon. Incidentally, one secondary amine constituting the ring RH2 becomes a reaction point with compound (h-32).

5 [0375]

(Step 8)

Compound (h-40) can be manufactured by using compound (h-39) in the same manner as in step 8 of manufacturing method 1.

[0376]

10 (Step 9)

Compound (h-41) can be manufactured by using compound (h-40) in the same manner as in step 5 of manufacturing method Y8-2.

[0377]

(Step 10)

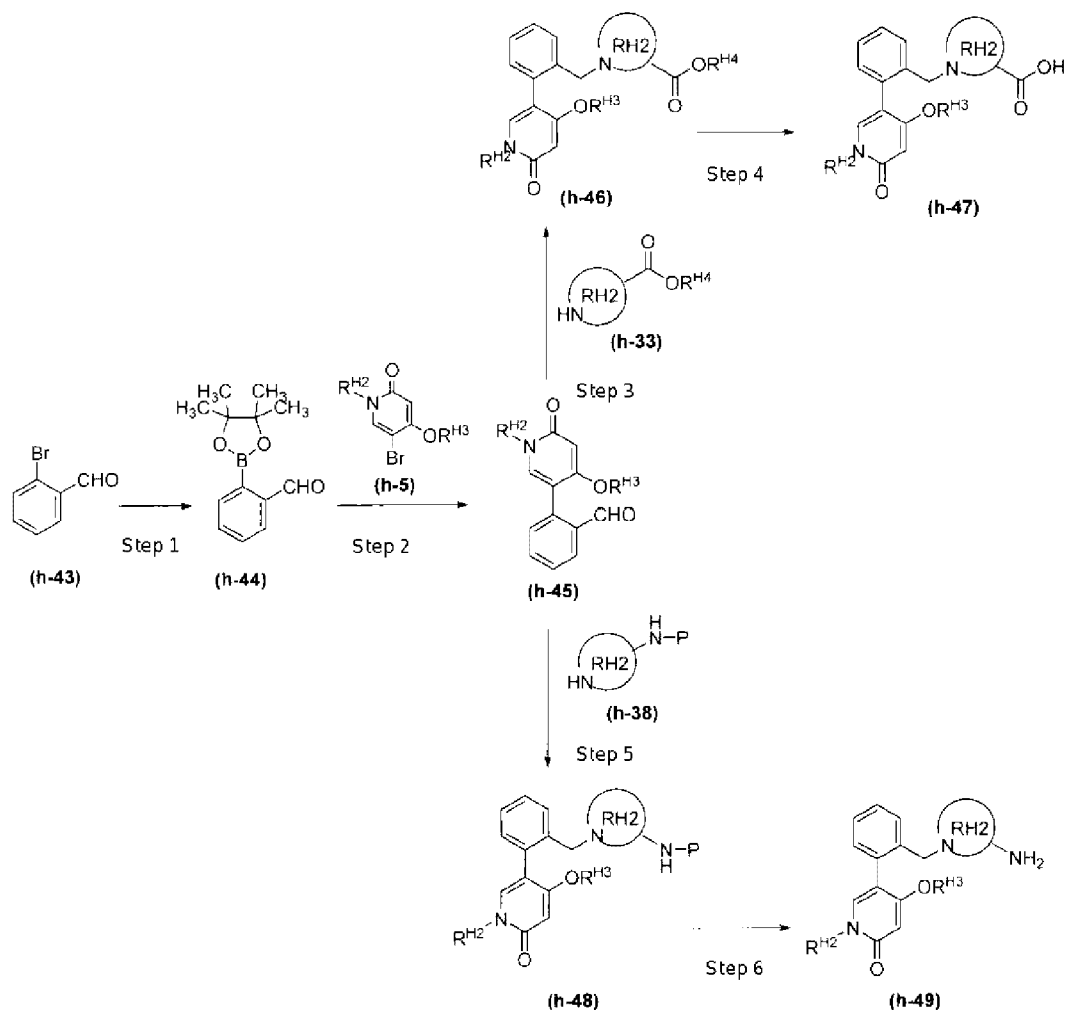
15 Compound (h-42) can be manufactured by using compound (h-41) in the same manner as in step 4 of manufacturing method 1.

[0378]

[Manufacturing method Y8-4]

20 Among compounds having a chemical structure represented by formula (H), the following compounds in which R^{H1} is a hydrogen atom, ring RH is ring RH2, and Z^H is methylene: (i) compound (h-47) in which carboxy is bonded to the wavy line portion and (ii) compound (h-49) in which amino is bonded to the wavy line portion can be manufactured according to the following steps:

25



wherein R^{H2} and R^{H3} are as defined above, R^{H4} represents lower alkyl, ring $RH2$ represents azetidinediyl, pyrrolidinediyl, piperidinediyl, or homopiperidinediyl, P represents an amine protecting group such as Boc, Cbz, PMB and the like.

[0379]

(Step 1)

Compound (h-44) can be manufactured by using 2-bromobenzaldehyde (h-43) in the same manner as in step 2 of manufacturing method Y8-1.

[0380]

(Step 2)

Compound (h-45) can be manufactured by using compound (h-44) in the same manner as in step 3 of manufacturing method Y8-1.

[0381]

5 (Step 3)

Compound (h-46) can be manufactured by using compound (h-45) and 1 equivalent to 5 equivalents of compound (h-33) in the same manner as in step 3 of manufacturing method Y8-3.

[0382]

10 (Step 4)

Compound (h-47) can be manufactured by using compound (h-46) in the same manner as in step 6 of manufacturing method 1.

[0383]

(Step 5)

15 Compound (h-48) can be manufactured by using compound (h-45) and 1 equivalent to 5 equivalents compound (h-38) in the same manner as in step 3 of manufacturing method Y8-3.

[0384]

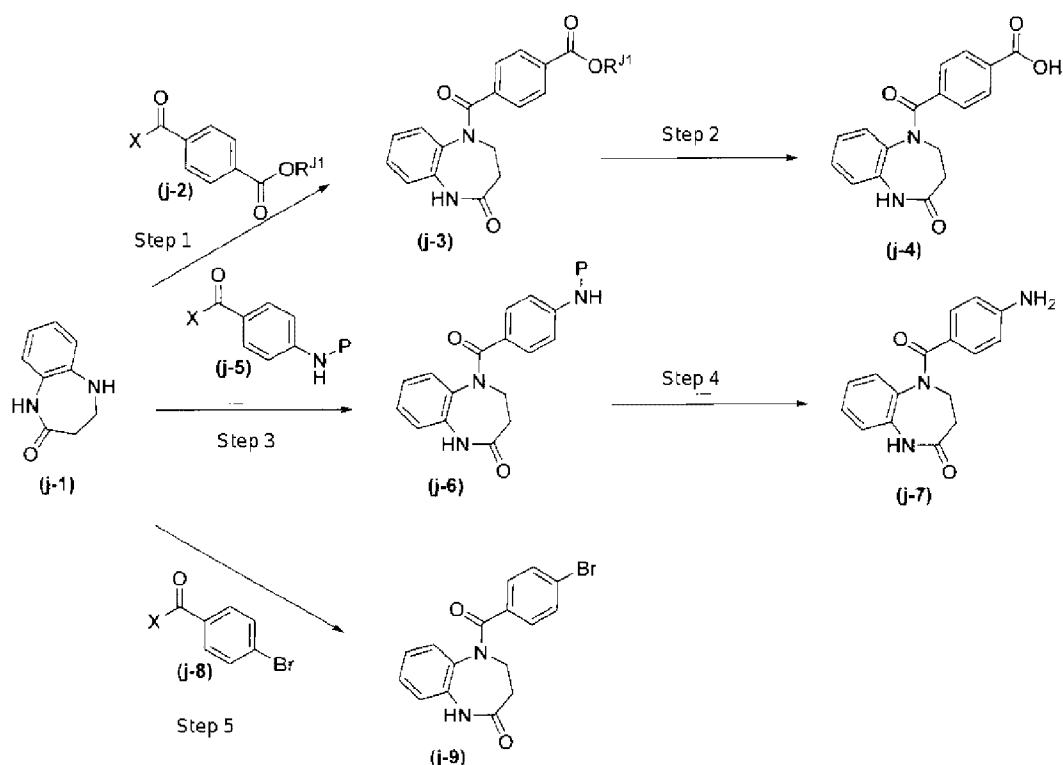
(Step 6)

20 Compound (h-49) can be manufactured by using compound (h-48) in the same manner as in step 4 of manufacturing method 1.

[0385]

[Manufacturing method Y9]

25 Among compounds having a chemical structure represented by formula (J), (i) compound (j-4) in which carboxy is bonded to the wavy line portion, (ii) compound (j-7) in which amino is bonded to the wavy line portion, and (iii) compound (j-9) in which a bromine atom is bonded to the wavy line portion can be manufactured according to the following steps:



wherein X represents a halogen, R^{J1} represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB and the like.

5 [0386]

(Step 1)

Compound (j-3) can be manufactured by reacting 1,3,4,5-tetrahydro-2H-benzo[b][1,4]diazepin-2-one (j-1) and 1 equivalent to 5 equivalents of compound (j-2) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

10 [0387]

Examples of the base include LDA, potassium carbonate, DBU, triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like.

15 [0388]

Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile and the like, and these can be used alone or as a mixture.

[0389]

5 Compound (j-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.99, Maruzen Co., Ltd. (2014) and the like] or methods based thereon.

[0390]

10 (Step 2)

 Compound (j-4) can be manufactured by using compound (j-3) in the same manner as in step 6 of manufacturing method 1.

[0391]

(Step 3)

15 Compound (j-6) can be manufactured in the same manner as in step 1 of manufacturing method Y9 using 1,3,4,5-tetrahydro-2H-benzo[b][1,4]diazepin-2-one (j-1) and 1 equivalent to 5 equivalents of compound (j-5).

[0392]

20 Compound (j-5) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.99, Maruzen Co., Ltd. (2014) and the like] or methods based thereon.

[0393]

25 (Step 4)

 Compound (j-7) can be manufactured by using compound (j-6) in the same manner as in step 4 of manufacturing method 1.

[0394]

(Step 5)

30 Compound (j-9) can be manufactured in the same manner as in step

1 of manufacturing method Y9 using 1,3,4,5-tetrahydro-2H-benzo[b][1,4]diazepin-2-one (j-1) and 1 equivalent to 5 equivalents of compound (j-8).

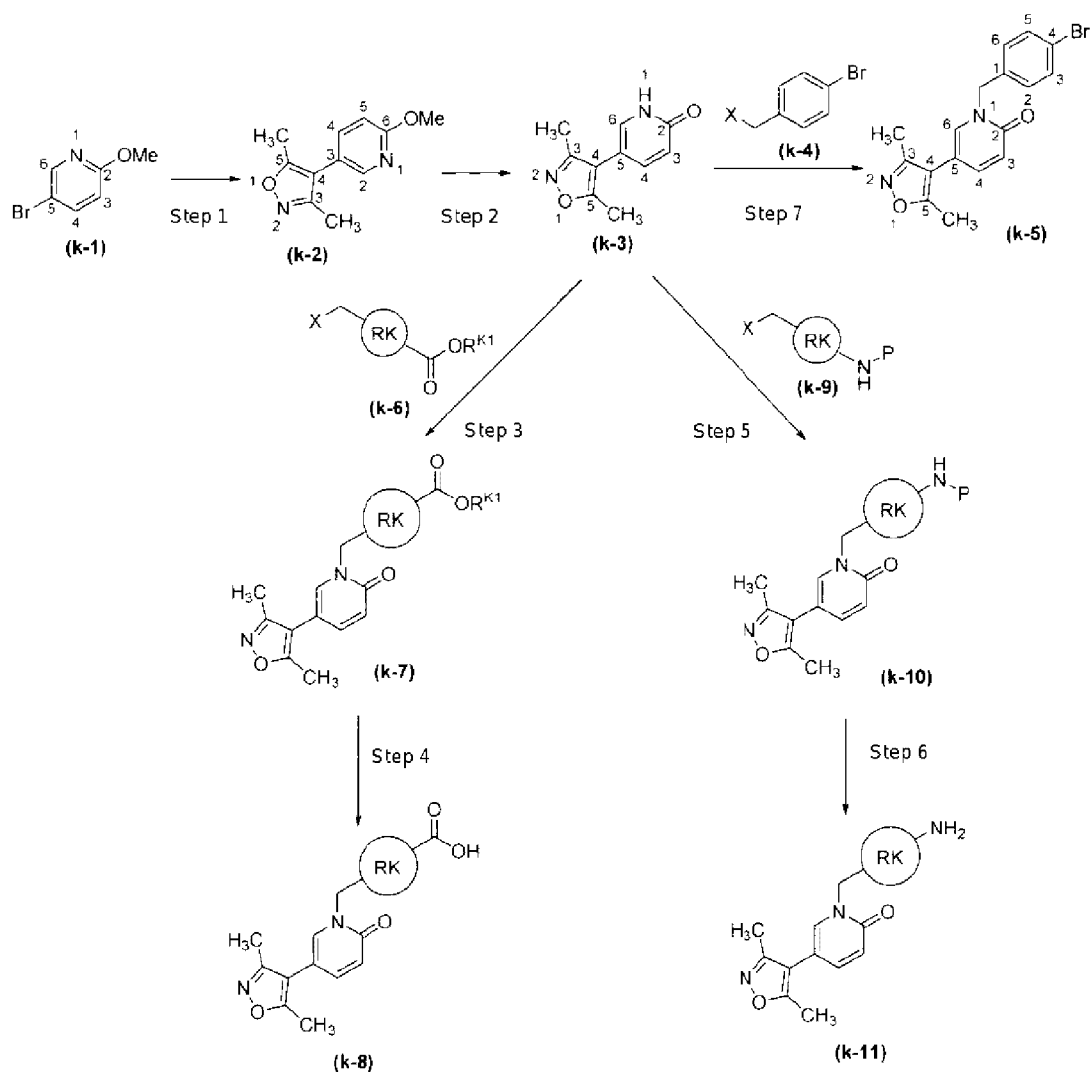
[0395]

5 Compound (j-8) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.99, Maruzen Co., Ltd. (2014) and the like] or methods based thereon.

[0396]

10 [Manufacturing method Y10]

Among compounds having a chemical structure represented by formula (K), (i) compound (k-8) in which carboxy is bonded to the wavy line portion, (ii) compound (k-11) in which amino is bonded to the wavy line portion, as well as among compounds having a chemical structure
15 represented by formula (K), compound (k-5) in which ring RK is benzenediyl and a bromine atom is bonded to the wavy line portion can be manufactured according to the following steps:



wherein ring RK is as defined above, X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, PMB and the like.

5 [0397]

(Step 1)

4-(6-Methoxypyridin-3-yl)-3,5-dimethylisoxazole (k-2) can be manufactured in the same manner as in step 3 of manufacturing method 3 by using 5-bromo-2-methoxypyridine (k-1) and 1 equivalent to 5
10 equivalents of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)isoxazole.

[0398]

(Step 2)

5 5-(3,5-Dimethylisoxazol-4-yl)pyridin-2(1H)-one (k-3) can be
manufactured by reacting 4-(6-methoxypyridin-3-yl)-3,5-
dimethylisoxazole (k-2) in the presence of 1 equivalent to a large excess of
acid in a solvent at a temperature between -20°C and the boiling point of
the solvent used for 5 minutes to 120 hours.

[0399]

10 Examples of the acid include lithium chloride/sulfuric acid,
hydrochloric acid, hydrobromic acid and the like.

[0400]

Examples of the solvent include DMF, DMA, NMP, DMSO, THF, water
and the like, and these can be used alone or as a mixture.

15 [0401]

(Step 3)

Compound (k-7) can be manufactured in the same manner as in step
1 of manufacturing method Y7 using 5-(3,5-dimethylisoxazole-4-
yl)pyridine-2(1H)-one (k-3) and 1 equivalent to 5 equivalents of compound
20 (k-6).

Compound (k-6) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

25 [0402]

(Step 4)

Compound (k-8) can be manufactured by using compound (k-7) in
the same manner as in step 6 of manufacturing method 1.

[0403]

30 (Step 5)

Compound (k-10) can be manufactured in the same manner as in step 1 of manufacturing method Y7 using compound (k-3) and 1 equivalent to 5 equivalents of compound (k-9).

Compound (k-9) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0404]

(Step 6)

Compound (k-11) can be manufactured by using compound (k-10) in the same manner as in step 4 of manufacturing method 1.

[0405]

(Step 7)

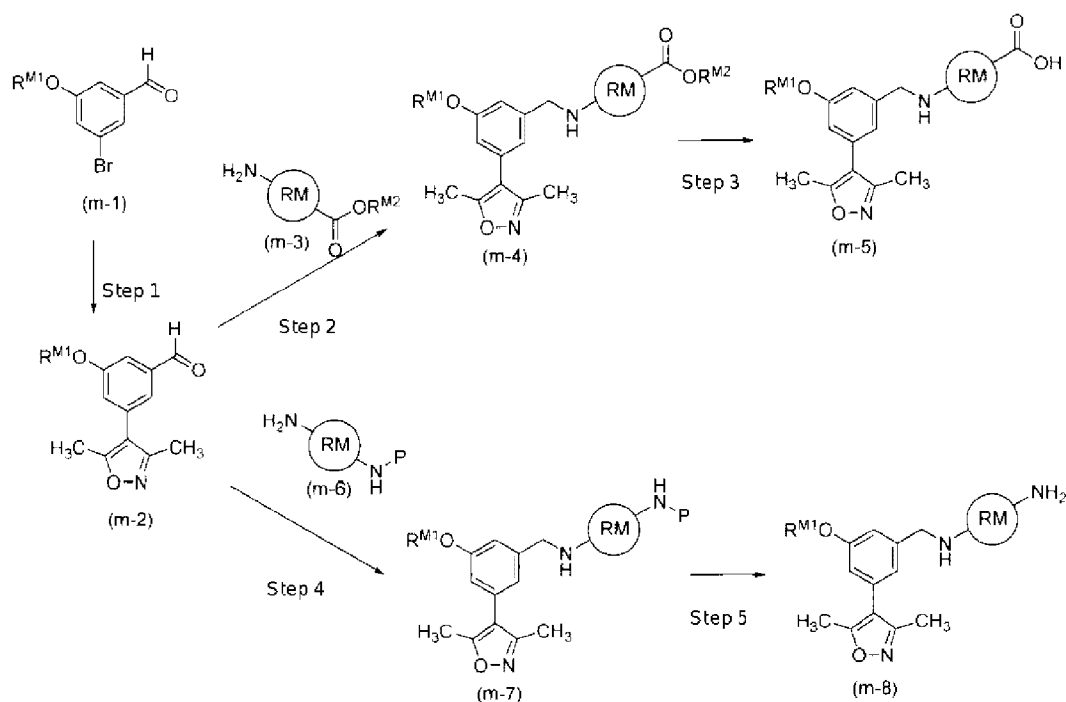
1-(4-Bromobenzyl)-5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one (k-5) can be manufactured in the same manner as in step 1 of manufacturing method Y7 using 5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one (k-3) and 1 equivalent to 5 equivalents of compound (k-4).

Compound (k-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0406]

[Manufacturing method Y11]

Among compounds having a chemical structure represented by formula (M), (i) compound (m-5) in which carboxy is bonded to the wavy line portion, and (ii) compound (m-8) in which amino is bonded to the wavy line portion can be manufactured according to the following steps:



wherein R^{M1} and ring RM are as defined above, and P represents an amine protecting group such as Boc, Cbz, PMB and the like.

5 [0407]

(Step 1)

Compound (m-2) can be manufactured in the same manner as in step 3 of manufacturing method 3 using compound (m-1) and 1 equivalent to 5 equivalents of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole.

[0408]

(Step 2)

Compound (m-4) can be manufactured in the same manner as in step 1 of manufacturing method 1-3 by using compound (m-2) and 1 equivalent to 5 equivalents of compound (m-3).

Compound (m-3) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental

Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0409]

(Step 3)

- 5 Compound (m-5) can be manufactured by using compound (m-4) in
the same manner as in step 6 of manufacturing method 1.

[0410]

(Step 4)

- 10 Compound (m-7) can be manufactured in the same manner as in
step 1 of manufacturing method 1-3 using compound (m-2) and 1
equivalent to 5 equivalents of compound (m-6).

- Compound (m-6) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)
15 and the like] or methods based thereon.

[0411]

(Step 5)

- Compound (m-8) can be manufactured by using compound (m-7) in
the same manner as in step 4 of manufacturing method 1.

- 20 [0412]

[Manufacturing method Y12]

- Among compounds having a chemical structure represented by
formula (N), (i) compound (n-4) in which carboxy is bonded to the wavy
line portion, (ii) compound (n-7) in which amino is bonded to the wavy line
25 portion, and (iii) compound (n-8) in which a bromine atom is bonded to the
wavy line portion can be manufactured according to the following steps:

Compound (n-1) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Nature Chemical Biology, 2016, Vol. 12, p.1097-1104 and the like] or methods based thereon.

5 [0417]

Compound (n-2) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

10 [0418]

(Step 2)

Compound (n-4) can be manufactured by using compound (n-3) in the same manner as in step 6 of manufacturing method 1.

[0419]

15 (Step 3)

Compound (n-6) can be manufactured in the same manner as in step 1 of manufacturing method Y12 using compound (n-1) and 1 equivalent to 5 equivalents of compound (n-5).

20 Compound (n-5) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0420]

(Step 4)

25 Compound (n-7) can be manufactured by using compound (n-6) in the same manner as in step 4 of manufacturing method 1.

[0421]

(Step 5)

30 Compound (n-8) can be manufactured in the same manner as in step 1 of manufacturing method Y12 using compound (n-1) and 1 equivalent to

5 equivalents of 4-(4-bromophenyl)piperidine.

[0422]

Next, there will be described a manufacturing method of compound (I) by using compounds (a-10), (a-12), (a-14), (a-18), (a-21), (a-23), (a-26), (a-29), (a-32), (a-35), (a-38), (a-41), (b-9), (b-10), (b-11), (b-16), (b-20), (b-24), (c-7), (c-11), (c-14), (d-6), (d-9), (d-11), (e-1), (f-1), (f-5), (g-8), (g-9), (g-7), (h-7), (h-12), (h-21), (h-29), (h-37), (h-42), (h-47), (h-49), (j-4), (j-7), (j-9), (k-8), (k-11), (k-5), (m-5), (m-8), (n-4), (n-7) and/or (n-8), which are obtained by the above-mentioned manufacturing method 1, manufacturing method 1-2, manufacturing method 1-3, Manufacturing method 1-4, manufacturing method 2, manufacturing method T2, manufacturing method 3, Manufacturing method Y4, manufacturing method 4, manufacturing method Y5, manufacturing method Y6, manufacturing method Y7, manufacturing method Y8-1, manufacturing method Y8-2, manufacturing method Y8-3, manufacturing method Y8-4, manufacturing method Y9, manufacturing method Y10, manufacturing method Y11, or manufacturing method Y12.

[0423]

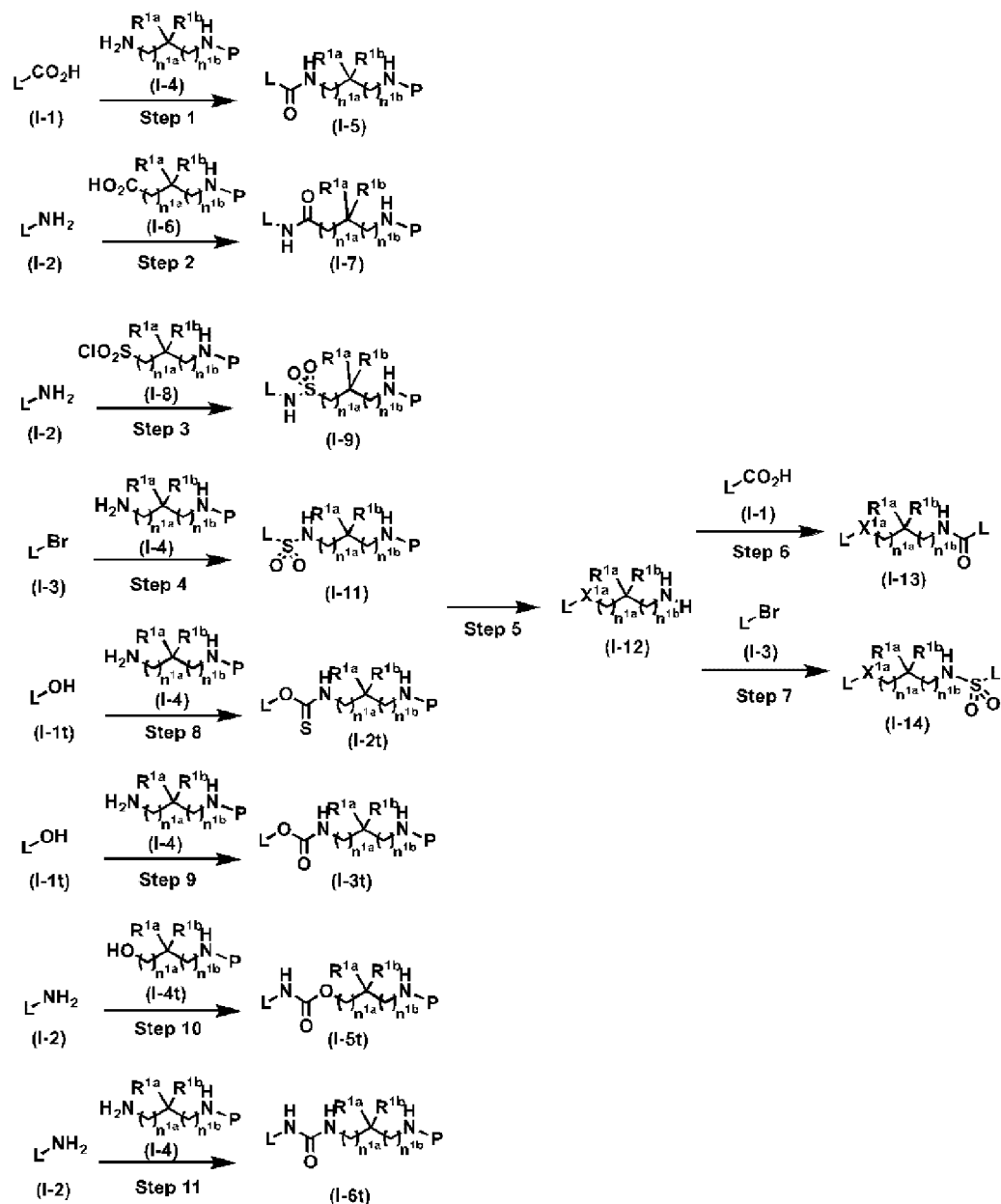
Compounds (a-10), (a-18), (a-26), (a-35), (b-10), (b-20), (c-7), (c-11), (d-6), (f-5), (g-8), (h-7), (h-21), (h-37), (h-47), (j-4), (k-8), (m-5) and (n-4) shall be collectively represented as L-CO₂H (I-1). Similarly, compounds (a-14), (a-21), (a-29), (a-38), (b-11), (b-24), (c-14), (d-9), (g-9), (h-12), (h-29), (h-42), (h-49), (j-7), (k-11), (m-8) and (n-7) shall be represented as L-NH₂ (I-2), and compounds in which X represents bromo among compounds (a-12) and (a-23), and compounds (b-9), (b-16), (d-11), (g-7), (j-9), (k-5) and (n-8) shall be represented as L-Br (I-3).

[0424]

[Manufacturing method 5]

Among compound (I) in which S is formula (S1), (i) compound (I-13) in which X^{1b} is -NH-C(=O)- and (ii) compound (I-14) in which X^{1b} is -

NH-SO₂- can be manufactured respectively according to the following steps:



5 wherein R^{1a}, R^{1b}, n^{1a}, n^{1b}, and X^{1a} are as defined above, L represents L¹ or L², and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0425]

(Step 1)

Compound (I-5) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-4) in the same manner as in step 2 of manufacturing method 2.

[0426]

5 Compound (I-4) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0427]

10 (Step 2)

Compound (I-7) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-6) in the same manner as in step 2 of manufacturing method 2.

[0428]

15 Compound (I-6) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0429]

20 (Step 3)

The compound (I-9) can be manufactured by reacting compound (I-2) and 1 equivalent to 5 equivalents of compound (I-8) in the presence of 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

25 [0430]

Examples of the base include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

[0431]

30 Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used

alone or as a mixture.

[0432]

Compound (I-8) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0433]

(Step 4)

Compound (I-11) can be manufactured by (i) reacting compound (I-3) in the presence of 1 equivalent to 5 equivalents of 4-methoxyphenylmethanethiol, 0.001 equivalent to 3 equivalents of palladium catalyst, 0.001 equivalent to 3 equivalents of phosphorus ligand, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours, and then, (ii) reacting the obtained compound in the presence of 1 equivalent to 5 equivalents of trichloroisocyanuric acid and 1 equivalent to a large excess of compound (I-4) in a solvent at a temperature between -20°C and room temperature for 5 minutes to 120 hours.

[0434]

Examples of the palladium catalyst used in (i) include $\text{Pd}_2(\text{dba})_3$ and the like.

[0435]

Examples of the phosphorus ligand used in (i) include xantphos and the like.

[0436]

Examples of the base used in (i) include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, potassium tert-butoxide, sodium carbonate, potassium carbonate, and the like.

[0437]

Examples of the solvent used in (i) include DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, and the like, and these can be used alone or

as a mixture.

[0438]

Examples of the solvent used in (ii) include acetonitrile, water, and the like, and these can be used alone or as a mixture.

5 [0439]

(Step 5)

Compound (I-12) can be manufactured by using compound (I-5), (I-7), (I-9), (I-11), (I-2t), (I-3t), (I-5t), or (I-6t) in the same manner as in step 4 of manufacturing method 1.

10 [0440]

(Step 6)

Compound (I-13) can be manufactured by using compound (I-12) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

15 [0441]

(Step 7)

Compound (I-14) can be manufactured by using compound (I-12) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

20 [0442]

(Step 8)

Compound (I-2t) can be manufactured by reacting compound (I-1t), 1 equivalent to 10 equivalents of compound (I-4), and 1 equivalent to 10 equivalents of thiocarbonyl reagent in the presence of 1 equivalent to 10
25 equivalents of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0443]

Examples of the thiocarbonyl reagent include thiophosgene, 1,1-thiocarbonyldiimidazole, and the like.

30 [0444]

Examples of the base include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

[0445]

Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DMF, NMP, pyridine, and the like, and these are used alone or as a mixture.

[0446]

As for compound (I-1t), compound (Iy-58) obtained in step 1 of manufacturing method YS12-1 and compound (f-1) obtained in step 1 of manufacturing method Y6 are collectively represented as compound (I-1t).

[0447]

(Step 9)

Compound (I-3t) can be manufactured by reacting compound (I-1t), 1 equivalent to 10 equivalents of compound (I-4), and 1 equivalent to 10 equivalents of carbonyl reagent in the presence of 1 equivalent to 10 equivalents of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0448]

Examples of the carbonyl reagent include phosgene, 1,1-carbonyldiimidazole (CDI), and the like.

[0449]

Examples of the base include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

[0450]

Examples of the solvent include dichloromethane, chloroform, 1,2-dichloroethane, toluene, ethyl acetate, acetonitrile, diethyl ether, THF, DMF, NMP, pyridine, and the like, and these are used alone or as a mixture.

[0451]

(Step 10)

Compound (I-5t) can be manufactured by using compound (I-2) and

1 equivalent to 10 equivalents of compound (I-4t) in the same manner as in step 9.

[0452]

Compound (I-4t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0453]

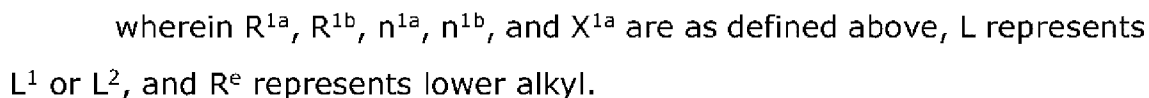
(Step 11)

Compound (I-6t) can be manufactured by using compound (I-2) and 1 equivalent to 10 equivalents of compound (I-4) in the same manner as in step 9.

[0454]

[Manufacturing method 6]

Among compound (I) in which S is formula (S1), compound (I-24) in which X^{1b} is $-C(=O)-NH-$ can be manufactured according to the following steps:



Compound (I-19) can be manufactured by using compound (I-1) and

1 equivalent to 5 equivalents of compound (I-15) in the same manner as in step 2 of manufacturing method 2.

[0456]

Compound (I-15) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0457]

(Step 2)

Compound (I-20) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-16) in the same manner as in step 2 of manufacturing method 2.

[0458]

Compound (I-16) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0459]

(Step 3)

Compound (I-21) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-17) in the same manner as in step 3 of manufacturing method 5.

[0460]

Compound (I-17) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0461]

(Step 4)

Compound (I-22) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (I-15) in the same manner as in

step 4 of manufacturing method 5.

[0462]

(Step 5)

Compound (I-23) can be manufactured by using compound (I-19),
5 (I-20), (I-21), (I-22), (I-9t), (I-10t), (I-12t), or (I-13t) in the same manner
as in step 6 of manufacturing method 1.

[0463]

(Step 6)

Compound (I-24) can be manufactured by using compound (I-23)
10 and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
as in step 2 of manufacturing method 2.

(Step 7)

Compound (I-9t) can be manufactured by using compound (I-1t)
and 1 equivalent to 10 equivalents of compound (I-15) in the same manner
15 as in step 8 of manufacturing method 5.

[0464]

(Step 8)

Compound (I-10t) can be manufactured by using compound (I-1t)
and 1 equivalent to 10 equivalents of compound (I-15) in the same manner
20 as in step 9 of manufacturing method 5.

[0465]

(Step 9)

Compound (I-12t) can be manufactured by using compound (I-2)
and 1 equivalent to 10 equivalents of compound (I-11t) in the same manner
25 as in step 9 of manufacturing method 5.

[0466]

Compound (I-11t) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 14, p.1, Maruzen Co., Ltd. (2004)
30 and the like] or methods based thereon.

[0467]

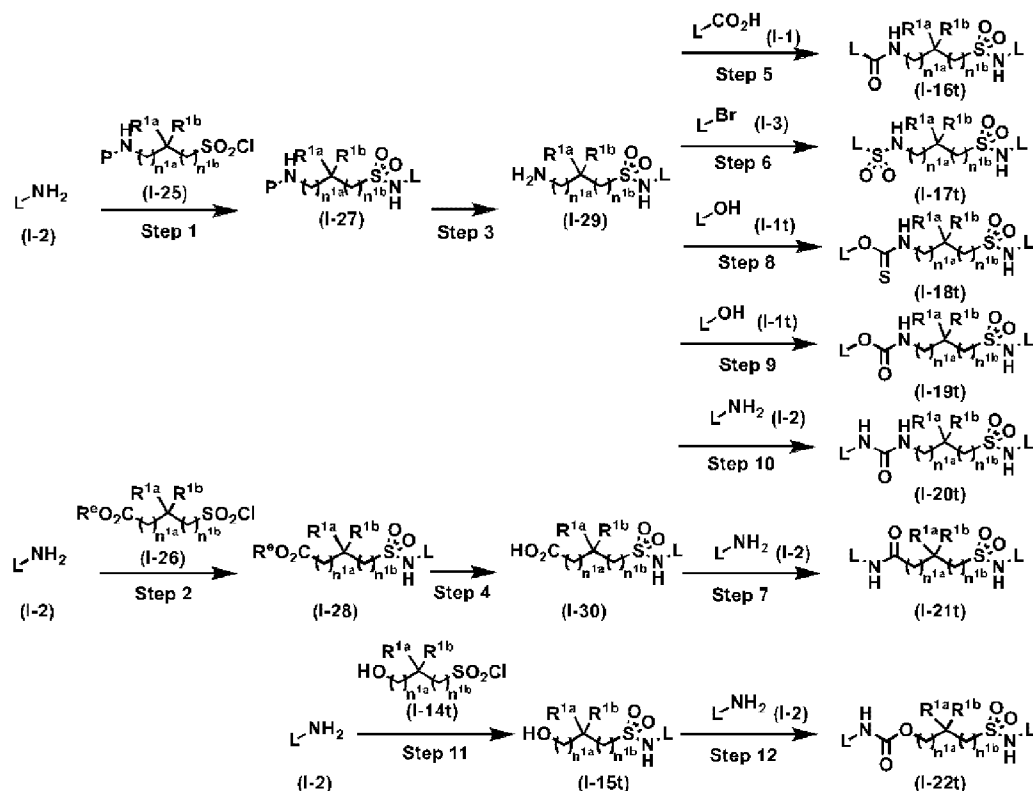
(Step 10)

Compound (I-13t) can be manufactured by using compound (I-2) and 1 equivalent to 10 equivalents of compound (I-15) in the same manner as in step 9 of manufacturing method 5.

[0468]

[Manufacturing method 7]

Among compound (I) in which S is formula (S1), the following compounds in which X^{1b} is $-\text{SO}_2-\text{NH}-$: (i) compound (I-16t) in which X^{1a} is $-\text{C}(=\text{O})-\text{NH}-$, (ii) compound (I-17t) in which X^{1a} is $-\text{SO}_2-\text{NH}-$, (iii) compound (I-18t) in which X^{1a} is $-\text{O}-\text{C}(=\text{S})-\text{NH}-$, (iv) compound (I-19t) in which X^{1a} is $-\text{O}-\text{C}(=\text{O})-\text{NH}-$, (v) compound (I-20t) in which X^{1a} is $-\text{NH}-\text{C}(=\text{O})-\text{NH}-$, (vi) compound (I-21t) in which X^{1a} is $-\text{NH}-\text{C}(=\text{O})-$, and (vii) compound (I-22t) in which X^{1a} is $-\text{NH}-\text{C}(=\text{O})-\text{O}-$ can be manufactured respectively according to the following steps:



wherein R^{1a} , R^{1b} , n^{1a} , and n^{1b} are as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

5 [0469]

(Step 1)

Compound (I-27) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-25) in the same manner as in step 3 of manufacturing method 5.

10 [0470]

Compound (I-25) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0471]

15 (Step 2)

Compound (I-28) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-26) in the same manner as in step 3 of manufacturing method 5.

[0472]

20 Compound (I-26) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0473]

(Step 3)

25 Compound (I-29) can be manufactured by using compound (I-27) in the same manner as in step 4 of manufacturing method 1.

[0474]

(Step 4)

30 Compound (I-30) can be manufactured by using compound (I-28) in the same manner as in step 6 of manufacturing method 1.

[0475]

(Step 5)

Compound (I-16t) can be manufactured by using compound (I-29) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner
5 as in step 2 of manufacturing method 2.

[0476]

(Step 6)

Compound (I-17t) can be manufactured by using compound (I-29) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner
10 as in step 4 of manufacturing method 5.

[0477]

(Step 7)

Compound (I-21t) can be manufactured by using compound (I-30) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
15 as in step 2 of manufacturing method 2.

[0478]

(Step 8)

Compound (I-18t) can be manufactured by using compound (I-29) and 1 equivalent to 5 equivalents of compound (I-1t) in the same manner
20 as in step 8 of manufacturing method 5.

[0479]

(Step 9)

Compound (I-19t) can be manufactured by using compound (I-29) and 1 equivalent to 5 equivalents of compound (I-1t) in the same manner
25 as in step 9 of manufacturing method 5.

[0480]

(Step 10)

Compound (I-20t) can be manufactured by using compound (I-29) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
30 as in step 9 of manufacturing method 5.

[0481]

(Step 11)

Compound (I-15t) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-14t) in the same manner
5 as in step 3 of manufacturing method 5.

[0482]

Compound (I-14t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

10 (Step 12)

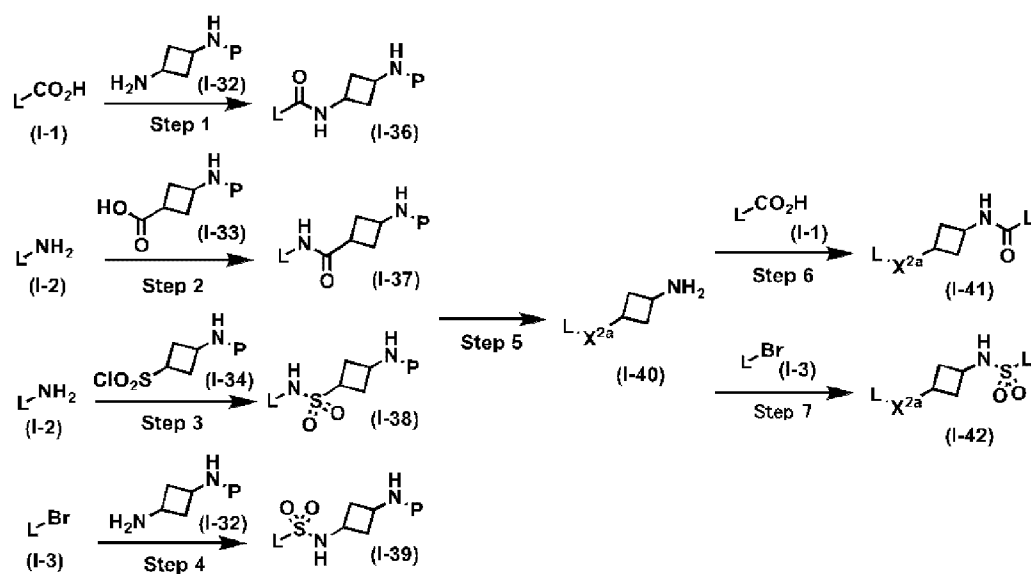
[0483]

Compound (I-22t) can be manufactured by using compound (I-15t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
as in step 9 of manufacturing method 5.

15 [0484]

[Manufacturing method 8]

Among compound (I) in which S is formula (S2), the following compounds in which Z² is CH: (i) compound (I-41) in which X^{2b} is -NH-C(=O)- and (ii) compound (I-42) in which X^{2b} is -NH-SO₂- can be
20 manufactured respectively according to the following steps:



wherein X^{2a} is as defined above, L represents L^1 or L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

5 [0485]

(Step 1)

Compound (I-36) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-32) in the same manner as in step 2 of manufacturing method 2.

10 [0486]

Compound (I-32) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

15 [0487]

(Step 2)

Compound (I-37) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-33) in the same manner as in step 2 of manufacturing method 2.

20 [0488]

Compound (I-33) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0489]

5 (Step 3)

Compound (I-38) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-34) in the same manner as in step 3 of manufacturing method 5.

[0490]

10 Compound (I-34) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0491]

(Step 4)

15 Compound (I-39) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (I-32) in the same manner as in step 4 of manufacturing method 5.

[0492]

(Step 5)

20 Compound (I-40) can be manufactured by using compound (I-36), (I-37), (I-38), or (I-39) in the same manner as in step 4 of manufacturing method 1.

[0493]

(Step 6)

25 Compound (I-41) can be manufactured by using compound (I-40) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0494]

(Step 7)

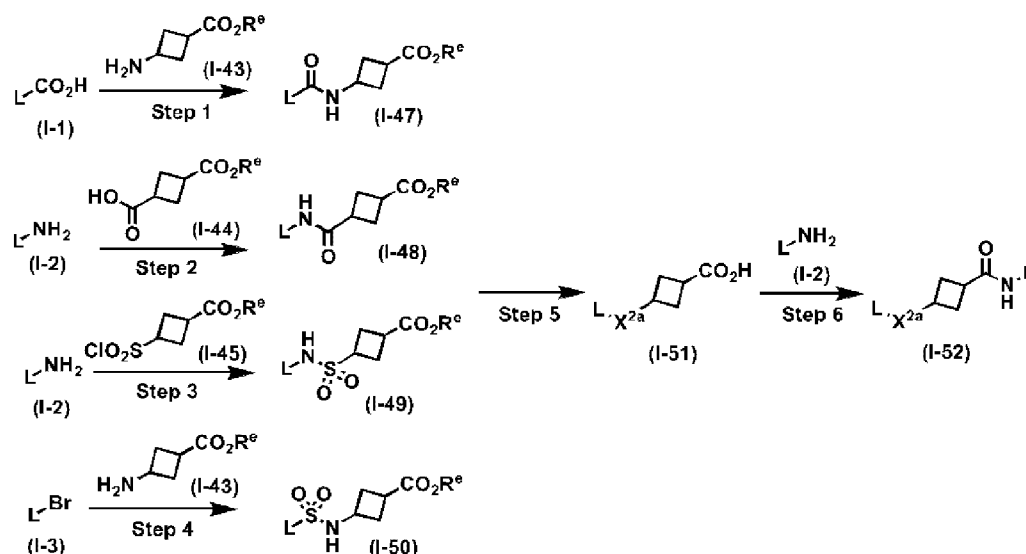
30 Compound (I-42) can be manufactured by using compound (I-40)

and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0495]

[Manufacturing method 9]

- 5 Among compound (I) in which S is formula (S2), compound (I-52) in which Z^2 is CH and X^{2b} is $-C(=O)-NH-$ can be manufactured according to the following steps:



10

wherein X^{2a} is as defined above, L represents L^1 or L^2 , and R^e represents lower alkyl.

[0496]

(Step 1)

- 15 Compound (I-47) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-43) in the same manner as in step 2 of manufacturing method 2.

[0497]

- 20 Compound (I-43) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)]

and the like] or methods based thereon.

[0498]

(Step 2)

Compound (I-48) can be manufactured by using compound (I-2) and
5 1 equivalent to 5 equivalents of compound (I-44) in the same manner as in
step 2 of manufacturing method 2.

[0499]

Compound (I-44) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0500]

(Step 3)

Compound (I-49) can be manufactured by using compound (I-2) and
15 1 equivalent to 5 equivalents of compound (I-45) in the same manner as in
step 3 of manufacturing method 5.

[0501]

Compound (I-45) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Organic Syntheses,
20 Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0502]

(Step 4)

Compound (I-50) can be manufactured by using compound (I-3) and
1 equivalent to 5 equivalents of compound (I-43) in the same manner as in
25 step 4 of manufacturing method 5.

[0503]

(Step 5)

Compound (I-51) can be manufactured by using compound (I-47),
(I-48), (I-49), or (I-50) in the same manner as in step 6 of manufacturing
30 method 1.

[0504]

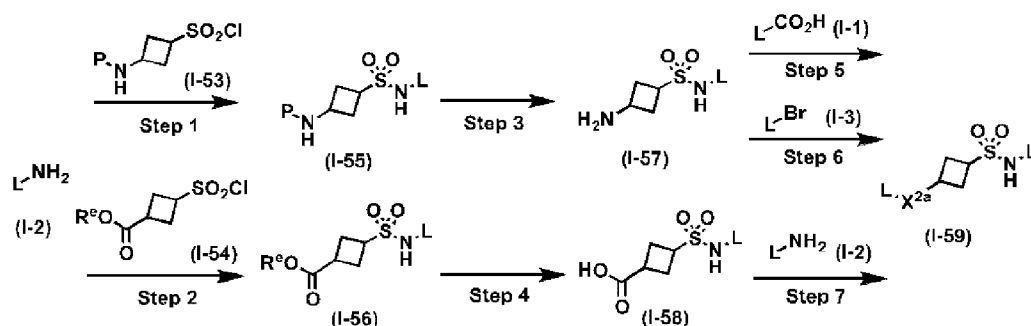
(Step 6)

Compound (I-52) can be manufactured by using compound (I-51) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0505]

[Manufacturing method 10]

Among compound (I) in which S is formula (S2), compound (I-59) in which Z² is CH and X^{2b} is -SO₂-NH- can be manufactured according to the following steps:



wherein X^{2a} is as defined above, L represents L¹ or L², R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0506]

(Step 1)

Compound (I-55) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-53) in the same manner as in step 3 of manufacturing method 5.

[0507]

Compound (I-53) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0508]

(Step 2)

Compound (I-56) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-54) in the same manner as in
5 step 3 of manufacturing method 5.

[0509]

Compound (I-54) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol.4, p.571 (1963) and the like] or methods based thereon.

10 [0510]

(Step 3)

Compound (I-57) can be manufactured by using compound (I-55) in the same manner as in step 4 of manufacturing method 1.

[0511]

15 (Step 4)

Compound (I-58) can be manufactured by using compound (I-56) in the same manner as in step 6 of manufacturing method 1.

[0512]

(Step 5)

20 Among compound (I-59), a compound in which X^{2a} is $-C(=O)-NH-$ can be manufactured by using compound (I-57) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0513]

25 (Step 6)

Among compound (I-59), a compound in which X^{2a} is $-SO_2-NH-$ can be manufactured by using compound (I-57) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

30 [0514]

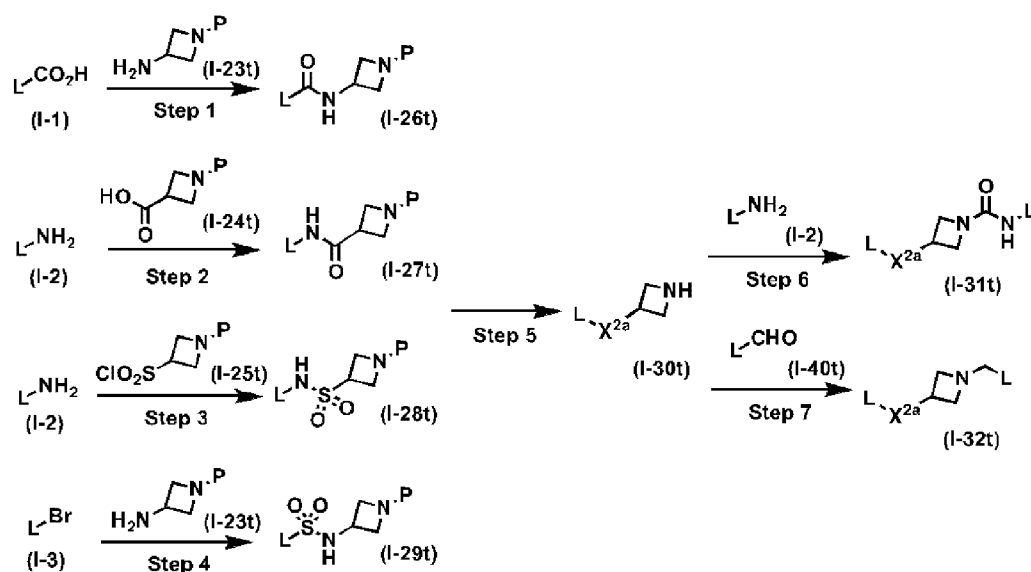
(Step 7)

Among compound (I-59), a compound in which X^{2a} is $-NH-C(=O)-$ can be manufactured by using compound (I-58) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0515]

[manufacturing method YS2]

In compound (I) in which S is formula (S2), the following compounds in which Z^2 is N: (i) compound (I-31t) in which X^{2b} is $-C(=O)-NH-$ and (ii) compound (I-32t) in which X^{2b} is $-CH_2-$ can be manufactured according to the following steps:



wherein X^{2a} is as defined above, L represents L^1 or L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0516]

(Step 1)

Compound (I-26t) can be manufactured by using compound (I-1) and 1 equivalent to 10 equivalents of compound (I-23t) in the same manner as in step 2 of manufacturing method 2.

[0517]

Compound (I-23t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)

5 and the like] or methods based thereon.

[0518]

(Step 2)

Compound (I-27t) can be manufactured by using compound (I-2) and 1 equivalent to 10 equivalents of compound (I-24t) in the same manner
10 as in step 2 of manufacturing method 2.

[0519]

Compound (I-24t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004)

15 and the like] or methods based thereon.

[0520]

(Step 3)

Compound (I-28t) can be manufactured by using compound (I-2) and 1 equivalent to 10 equivalents of compound (I-25t) in the same manner
20 as in step 3 of manufacturing method 5.

[0521]

Compound (I-25t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

25 [0522]

(Step 4)

Compound (I-29t) can be manufactured by using compound (I-3) and 1 equivalent to 10 equivalents of compound (I-23t) in the same manner
as in step 4 of manufacturing method 5.

30 [0523]

(Step 5)

Compound (I-30t) can be manufactured using compound (I-26t), compound (I-27t), compound (I-28t), or compound (I-29t) in the same manner as in step 4 of manufacturing method 1.

5 [0524]

(Step 6)

Compound (I-31t) can be manufactured by using compound (I-30t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

10 (Step 7)

[0525]

Compound (I-32t) can be manufactured by using compound (I-30t) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

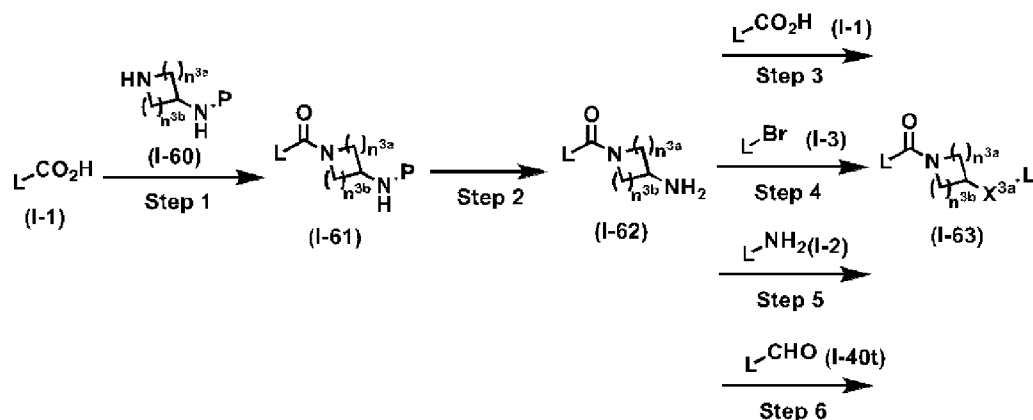
15 [0526]

Compound (I-40t) can be obtained according to step 10 of manufacturing method 17.

[0527]

[Manufacturing method 11]

20 Among compound (I) in which S is formula (S3), compound (I-63) in which Z^3 is CH and X^3 is X^{3a} can be manufactured according to the following steps:



wherein n^{3a} and n^{3b} are as defined above, L represents L^1 or L^2 , X^{3a} represents $-NH-C(=O)-$, $-NH-SO_2-$, $-NH-C(=O)-NH-$, or $-NHCH_2-$, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.
[0528]

(Step 1)

Compound (I-61) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-60) in the same manner as in step 2 of manufacturing method 2.
[0529]

Compound (I-60) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.
[0530]

(Step 2)

[0530]

Compound (I-62) can be manufactured by using compound (I-61) in the same manner as in step 4 of manufacturing method 1.
[0531]

(Step 3)

[0531]

Among compound (I-63), a compound in which X^{3a} is $-NH-C(=O)-$ can be manufactured by using compound (I-62) and 1 equivalent to 5

equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0532]

(Step 4)

5 Among compound (I-63), a compound in which X^{3a} is $-NH-SO_2-$ can be manufactured by using compound (I-62) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0533]

10 (Step 5)

 Among compound (I-63), a compound in which X^{3a} is $-NH-C(=O)-NH-$ can be manufactured by using compound (I-62) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

15 [0534]

(Step 6)

 Among compound (I-63), a compound in which X^{3a} is $-NHCH_2-$ can be manufactured by using compound (I-62) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

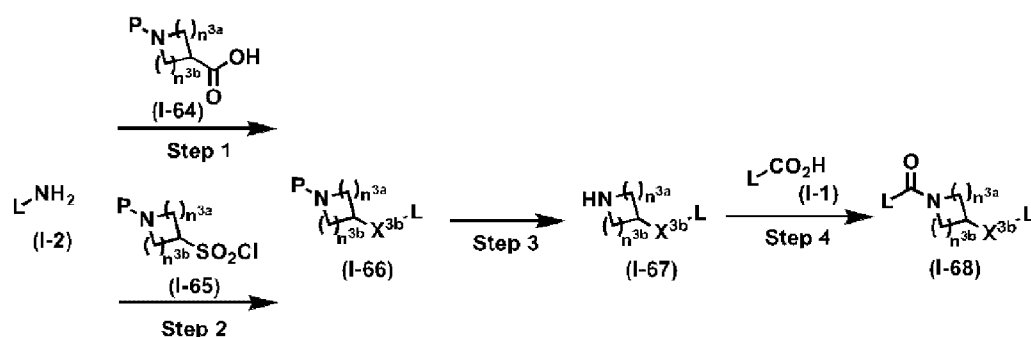
20

[0535]

[Manufacturing method 12]

 Among compound (I) in which S is formula (S3), compound (I-68) in which Z^3 is CH and X^3 is X^{3b} can be manufactured according to the following steps:

25



wherein n^{3a} and n^{3b} are as defined above, L represents L^1 or L^2 , X^{3b} represents $-C(=O)-NH-$ or $-SO_2-NH-$, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0536]

(Step 1)

Among compound (I-66), a compound in which X^{3b} is $-C(=O)-NH-$ can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-64) in the same manner as in step 2 of manufacturing method 2.

[0537]

Compound (I-64) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0538]

(Step 2)

Among compound (I-66), a compound in which X^{3b} is $-SO_2-NH-$ can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-65) in the same manner as in step 3 of manufacturing method 5.

[0539]

Compound (I-65) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses,

Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0540]

(Step 3)

Compound (I-67) can be manufactured by using compound (I-66) in
5 the same manner as in step 4 of manufacturing method 1.

[0541]

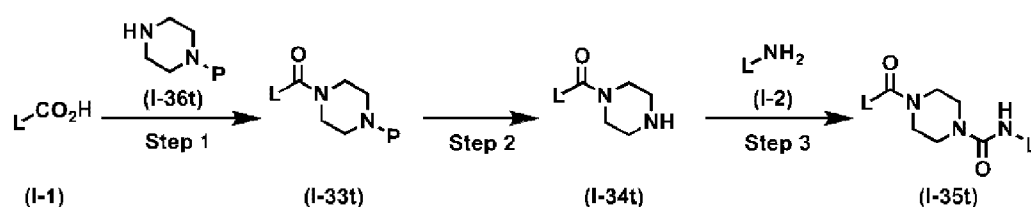
(Step 4)

Compound (I-68) can be manufactured by using compound (I-67)
and 1 equivalent to 5 equivalents of compound (I-1) in the same manner
10 as in step 2 of manufacturing method 2.

[0542]

[Manufacturing method YS3]

Among compound (I) in which S is formula (S3), compound (I-35t)
in which Z^3 is N, X^3 is $-C(=O)-NH-$, and n^{3a} and n^{3b} are 2 can be
15 manufactured according to the following steps:



wherein L represents L^1 or L^2 , and P represents an amine protecting
20 group such as Boc, Cbz, PMB, and the like.

[0543]

(Step 1)

Compound (I-33t) can be manufactured by using compound (I-1)
and 1 equivalent to 10 equivalents of compound (I-36t) in the same manner
25 as in step 2 of manufacturing method 2.

[0544]

Compound (I-36t) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0545]

5 (Step 2)

Compound (I-34t) can be manufactured by using compound (I-33t) in the same manner as in step 4 of manufacturing method 1.

[0546]

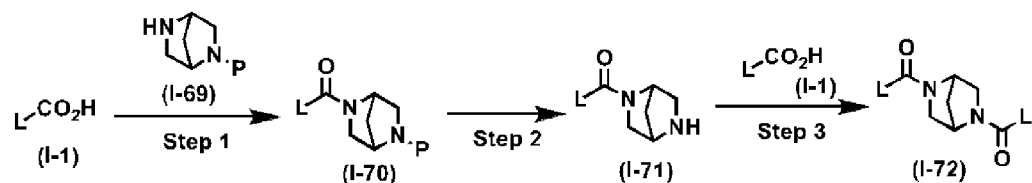
(Step 3)

10 Compound (I-35t) can be manufactured by using compound (I-34t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0547]

[Manufacturing method 13]

15 Compound (I) in which S is formula (S4) can be manufactured according to the following steps:



20 wherein L represents L^1 or L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0548]

(Step 1)

25 Compound (I-70) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-69) in the same manner as in step 2 of manufacturing method 2.

[0549]

Compound (I-69) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

5 [0550]

(Step 2)

Compound (I-71) can be manufactured by using compound (I-70) in the same manner as in step 4 of manufacturing method 1.

[0551]

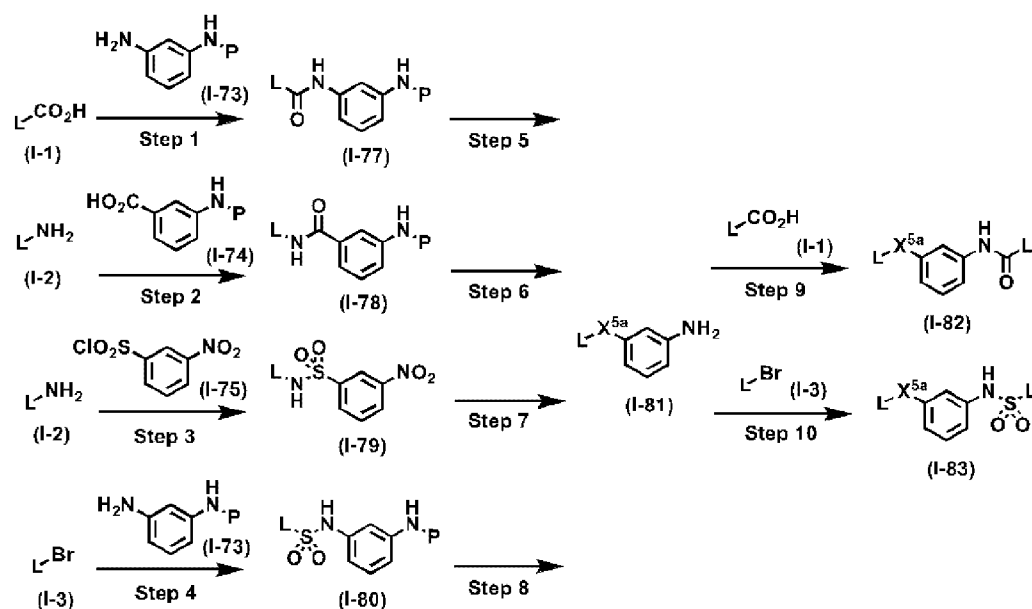
10 (Step 3)

Compound (I-72) can be manufactured by using compound (I-71) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0552]

15 [Manufacturing method 14]

Among compound (I) in which S is formula (S5), (i) compound (I-82) in which X^{5b} is $-NH-C(=O)-$ and (ii) compound (I-83) in which X^{5b} is $-NH-SO_2-$ can be manufactured respectively according to the following steps:



20

wherein X^{5a} is as defined above, L represents L^1 or L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.
[0553]

5 (Step 1)

Compound (I-77) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-73) in the same manner as in step 2 of manufacturing method 2.

[0554]

10 Compound (I-73) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0555]

15 (Step 2)

Compound (I-78) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-74) in the same manner as in step 2 of manufacturing method 2.

[0556]

20 Compound (I-74) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0557]

25 (Step 3)

Compound (I-79) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-75) in the same manner as in step 3 of manufacturing method 5.

[0558]

30 Compound (I-75) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol.4, p.571 (1963) and the like] or methods based thereon.

[0559]

(Step 4)

5 Compound (I-80) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (I-73) in the same manner as in step 4 of manufacturing method 5.

[0560]

(Step 5)

10 Among compound (I-81), a compound in which X^{5a} is -C(=O)-NH- can be manufactured by using compound (I-77) in the same manner as in step 4 of manufacturing method 1.

[0561]

(Step 6)

15 Among compound (I-81), a compound in which X^{5a} is -NH-C(=O)- can be manufactured by using compound (I-78) in the same manner as in step 4 of manufacturing method 1.

[0562]

(Step 7)

20 Among compound (I-81), a compound in which X^{5a} is -NH-SO₂- can be manufactured by using compound (I-79) in the same manner as in step 8 of manufacturing method 1.

[0563]

(Step 8)

25 Among compound (I-81), a compound in which X^{5a} is -SO₂-NH- can be manufactured by using compound (I-80) in the same manner as in step 4 of manufacturing method 1.

[0564]

(Step 9)

30 Compound (I-82) can be manufactured by using compound (I-81)

and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0565]

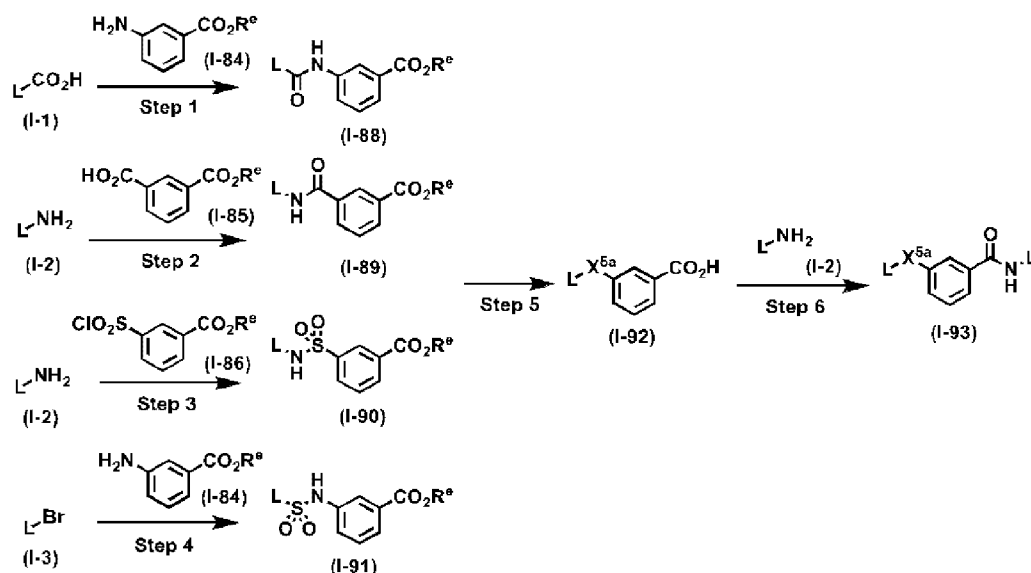
(Step 10)

- 5 Compound (I-83) can be manufactured by using compound (I-81) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0566]

[Manufacturing method 15]

- 10 Among compound (I) in which S is formula (S5), compound (I-93) in which X^{5b} is $-C(=O)-NH-$ can be manufactured according to the following steps:



15

wherein X^{5a} is as defined above, L represents L^1 or L^2 , and R^e represents lower alkyl.

[0567]

(Step 1)

- 20 Compound (I-88) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-84) in the same manner as in

step 2 of manufacturing method 2.

[0568]

Compound (I-84) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
5 Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0569]

(Step 2)

Compound (I-89) can be manufactured by using compound (I-2) and
10 1 equivalent to 5 equivalents of compound (I-85) in the same manner as in step 2 of manufacturing method 2.

[0570]

Compound (I-85) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental
15 Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0571]

(Step 3)

Compound (I-90) can be manufactured by using compound (I-2) and
20 1 equivalent to 5 equivalents of compound (I-86) in the same manner as in step 3 of manufacturing method 5.

[0572]

Compound (I-86) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses,
25 Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0573]

(Step 4)

Compound (I-91) can be manufactured by using compound (I-3) and
30 1 equivalent to 5 equivalents of compound (I-84) in the same manner as in step 4 of manufacturing method 5.

[0574]

(Step 5)

Compound (I-92) can be manufactured by using compound (I-88), (I-89), (I-90), or (I-91) in the same manner as in step 6 of manufacturing method 1.

[0575]

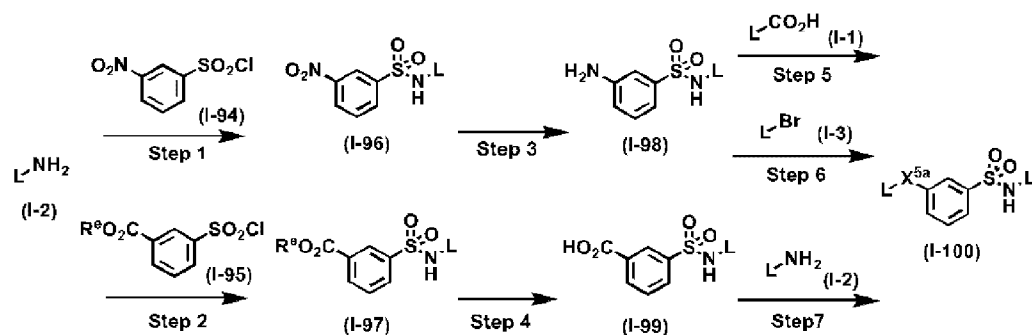
(Step 6)

Compound (I-93) can be manufactured by using compound (I-92) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0576]

[Manufacturing method 16]

Among compound (I) in which S is formula (S5), compound (I-100) in which X^{5b} is $-\text{SO}_2-\text{NH}-$ can be manufactured according to the following steps:



wherein X^{5a} is as defined above, L represents L^1 or L^2 , and R^e represents lower alkyl.

[0577]

(Step 1)

Compound (I-96) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-94) in the same manner as in step 3 of manufacturing method 5.

[0578]

Compound (I-94) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

5 [0579]

(Step 2)

Compound (I-97) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-95) in the same manner as in step 3 of manufacturing method 5.

10 [0580]

Compound (I-95) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0581]

15 (Step 3)

Compound (I-98) can be manufactured by using compound (I-96) in the same manner as in step 8 of manufacturing method 1.

[0582]

(Step 4)

20 Compound (I-99) can be manufactured by using compound (I-97) in the same manner as in step 6 of manufacturing method 1.

[0583]

(Step 5)

25 Among compound (I-100), a compound in which X^{5a} is $-C(=O)-NH-$ can be manufactured by using compound (I-98) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0584]

(Step 6)

30 Among compound (I-100), a compound in which X^{5a} is $-SO_2-NH-$ can

be manufactured by using compound (I-98) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0585]

5 (Step 7)

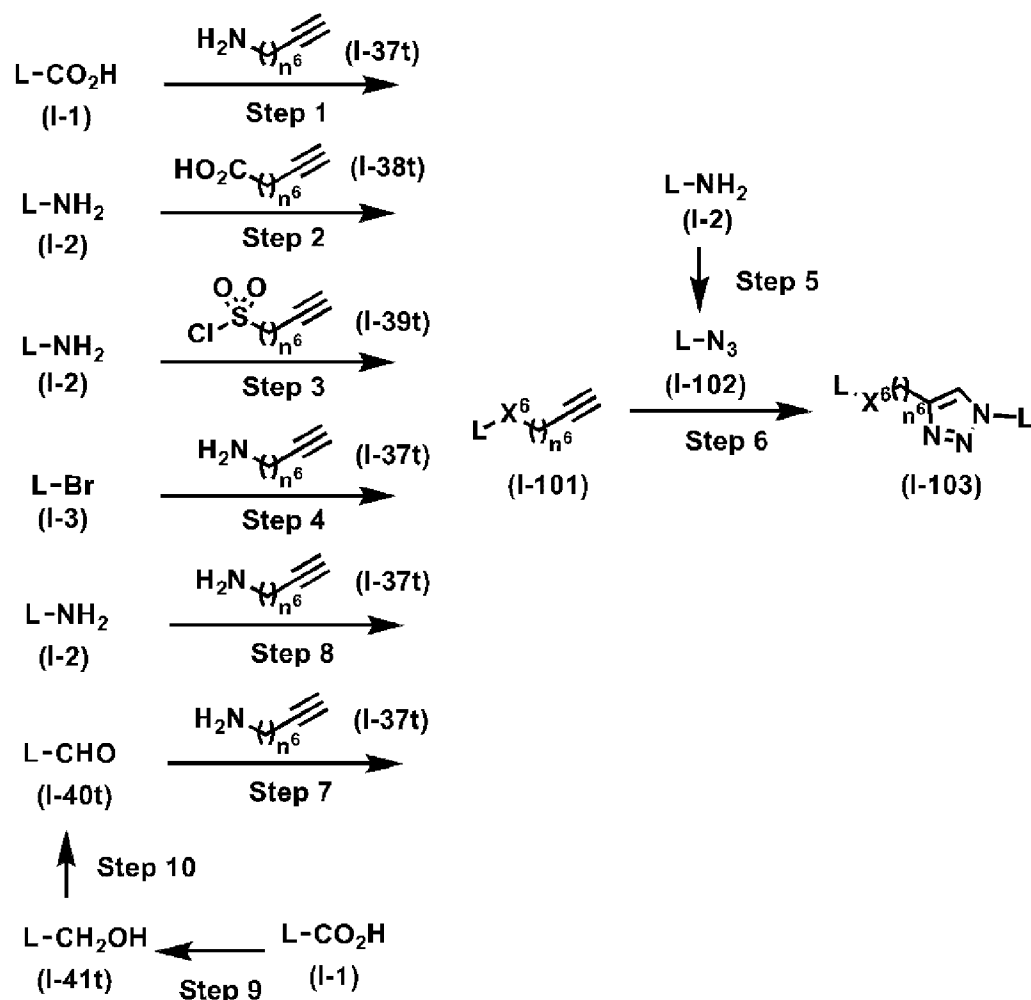
Among compound (I-100), a compound in which X^{5a} is $-NH-C(=O)-$ can be manufactured by using compound (I-99) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

10 [0586]

[Manufacturing method 17]

Among compound (I) in which S is formula (S6), compound (I-103) in which Ar^6 is triazole can be manufactured according to the following steps:

15



wherein X⁶ and n⁶ are as defined above, and L represents L¹ or L².

[0587]

5 (Step 1)

Among Compound (I-101), a compound in which X⁶ is -C(=O)-NH- can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-37t) in the same manner as in step 2 of manufacturing method 2.

10 [0588]

Compound (I-37t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004)]

and the like] or methods based thereon.

[0589]

(Step 2)

Among compound (I-101), a compound in which X⁶ is -NH-C(=O)-
5 can be manufactured by using compound (I-2) and 1 equivalent to 5
equivalents of compound (I-38t) in the same manner as in step 2 of
manufacturing method 2.

[0590]

Compound (I-38t) can be obtained as a commercially available
10 product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0591]

(Step 3)

15 Among compound (I-101), a compound in which X⁶ is -NH-SO₂- can
be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents
of compound (I-39t) in the same manner as in step 3 of manufacturing
method 5.

[0592]

20 Compound (I-39t) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Organic Syntheses,
Coll. Vol. 4, p.571 (1963) and the like] or methods based thereon.

[0593]

(Step 4)

25 Among compound (I-101), a compound in which X⁶ is -SO₂-NH- can
be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents
of compound (I-37t) in the same manner as in step 4 of manufacturing
method 5.

[0594]

30 (Step 5)

Compound (I-102) can be manufactured by reacting compound (I-2) and 1 equivalent to 5 equivalents of an azidation agent in the presence of, according to necessity, 1 equivalent to 5 equivalents of an additive in a solvent at a temperature between room temperature and the boiling point
5 of the solvent used for 5 minutes to 120 hours.

[0595]

Examples of the azidation agent include 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP) and the like.

[0596]

10 Examples of the additive include 4-dimethylaminopyridine (DMAP), triethylamine, and the like.

[0597]

Examples of the solvent include dichloromethane, acetonitrile, THF, and the like, and these can be used alone or as a mixture.

15 [0598]

(Step 6)

Compound (I-103) can be manufactured by reacting compound (I-101) and 1 equivalent to 5 equivalents of compound (I-102) in the presence of 0.001 equivalent to 2 equivalents of copper catalyst and 0.001 equivalent
20 to 2 equivalents of sodium L-ascorbate in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours.

[0599]

25 Examples of the copper catalyst include copper sulfate pentahydrate and the like.

[0600]

Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, water, 1,4-dioxane, s-butanol, and the like, and these can be used alone or as a mixture.

30 [0601]

(Step 7)

Among compound (I-101), a compound in which X⁶ is -CH₂-NH- can be manufactured by using compound (I-40t) and 1 equivalent to 5 equivalents of compound (I-37t) in the same manner as in step 1 of manufacturing method 1-3.

[0602]

(Step 8)

Among compound (I-101), a compound in which X⁶ is -NH-C(=O)-NH- can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-37t) in the same manner as in step 9 of manufacturing method 5.

[0603]

(Step 9)

Compound (I-41t) can be manufactured by reacting compound (I-1) in the presence of 1 equivalent to 10 equivalents of reducing agent in a solvent at a temperature between -78°C and the boiling point of the solvent used for 5 minutes to 120 minutes.

[0604]

Examples of the reducing agent include lithium aluminum hydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, borane dimethyl sulfide complex, lithium borohydride, sodium borohydride, and the like.

[0605]

Examples of the solvent include methanol, ethanol, dichloromethane, chloroform, 1,2-dichloroethane, toluene, acetonitrile, diethyl ether, THF, DME, 1,4-dioxane, DMF, DMA, NMP, and the like, and these are used alone or as a mixture.

[0606]

(Step 10)

Compound (I-40t) can be manufactured by reacting compound (I-

41t) in the presence of 1 equivalent to 10 equivalents of oxidizing agent in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 minutes.

[0607]

- 5 Examples of the oxidizing agent include manganese dioxide, DMP, sulfur trioxide-pyridine, DMSO/oxalyl chloride, and the like.

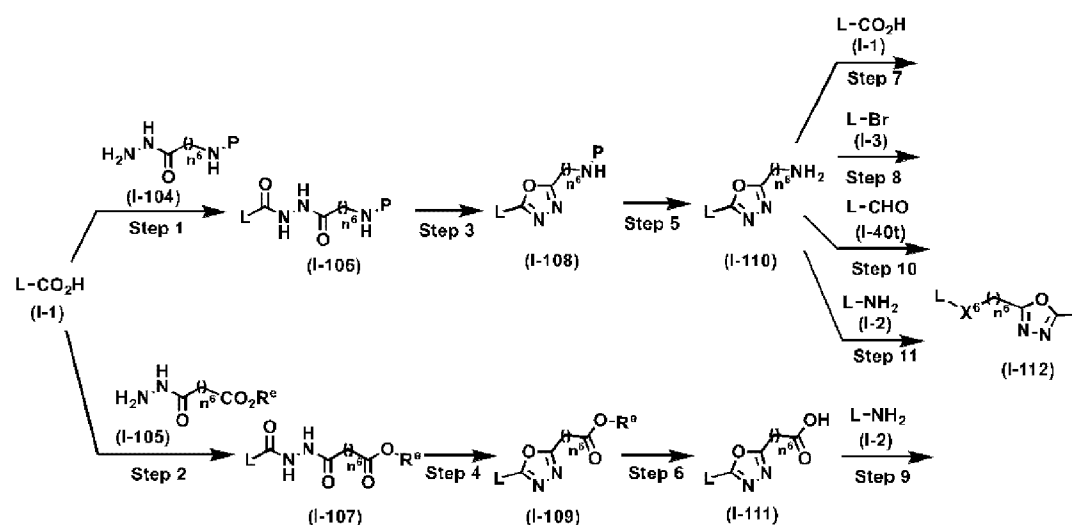
[0608]

- Examples of the solvent include dichloromethane, THF, DME, 1,4-dioxane, DMF, DMA, NMP, DMSO, and the like, and these are used alone or
10 as a mixture.

[0609]

[Manufacturing method 18]

- Among compound (I) in which S is formula (S6), compound (I-112) in which Ar⁶ is 1,3,4-oxadiazolediyl can be manufactured according to the
15 following steps:



- wherein X⁶ and n⁶ are as defined above, L represents L¹ or L², R^e
20 represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0610]

(Step 1)

Compound (I-106) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-104) in the same manner
5 as in step 2 of manufacturing method 2.

[0611]

Compound (I-104) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.406, Maruzen Co., Ltd. (2004)
10 and the like] or methods based thereon.

[0612]

(Step 2)

Compound (I-107) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-105) in the same manner
15 as in step 2 of manufacturing method 2.

[0613]

Compound (I-105) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.406, Maruzen Co., Ltd. (2004)
20 and the like] or methods based thereon.

[0614]

(Step 3)

Compound (I-108) can be manufactured by reacting compound (I-106) in the presence of 1 equivalent to 5 equivalents of triphenylphosphine,
25 1 equivalent to 5 equivalents of carbon tetrachloride, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours.

[0615]

30 Examples of the base include triethylamine, N,N-

diisopropylethylamine, DBU, pyridine, and the like.

[0616]

Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, THF, acetonitrile, 1,4-dioxane, and the like, and these can be
5 used alone or as a mixture.

[0617]

(Step 4)

Compound (I-109) can be manufactured by using compound (I-107) in the same manner as in step 3 of manufacturing method 18.

10 [0618]

(Step 5)

Compound (I-110) can be manufactured by using compound (I-108) in the same manner as in step 4 of manufacturing method 1.

[0619]

15 (Step 6)

Compound (I-111) can be manufactured by using compound (I-109) in the same manner as in step 6 of manufacturing method 1.

[0620]

(Step 7)

20 Among compound (I-112), a compound in which X⁶ is -C(=O)-NH- can be manufactured by using compound (I-110) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0621]

25 (Step 8)

Among compound (I-112), a compound in which X⁶ is -SO₂-NH- can be manufactured by using compound (I-110) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

30 [0622]

(Step 9)

Among compound (I-112), a compound in which X^6 is $-NH-C(=O)-$ can be manufactured by using compound (I-111) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0623]

(Step 10)

Among compound (I-112), a compound in which X^6 is $-CH_2-NH-$ can be manufactured by using compound (I-110) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0624]

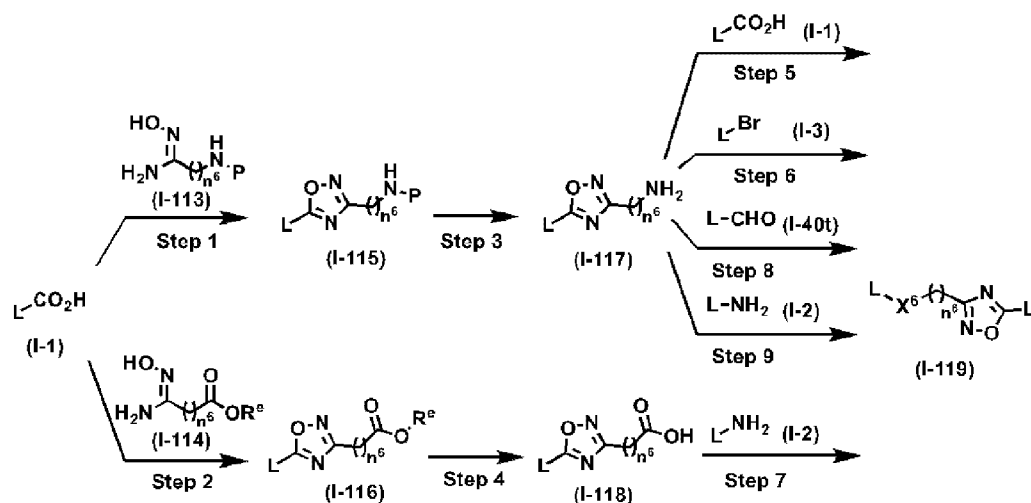
(Step 11)

Among compound (I-112), a compound in which X^6 is $-NH-C(=O)-NH-$ can be manufactured by using compound (I-110) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0625]

[Manufacturing method 19]

Among compound (I) in which S is formula (S6), compound (I-119) in which Ar^6 is 1,2,4-oxadiazole-2,4-diyl can be manufactured according to the following steps:



wherein X^6 and n^6 are as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0626]

(Step 1)

Compound (I-115) can be manufactured by reacting compound (I-1) and 1 equivalent to 5 equivalents of compound (I-113) in the presence of 1 equivalent to a large excess of condensing agent and 1 equivalent to a large excess of base in a solvent at a temperature between 60°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0627]

Examples of the condensing agent include DCC, EDC, HATU, COMU, and the like.

[0628]

Examples of the base include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

[0629]

Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, and the like, and these can be used alone or as a mixture.

[0630]

Compound (I-113) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Chemical Reviews, Volume 62, Issue 2, p.155 (1962) and the like] or methods based thereon.

5 [0631]

(Step 2)

Compound (I-116) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (I-114) in the same manner as in step 1 of manufacturing method 19.

10 [0632]

Compound (I-114) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Chemical Reviews, Volume 62, Issue 2, p.155 (1962) and the like] or methods based thereon.

[0633]

15 (Step 3)

Compound (I-117) can be manufactured by using compound (I-115) in the same manner as in step 4 of manufacturing method 1.

[0634]

(Step 4)

20 Compound (I-118) can be manufactured by using compound (I-116) in the same manner as in step 6 of manufacturing method 1.

[0635]

(Step 5)

25 Among compound (I-119), a compound in which X⁶ is -C(=O)-NH- can be manufactured by using compound (I-117) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0636]

(Step 6)

30 Among compound (I-119), a compound in which X⁶ is -SO₂-NH- can

be manufactured by using compound (I-117) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0637]

5 (Step 7)

Among compound (I-119), a compound in which X^6 is $-NH-C(=O)-$ can be manufactured by using compound (I-118) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

10 [0638]

(Step 8)

Among compound (I-119), a compound in which X^6 is $-CH_2-NH-$ can be manufactured by using compound (I-117) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

15

[0639]

(Step 9)

Among compound (I-119), a compound in which X^6 is $-NH-C(=O)-NH-$ can be manufactured by using compound (I-117) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

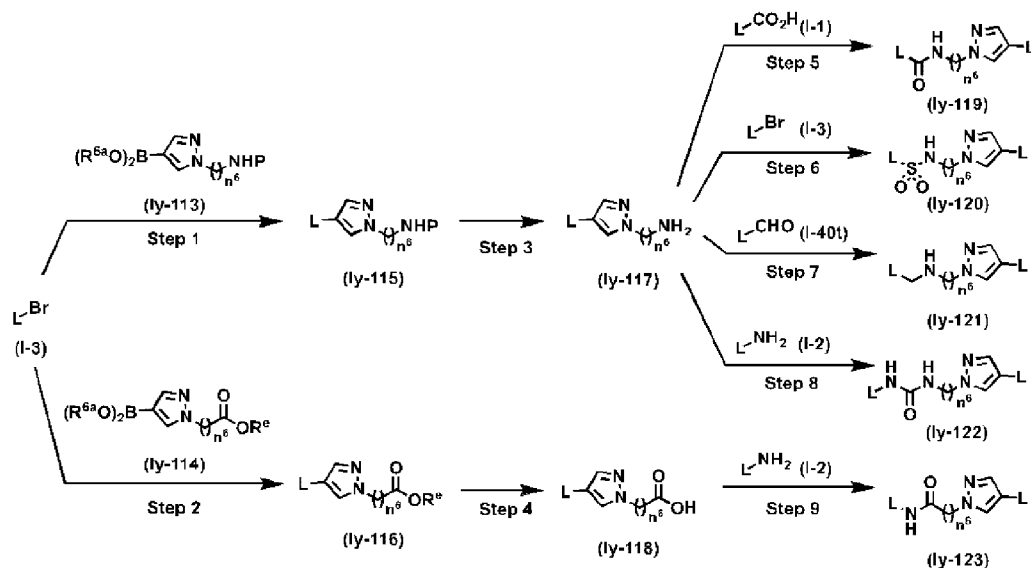
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[0640]

[Manufacturing method YS6-1]

Among compound (I) in which S is formula (S6), the following compounds in which Ar^6 is pyrazolediyl: (i) compound (Iy-119) in which X^6 is $-C(=O)-NH-$, (ii) compound (Iy-120) in which X^6 is $-SO_2-NH-$, (iii) compound (Iy-121) in which X^6 is $-CH_2-NH-$, (iv) compound (Iy-122) in which X^6 is $-NH-C(=O)-NH-$, and (v) compound (Iy-123) in which X^6 is $-NH-C(=O)-$ can be manufactured respectively according to the following

30 steps:



wherein n^6 is as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, R^{6a} represents a hydrogen atom or lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0641]

(Step 1)

Compound (Iy-115) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-113) in the same manner as in step 3 of manufacturing method 3.

[0642]

Compound (Iy-113) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0643]

(Step 2)

Compound (Iy-116) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-114) in the same manner as in step 3 of manufacturing method 3.

[0644]

Compound (Iy-114) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004)

5 and the like] or methods based thereon.

[0645]

(Step 3)

Compound (Iy-117) can be manufactured by using compound (Iy-115) in the same manner as in step 4 of manufacturing method 1.

10 [0646]

(Step 4)

Compound (Iy-118) can be manufactured by using compound (Iy-116) in the same manner as in step 6 of manufacturing method 1.

[0647]

15 (Step 5)

Compound (Iy-119) can be manufactured by using compound (Iy-117) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0648]

20 (Step 6)

Compound (Iy-120) can be manufactured by using compound (Iy-117) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0649]

25 (Step 7)

Compound (Iy-121) can be manufactured by using compound (Iy-117) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0650]

30 (Step 8)

Compound (Iy-122) can be manufactured by using compound (Iy-117) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0651]

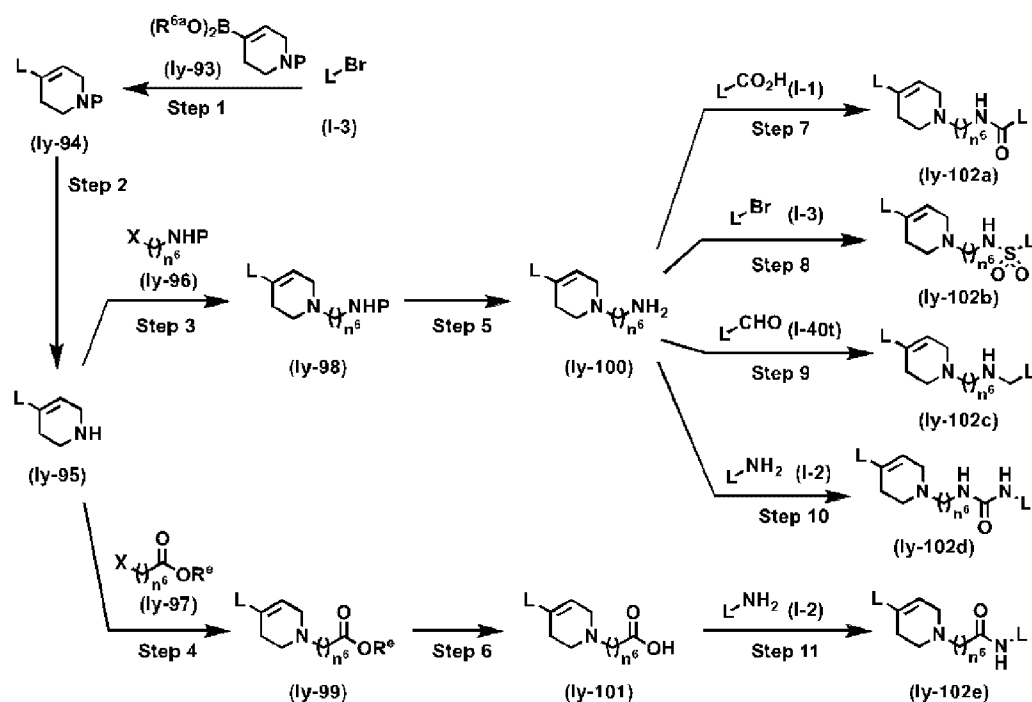
5 (Step 9)

Compound (Iy-123) can be manufactured by using compound (Iy-118) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0652]

10 [Manufacturing method YS6-2]

Among compound (I) in which S is formula (S6), the following compounds in which Ar⁶ is tetrahydropyridinediyl: (i) compound (Iy-102a) in which X⁶ is -C(=O)-NH-, (ii) compound (Iy-102b) in which X⁶ is -SO₂-NH-, (iii) compound (Iy-102c) in which X⁶ is -CH₂-NH-, (iv) compound (Iy-102d) in which X⁶ is -NH-C(=O)-NH-, and (v) compound (Iy-102e) in which X⁶ is -NH-C(=O)- can be manufactured respectively according to the following steps:



wherein n^6 is as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, R^{6a} represents a hydrogen atom or lower alkyl, X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0653]

(Step 1)

Compound (Iy-94) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-93) in the same manner as in step 3 of manufacturing method 3.

[0654]

Compound (Iy-93) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0655]

(Step 2)

Compound (Iy-95) can be manufactured by using compound (Iy-94) in the same manner as in step 4 of manufacturing method 1.

[0656]

(Step 3)

Compound (Iy-98) can be manufactured by using compound (Iy-95) and 1 equivalent to 5 equivalents of compound (Iy-96) in the same manner as in step 1 of manufacturing method 1-2.

[0657]

Compound (Iy-96) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0658]

(Step 4)

Compound (Iy-99) can be manufactured by using compound (Iy-95) and 1 equivalent to 5 equivalents of compound (Iy-97) in the same manner as in step 1 of manufacturing method 1-2.

5 [0659]

Compound (Iy-97) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

10 [0660]

(Step 5)

Compound (Iy-100) can be manufactured by using compound (Iy-98) in the same manner as in step 4 of manufacturing method 1.

[0661]

15 (Step 6)

Compound (Iy-101) can be manufactured by using compound (Iy-99) in the same manner as in step 6 of manufacturing method 1.

[0662]

(Step 7)

20 Compound (Iy-102a) can be manufactured by using compound (Iy-100) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0663]

(Step 8)

25 Compound (Iy-102b) can be manufactured by using compound (Iy-100) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0664]

(Step 9)

30 Compound (Iy-102c) can be manufactured by using compound (Iy-

100) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0665]

(Step 10)

- 5 Compound (Iy-102d) can be manufactured by using compound (Iy-100) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0666]

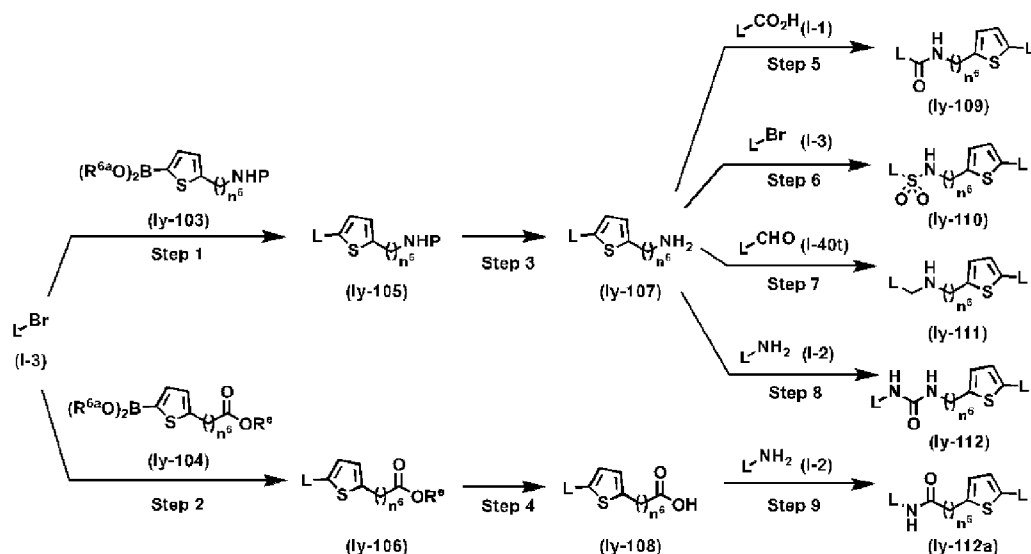
(Step 11)

- 10 Compound (Iy-102e) can be manufactured by using compound (Iy-101) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0667]

[Manufacturing method YS6-3]

- 15 In compound (I) in which S is formula (S6), the following compounds in which Ar⁶ is thiophenediyl: (i) compound (Iy-109) in which X⁶ is -C(=O)-NH-, (ii) compound (Iy-110) in which X⁶ is -SO₂-NH-, (iii) compound (Iy-111) in which X⁶ is -CH₂-NH-, (iv) compound (Iy-112) in which X⁶ is -NH-C(=O)-NH-, and (v) compound (Iy-112a) in which X⁶ is -NH-C(=O)- can be
20 manufactured respectively according to the following steps:



wherein n^6 is as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, R^{6a} represents a hydrogen atom or lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0668]

(Step 1)

Compound (Iy-105) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-103) in the same manner as in step 3 of manufacturing method 3.

[0669]

Compound (Iy-103) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0670]

(Step 2)

Compound (Iy-106) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-104) in the same manner as in step 3 of manufacturing method 3.

[0671]

Compound (Iy-104) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

5 [0672]

(Step 3)

Compound (Iy-107) can be manufactured by using compound (Iy-105) in the same manner as in step 4 of manufacturing method 1.

[0673]

10 (Step 4)

Compound (Iy-108) can be manufactured by using compound (Iy-106) in the same manner as in step 6 of manufacturing method 1.

[0674]

(Step 5)

15 Compound (Iy-109) can be manufactured by using compound (Iy-107) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0675]

(Step 6)

20 Compound (Iy-110) can be manufactured by using compound (Iy-107) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0676]

(Step 7)

25 Compound (Iy-111) can be manufactured by using compound (Iy-107) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0677]

(Step 8)

30 Compound (Iy-112) can be manufactured by using compound (Iy-

107) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0678]

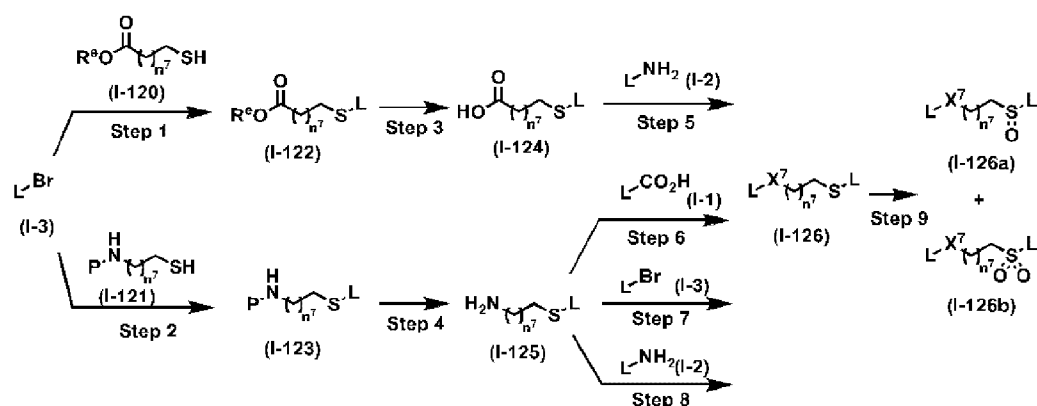
(Step 9)

- 5 Compound (Iy-112a) can be manufactured by using compound (Iy-108) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0679]

[Manufacturing method 20]

- 10 Among compound (I), compound (I-126), compound (I-126a), and compound (I-126b), in which S is formula (S7), can be manufactured respectively according to the following steps:



15

wherein X^7 and n^7 are as defined above, L represents L^1 or L^2 , R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0680]

20 (Step 1)

Compound (I-122) can be manufactured by reacting compound (I-3) and 1 equivalent to 5 equivalents of compound (I-120) in the presence of 0.001 equivalent to 3 equivalents of palladium catalyst, 0.001 equivalent

to 3 equivalents of phosphorus ligand, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours.

[0681]

5 Examples of the palladium catalyst include $\text{Pd}_2(\text{dba})_3$ and the like.

[0682]

 Examples of the phosphorus ligand include xantphos and the like.

[0683]

10 Examples of the base include triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, potassium tert-butoxide, sodium carbonate, potassium carbonate, and the like.

[0684]

15 Examples of the solvent include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

[0685]

 Compound (I-120) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol.3, p.363 (1955) and the like] or methods based thereon.

20 [0686]

(Step 2)

 Compound (I-123) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (I-121) in the same manner as in step 1 of manufacturing method 20.

25 [0687]

 Compound (I-121) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Organic Syntheses, Coll. Vol.3, p.363 (1955) and the like] or methods based thereon.

[0688]

30 (Step 3)

Compound (I-124) can be manufactured by using compound (I-122) in the same manner as in step 6 of manufacturing method 1.

[0689]

(Step 4)

5 Compound (I-125) can be manufactured by using compound (I-123) in the same manner as in step 4 of manufacturing method 1.

[0690]

(Step 5)

10 Among compound (I-126), a compound in which X^7 is $-NH-C(=O)-$ can be manufactured by using compound (I-124) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0691]

(Step 6)

15 Among compound (I-126), a compound in which X^7 is $-C(=O)-NH-$ can be manufactured by using compound (I-125) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0692]

20 (Step 7)

 Among compound (I-126), a compound in which X^7 is $-SO_2-NH-$ can be manufactured by using compound (I-125) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

25 [0693]

(Step 8)

 Among compound (I-126), a compound in which X^7 is $-NH-C(=O)-NH-$ can be manufactured by using compound (I-125) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

30

[0694]

(Step 9)

Compounds (I-126a) and (I-126b) can be manufactured by reacting compound (I-126) in the presence of 1 equivalent to 10 equivalents of oxidizing agent in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0695]

Examples of the oxidizing agent include meta-chloroperbenzoic acid (m-CPBA), benzoyl peroxide, peracetic acid, aqueous hydrogen peroxide, sodium periodate, and the like.

[0696]

Examples of the solvent include dichloromethane, 1,2-dichloroethane, toluene, and the like, and these are used alone or as a mixture.

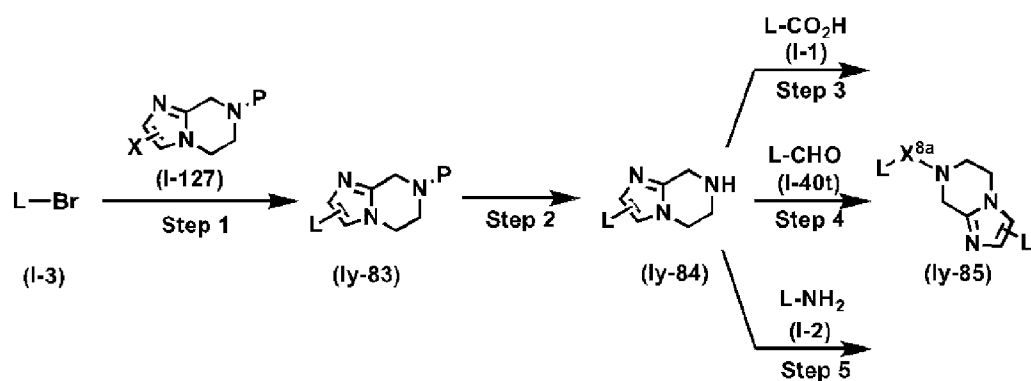
[0697]

In addition, either of compounds (I-126a) and (I-126b) can be obtained selectively or they are obtained as a mixture by adjusting the reaction conditions such as, for example, the number of equivalents of the oxidizing agent, temperature, and the like.

[0698]

[Manufacturing method YS-8-1]

Among compound (I) in which S is formula (S8), compound (Iy-85) in which X^{8b} is a bond can be manufactured according to the following steps:



wherein X^{8a} is as defined above, L represents L^1 or L^2 , X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0699]

(Step 1)

Compound (Iy-83) can be manufactured by (i) reacting compound (I-3) in the presence of 1 equivalent to 5 equivalents of bis(pinacolato)diboron, 0.001 equivalent to 3 equivalents of palladium catalyst, 0.001 equivalent to 3 equivalents of phosphorus ligand as necessary, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours, and then (ii) reacting the obtained compound in the presence of 1 equivalent to 5 equivalents of compound (I-127), 0.001 equivalent to 3 equivalents of palladium catalyst, 0.001 equivalent to 3 equivalents of phosphorus ligand as necessary, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours.

[0700]

Examples of the palladium catalyst used in (i) include Pd(dppf)Cl_2 , $\text{Pd}_2(\text{dba})_3$, $\text{Pd(PPh}_3)_4$, and the like.

[0701]

Examples of the phosphorus ligand used in (i) include tricyclohexylphosphine and the like.

[0702]

Examples of the base used in (i) include potassium acetate,
5 potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate, and the like.

[0703]

Examples of the solvent used in (i) include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane,
10 water, and the like, and these can be used alone or as a mixture.

[0704]

Examples of the palladium catalyst used in (ii) include Pd(dppf)Cl₂, Pd₂(dba)₃, Pd(PPh₃)₄, and the like.

[0705]

Examples of the phosphorus ligand used in (ii) include triphenylphosphine, tricyclohexylphosphine, and the like.

[0706]

Examples of the base used in (ii) include potassium acetate, potassium carbonate, sodium carbonate, cesium carbonate, potassium
20 phosphate, and the like.

[0707]

Examples of the solvent used in (ii) include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, water, and the like, and these can be used alone or as a mixture.

25 [0708]

Compound (I-127) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.341, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

30 [0709]

(Step 2)

Compound (Iy-84) can be manufactured by using compound (Iy-83) in the same manner as in step 4 of manufacturing method 1.

[0710]

5 (Step 3)

Among compound (Iy-85), a compound in which X^{8a} is $-C(=O)-$ can be manufactured by using compound (Iy-84) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

10 [0711]

(Step 4)

Among compound (Iy-85), a compound in which X^{8a} is $-CH_2-$ can be manufactured by using compound (Iy-84) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

15

[0712]

(Step 5)

Among compound (Iy-85), a compound in which X^{8a} is $-NH-C(=O)-$ can be manufactured by using compound (Iy-84) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

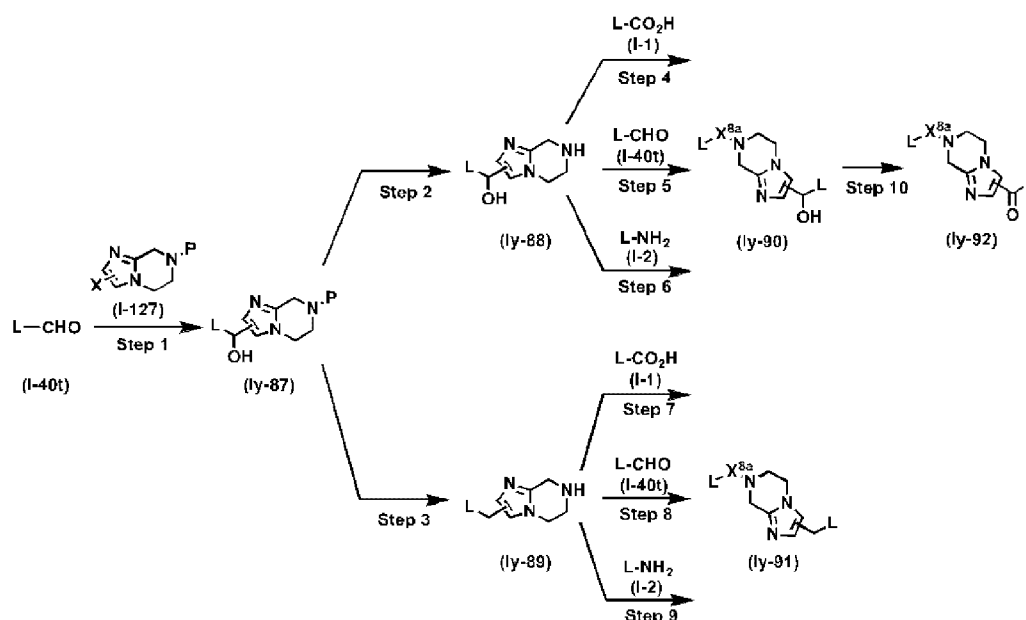
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[0713]

[Manufacturing method YS-8-2]

Among compound (I) in which S is formula (S8), (i) compound (Iy-92) in which X^{8b} is $-C(=O)-$, (ii) compound (Iy-91) in which X^{8b} is $-CH_2-$, and (iii) compound (Iy-90) in which X^{8b} is $-CH(OH)-$ can be manufactured respectively according to the following steps:

25



wherein X^{8a} is as defined above, L represents L¹ or L², X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, and the like.

[0714]

(Step 1)

Compound (Iy-87) can be manufactured by reacting 1 equivalent to 10 equivalents of compound (I-127) and 1 equivalent to 10 equivalents of organometallic reagent in a solvent at a temperature between -78°C and the boiling point of the solvent used for 5 minutes to 24 hours, and by subsequently adding compound (I-40t) to the reaction mixture and reacting the mixture at a temperature between -78°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0715]

Examples of the organometallic reagent include n-butyllithium, s-butyllithium, t-butyllithium, isopropylmagnesium chloride-lithium chloride, and the like. These organometallic reagents can be obtained as commercial products, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.7 (Li) and p.59 (Mg), Maruzen

Co., Ltd. (2004) and the like] or methods based thereon.

[0716]

Examples of the solvent include toluene, diethyl ether, THF, DME, 1,4-dioxane, hexane, and the like, and these are used alone or as a mixture.

5 [0717]

(Step 2)

Compound (Iy-88) can be manufactured by using compound (Iy-87) in the same manner as in step 4 of manufacturing method 1.

[0718]

10 (Step 3)

When P in compound (Iy-87) is, for example, Boc, compound (Iy-89) can be manufactured by reacting compound (Iy-87) in the presence of 1 equivalent to a large excess of acid and 1 equivalent to a large excess of reducing agent without a solvent or in a solvent at a temperature between room temperature and 150°C for 5 minutes to 120 hours.

15

[0719]

Examples of the acid include hydrochloric acid, sulfuric acid, formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, titanium tetrachloride, boron trifluoride, and the like.

20 [0720]

Examples of the reducing agent include triethylsilane, diethylsilane, triphenylsilane, and the like.

[0721]

Examples of the solvent include toluene, dichloromethane, THF, DME, 1,4-dioxane, dichloroethane, and the like, and these are used alone or as a mixture.

25

[0722]

Further, when P in compound (Iy-87) is, for example, Cbz, compound (Iy-89) can be manufactured by reacting compound (Iy-87) in the presence of 0.001 equivalent to 0.5 equivalent of palladium catalyst

30

and 1 equivalent to a large excess of acid under a hydrogen atmosphere in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0723]

5 Examples of the palladium catalyst include palladium on carbon, palladium hydroxide, and the like.

[0724]

 Examples of the acid include hydrochloric acid, sulfuric acid, formic acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid,
10 methanesulfonic acid, and the like.

[0725]

 Examples of the solvent include methanol, ethanol, ethyl acetate, THF, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

[0726]

15 (Step 4)

 Among compound (Iy-90), a compound in which X^{8a} is -C(=O)- can be manufactured by using compound (Iy-88) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

20 [0727]

(Step 5)

 Among compound (Iy-90), a compound in which X^{8a} is -CH₂- can be manufactured by using compound (Iy-88) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing
25 method 1-3.

[0728]

(Step 6)

 Among compound (Iy-90), a compound in which X^{8a} is -NH-C(=O)- can be manufactured by using compound (Iy-88) and 1 equivalent to 5
30 equivalents of compound (I-2) in the same manner as in step 9 of

manufacturing method 5.

[0729]

(Step 7)

Among compound (Iy-91), a compound in which X^{8a} is $-C(=O)-$ can be manufactured by using compound (Iy-89) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0730]

(Step 8)

Among compound (Iy-91), a compound in which X^{8a} is $-CH_2-$ can be manufactured by using compound (Iy-89) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0731]

(Step 9)

Among compound (Iy-91), a compound in which X^{8a} is $-NH-C(=O)-$ can be manufactured by using compound (Iy-89) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0732]

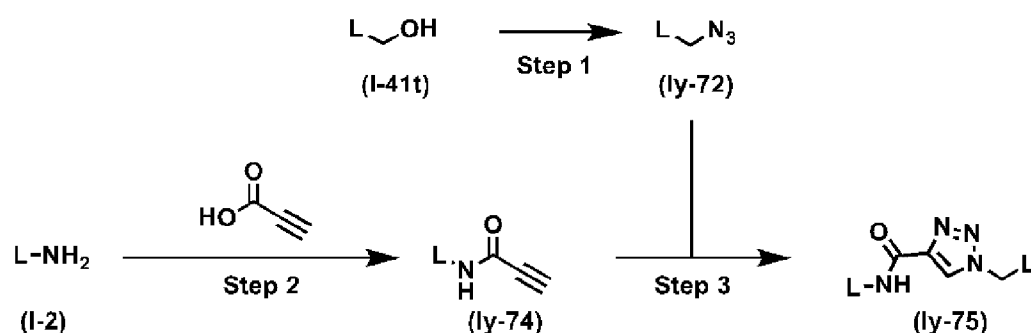
(Step 10)

Compound (Iy-92) can be manufactured by using compound (Iy-90) in the same manner as in step 2 of manufacturing method Y6.

[0733]

[Manufacturing method YS9-1]

Among compound (I) in which S is formula (S9), compound (Iy-75) in which Ar^9 is triazolediyl and Z^9 is $-CH_2-$ can be manufactured according to the following steps:



wherein L represents L^1 or L^2 .

[0734]

5 (Step 1)

Compound (Iy-72) can be manufactured by reacting compound (I-41t) in the presence of 1 equivalent to 10 equivalents of diphenylphosphoryl azide and a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours.

[0735]

Examples of the base include potassium tert-butoxide, potassium carbonate, sodium hydroxide, DBU, triethylamine, N,N-diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

15 [0736]

Examples of the solvent include toluene, dichloroethane, THF, 1,4-dioxane, and the like, and these can be used alone or as a mixture.

[0737]

(Step 2)

20 Compound (Iy-74) can be manufactured by using compound (I-2) and 1 equivalent to 10 equivalents of propiolic acid in the same manner as in step 2 of manufacturing method 2.

[0738]

(Step 3)

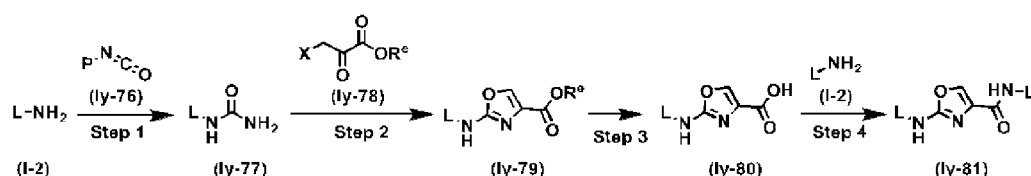
25 Compound (Iy-75) can be manufactured by using compound (Iy-74)

and 1 equivalent to 5 equivalents of compound (Iy-72) in the same manner as in step 6 of manufacturing method 17.

[0739]

[Manufacturing method YS9-2]

- 5 Among compound (I) in which S is formula (S9), compound (Iy-81) in which Ar⁹ is oxazolediyl and Z⁹ is -NH- can be manufactured according to the following steps:



10

wherein L represents L¹ or L², X represents a halogen, R^e represents lower alkyl, and P represents an amine protecting group such as trimethylsilyl, -C(=O)-CCl₃, and the like.

[0740]

- 15 (Step 1)

Compound (Iy-77) can be manufactured by reacting compound (I-2) and 1 equivalent to 10 equivalents of compound (Iy-76) in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

20 [0741]

Compound (Iy-76) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 4th Edition, Volume 20, p.473, Maruzen Co., Ltd. (2001) and the like] or methods based thereon.

25 [0742]

Examples of the solvent include dichloromethane, toluene, acetonitrile, THF, 1,4-dioxane, and the like, and these are used alone or as

a mixture.

[0743]

(Step 2)

Compound (Iy-79) can be manufactured by reacting compound (Iy-
5 77) and 1 equivalent to 10 equivalents of compound (Iy-78) in a solvent at
a temperature between -20°C and the boiling point of the solvent used for
5 minutes to 120 hours.

[0744]

Compound (Iy-78) can be obtained as a commercially available
10 product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 15, p.153, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0745]

Examples of the solvent include toluene, acetonitrile, ethanol, 1,4-
15 dioxane, DMF, DMA, NMP, and the like, and these are used alone or as a
mixture.

[0746]

(Step 3)

Compound (Iy-80) can be manufactured by using compound (Iy-79)
20 in the same manner as in step 6 of manufacturing method 1.

[0747]

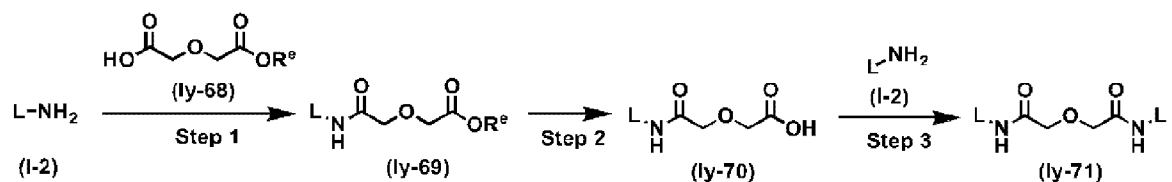
(Step 4)

Compound (Iy-81) can be manufactured by using compound (Iy-80)
and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
25 as in step 2 of manufacturing method 2.

[0748]

[Manufacturing method YS10-1]

Among compound (I) in which S is formula (S10), compound (Iy-
71) in which Z¹⁰ is -O- can be manufactured according to the following
30 steps:



wherein L represents L^1 or L^2 and R^e represents lower alkyl.

5 [0749]

(Step 1)

Compound (Iy-69) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (Iy-68) in the same manner as in step 2 of manufacturing method 2.

10 [0750]

Compound (Iy-68) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

15 [0751]

(Step 2)

Compound (Iy-70) can be manufactured by using compound (Iy-69) in the same manner as in step 6 of manufacturing method 1.

[0752]

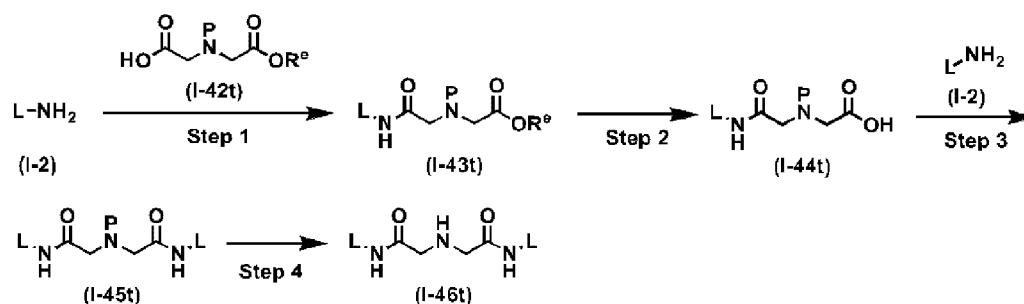
20 (Step 3)

Compound (Iy-71) can be manufactured by using compound (Iy-70) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0753]

25 [Manufacturing method YS10-2]

Among compound (I) in which S is formula (S10), compound (I-46t) in which Z^{10} is -NH- can be manufactured according to the following steps:



wherein L represents L^1 or L^2 , R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, Fmoc, and the like.

[0754]

(Step 1)

Compound (I-43t) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-42t) in the same manner as in step 2 of manufacturing method 2.

[0755]

Compound (I-42t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0756]

(Step 2)

Compound (I-44t) can be manufactured by using compound (I-43t) in the same manner as in step 6 of manufacturing method 1.

[0757]

(Step 3)

Compound (I-45t) can be manufactured by using compound (I-44t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0758]

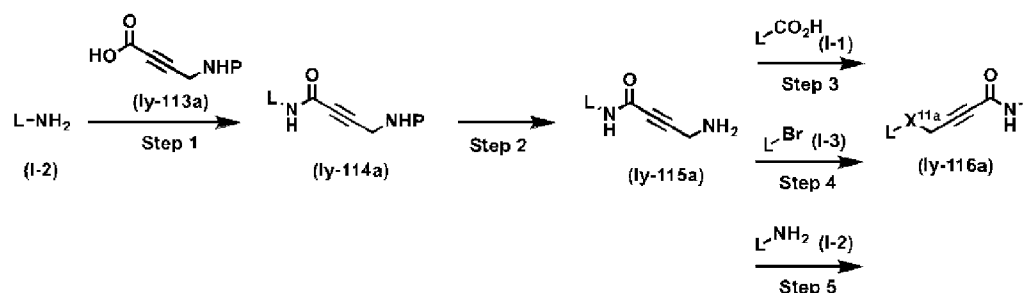
(Step 4)

Compound (I-46t) can be manufactured by using compound (I-45t) in the same manner as in step 4 of manufacturing method 1 when P in compound (I-45t) is, for example, Boc, Cbz, or PMB, and can be manufactured by using compound (I-45t) in the same manner as in step 3 of manufacturing method 2 when P in compound (I-45t) is, for example, Fmoc.

[0759]

10 [Manufacturing method YS11-1]

Among compound (I) in which S is formula (S11), compound (Iy-116a) in which X^{11b} is $-C(=O)-NH-$ can be manufactured according to the following steps:



15

wherein X^{11a} is as defined above, L represents L^1 or L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0760]

20 (Step 1)

Compound (Iy-114a) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (Iy-113a) in the same manner as in step 2 of manufacturing method 2.

[0761]

25 Compound (Iy-113a) can be obtained as a commercially available

product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0762]

5 (Step 2)

Compound (Iy-115a) can be manufactured by using compound (Iy-114a) in the same manner as in step 4 of manufacturing method 1.

[0763]

(Step 3)

10 Among compound (Iy-116a), a compound in which X^{11a} is $-C(=O)-NH-$ can be manufactured by using compound (Iy-115a) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0764]

15 (Step 4)

Among compound (Iy-116a), a compound in which X^{11a} is $-SO_2-NH-$ can be manufactured by using compound (Iy-115a) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

20 [0765]

(Step 5)

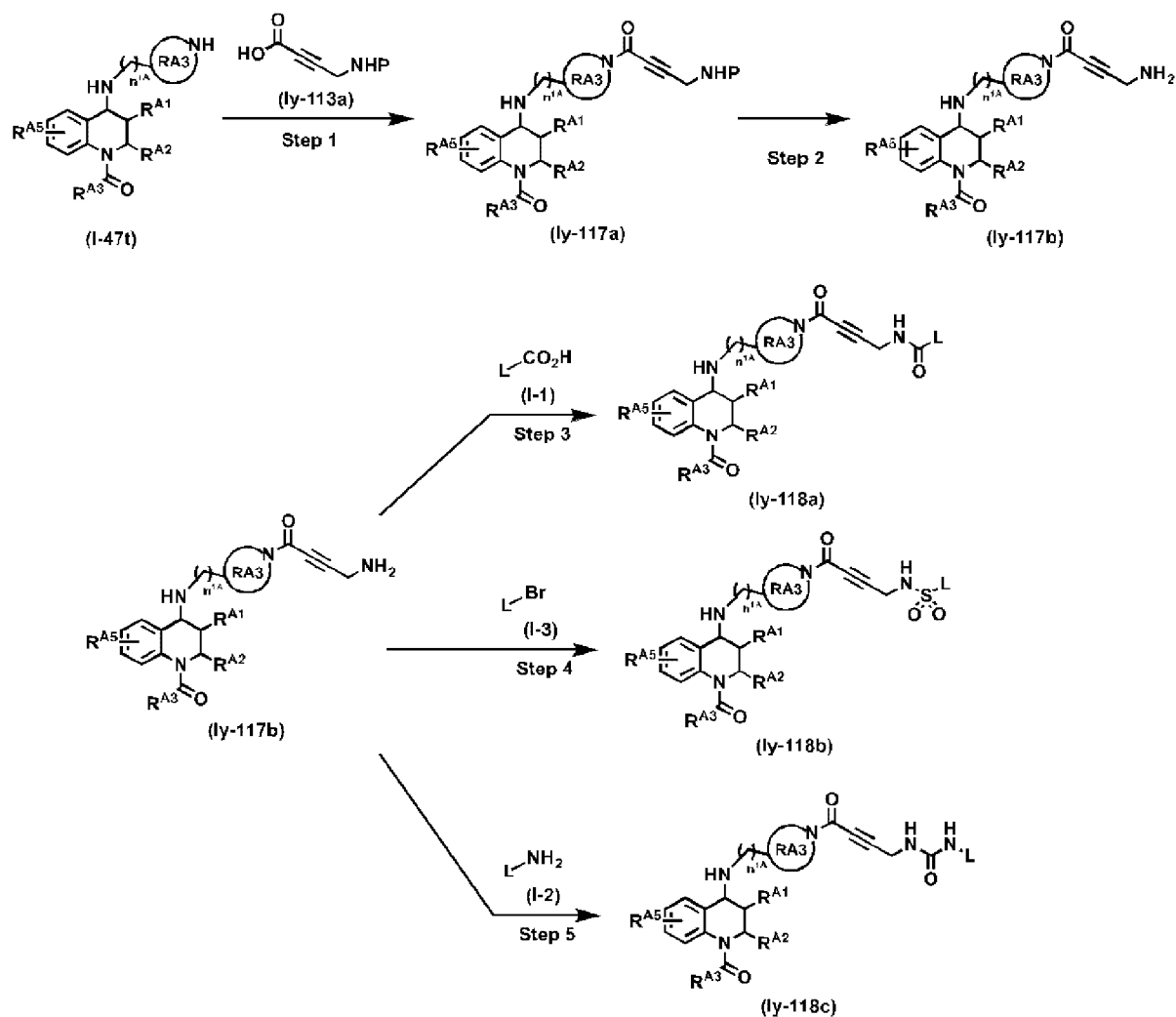
Among compound (Iy-116a), a compound in which X^{11a} is $-NH-C(=O)-NH-$ can be manufactured by using compound (Iy-115a) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in
25 step 9 of manufacturing method 5.

[0766]

[manufacturing method YS11-2]

Among compound (I) in which L^1 is (A) and S is formula (S11), the following compounds in which ring RA is ring RA3 and X^{11b} is $-C(=O)-$: (i)
30 compound (Iy-118a) in which X^{11a} is $-C(=O)-NH-$, (ii) compound (Iy-118b)

in which X^{11a} is $-\text{SO}_2-\text{NH}-$, and (iii) compound (Iy-118c) in which X^{11a} is $-\text{NH}-\text{C}(=\text{O})-\text{NH}-$ can be manufactured respectively according to the following steps:



5

wherein $\text{R}^{\text{A}1}$, $\text{R}^{\text{A}2}$, $\text{R}^{\text{A}3}$, $\text{R}^{\text{A}5}$, $n^{1\text{A}}$, and ring $\text{RA}3$ are as defined above, L represents L^2 , and P represents an amine protecting group such as Boc, Cbz, PMB, and the like. Incidentally, one secondary amine constituting the ring $\text{RA}3$ becomes a reaction point with compound (Iy-113a).

[0767]

(Step 1)

Compound (Iy-117a) can be manufactured by using compound (I-47t) and 1 equivalent to 5 equivalents of compound (Iy-113a) in the same manner as in step 2 of manufacturing method 2.

[0768]

5 As for compound (I-47t), compound (a-32) obtained in step 6 of manufacturing method 1-3 and compound (a-41) obtained in step 6 of manufacturing method 1-4 shall be collectively represented as compound (I-47t).

[0769]

10 Compound (Iy-113a) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0770]

15 (Step 2)

 Compound (Iy-117b) can be manufactured by using compound (I-117a) in the same manner as in step 4 of manufacturing method 1.

[0771]

(Step 3)

20 Compound (Iy-118a) can be manufactured by using compound (Iy-117b) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0772]

(Step 4)

25 Compound (Iy-118b) can be manufactured by using compound (Iy-117b) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0773]

(Step 5)

30 Compound (Iy-118c) can be manufactured by using compound (Iy-

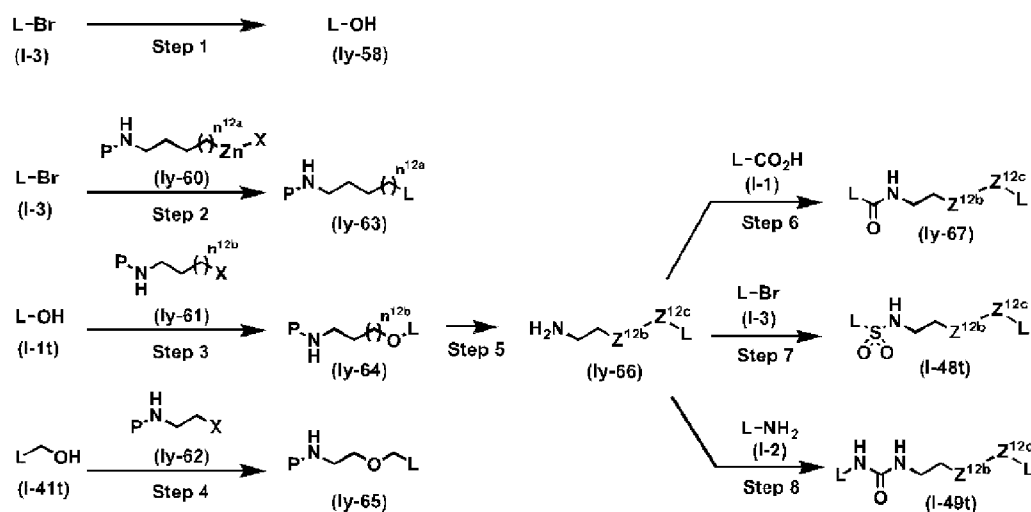
117b) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0774]

[Manufacturing method YS12-1]

- 5 Among compound (I) in which S is formula (S12), the following compounds in which Z^{12a} is CH_2 , (i) compound (Iy-67) in which X^{12} is $-\text{C}(=\text{O})-\text{NH}-$, (ii) compound (I-48t) in which X^{12} is $-\text{SO}_2-\text{NH}-$, and (iii) compound (I-49t) in which X^{12} is $-\text{NH}-\text{C}(=\text{O})-\text{NH}-$ can be manufactured respectively according to the following steps:

10



- wherein Z^{12b} and Z^{12c} are as defined above, n^{12a} and n^{12b} are the same or different and each represents 0 or 1, L represents L^1 or L^2 , X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0775]

(Step 1)

- Compound (Iy-58) can be manufactured by (i) reacting compound (I-3) in the presence of 1 equivalent to 5 equivalents of bis(pinacolato)diboron, 0.001 equivalent to 3 equivalents of palladium catalyst, and 0.001 equivalent to 3 equivalents of phosphorus ligand as

necessary, and 1 equivalent to a large excess of base in a solvent at a temperature between room temperature and the boiling point of the solvent used for 5 minutes to 120 hours, and then (ii) reacting the obtained compound in the presence of 1 equivalent to a large excess of oxidizing agent in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0776]

Examples of the palladium catalyst used in (i) include Pd(dppf)Cl₂, Pd₂(dba)₃, Pd(PPh₃)₄, and the like.

10 [0777]

Examples of the phosphorus ligand used in (i) include tricyclohexylphosphine and the like.

[0778]

Examples of the base used in (i) include potassium acetate, potassium carbonate, sodium carbonate, cesium carbonate, potassium phosphate, and the like.

[0779]

Examples of the solvent used in (i) include chloroform, dichloromethane, DMF, DMA, NMP, DMSO, THF, acetonitrile, 1,4-dioxane, water, and the like, and these can be used alone or as a mixture.

20 [0780]

Examples of the oxidizing agent used in (ii) include a hydrogen peroxide solution, sodium perborate, and the like.

[0781]

Examples of the solvent used in (ii) include THF, 1,4-dioxane, water, and the like, and these can be used alone or as a mixture.

[0782]

(Step 2)

Compound (Iy-63) can be manufactured by reacting compound (I-3) and 1 equivalent to 10 equivalents of compound (Iy-60) in the presence

30

of 0.001 equivalent to 3 equivalents of palladium catalyst and, as necessary, 0.001 equivalent to 3 equivalents of phosphorus ligand in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

5 [0783]

Compound (Iy-60) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.77, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

10 [0784]

Examples of the palladium catalyst include Pd(dppf)Cl₂, Pd₂(dba)₃, Pd(PPh₃)₄, and the like.

[0785]

Examples of the phosphorus ligand include tricyclohexylphosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), and the like.

15 [0786]

Examples of the solvent include THF, DMF, DMA, NMP, and the like, and these are used alone or as a mixture.

[0787]

20 (Step 3)

Compound (Iy-64) can be manufactured by reacting compound (I-1t) in the presence of 1 equivalent to 5 equivalents of compound (Iy-61) and 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

25

[0788]

Examples of the base include sodium hydride, potassium tert-butoxide, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, DBU, potassium carbonate, cesium carbonate, and the like.

30 [0789]

Examples of the solvent include toluene, diethyl ether, THF, DME, 1,4-dioxane, DMF, DMA, NMP, pyridine, acetonitrile, and the like, and these are used alone or as a mixture.

Compound (Iy-61) can be obtained as a commercially available
5 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0790]

As for compound (I-1t), compound (Iy-58) obtained in step 1 and
10 compound (f-1) obtained in step 1 of manufacturing method Y6 shall be collectively represented as compound (I-1t).

[0791]

(Step 4)

Compound (Iy-65) can be manufactured by reacting compound (I-
15 41t) and 1 equivalent to 10 equivalents of compound (Iy-62) in the presence of 1 equivalent to 10 equivalents of base in a solvent at a temperature between -20°C and 150°C for 5 minutes to 120 hours.

[0792]

Compound (Iy-62) can be obtained as a commercially available
20 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0793]

Examples of the base include sodium hydride, potassium tert-
25 butoxide, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, DBU, and the like.

[0794]

Examples of the solvent include toluene, diethyl ether, THF, DME,
1,4-dioxane, DMF, DMA, NMP, pyridine, and the like, and these are used
30 alone or as a mixture.

[0795]

Compound (I-41t) can be obtained according to step 9 of manufacturing method 17.

[0796]

5 (Step 5)

Compound (Iy-66) can be manufactured by using compound (Iy-63), compound (Iy-64), or compound (Iy-65) in the same manner as in step 4 of manufacturing method 1.

[0797]

10 (Step 6)

Compound (Iy-67) can be manufactured by using compound (Iy-66) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0798]

15 (Step 7)

Compound (I-48t) can be manufactured by using compound (Iy-66) and 1 equivalent to 5 equivalents of compound (I-3) in the same manner as in step 4 of manufacturing method 5.

[0799]

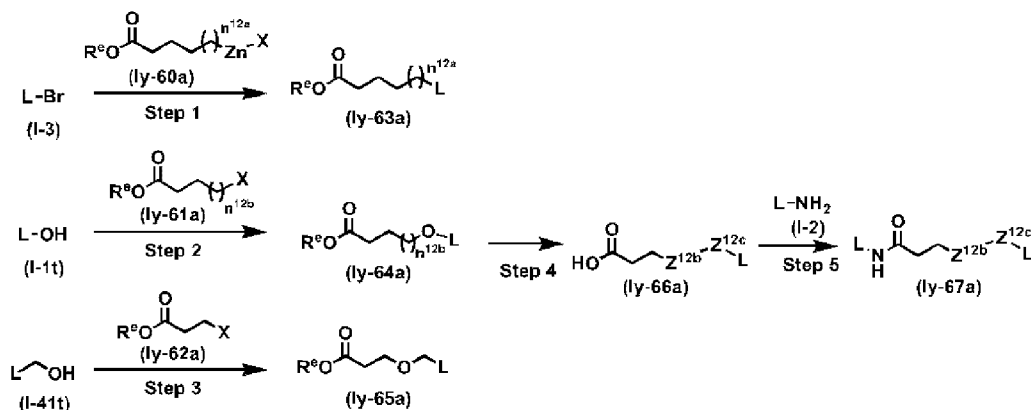
20 (Step 8)

Compound (I-49t) can be manufactured by using compound (Iy-66) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 9 of manufacturing method 5.

[0800]

25 [Manufacturing method YS12-2]

Among compound (I) in which S is formula (S12), compound (Iy-67a) in which Z^{12a} is CH_2 and X^{12} is $-NH-C(=O)-$ can be manufactured according to the following steps:



wherein Z^{12b} and Z^{12c} are as defined above, n^{12a} and n^{12b} are the same or different and each represents 0 or 1, L represents L¹ or L², X represents a halogen, and R^e represents lower alkyl.

[0801]

(Step 1)

Compound (Iy-63a) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-60a) in the same manner as in step 2 of manufacturing method YS12-1.

[0802]

Compound (Iy-60a) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.77, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0803]

(Step 2)

Compound (Iy-64a) can be manufactured by using compound (I-1t) and 1 equivalent to 5 equivalents of compound (Iy-61a) in the same manner as in step 3 of manufacturing method YS12-1.

[0804]

Compound (Iy-61a) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental

Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0805]

As for compound (I-1t), compound (Iy-58) obtained in step 1 of manufacturing method YS12-1 and compound (f-1) obtained in step 1 of manufacturing method Y6 shall be collectively represented as compound (I-1t).

[0806]

(Step 3)

Compound (Iy-65a) can be manufactured by using compound (I-41t) and 1 equivalent to 5 equivalents of compound (Iy-62a) in the same manner as in step 4 of manufacturing method YS12-1.

[0807]

Compound (Iy-62a) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0808]

Compound (I-41t) can be obtained according to step 9 of manufacturing method 17.

[0809]

(Step 4)

Compound (Iy-66a) can be manufactured by using compound (Iy-63a), compound (Iy-64a), or compound (Iy-65a) in the same manner as in step 6 of manufacturing method 1.

[0810]

(Step 5)

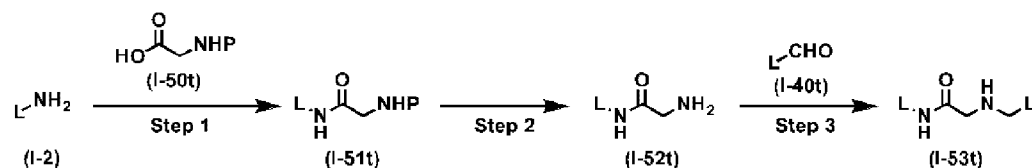
Compound (Iy-67a) can be manufactured by using compound (Iy-66a) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0811]

[Manufacturing method YS12-3]

Among compound (I) in which S is formula (S12), compound (I-53t) in which Z^{12a} is NH can be manufactured according to the following steps:

5



wherein L represents L¹ or L², and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

10 [0812]

(Step 1)

Compound (I-51t) can be manufactured by using compound (I-2) and 1 equivalent to 5 equivalents of compound (I-50t) in the same manner as in step 2 of manufacturing method 2.

15 [0813]

Compound (I-50t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 16, p.175, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

20 [0814]

(Step 2)

Compound (I-52t) can be manufactured by using compound (I-51t) in the same manner as in step 4 of manufacturing method 1.

[0815]

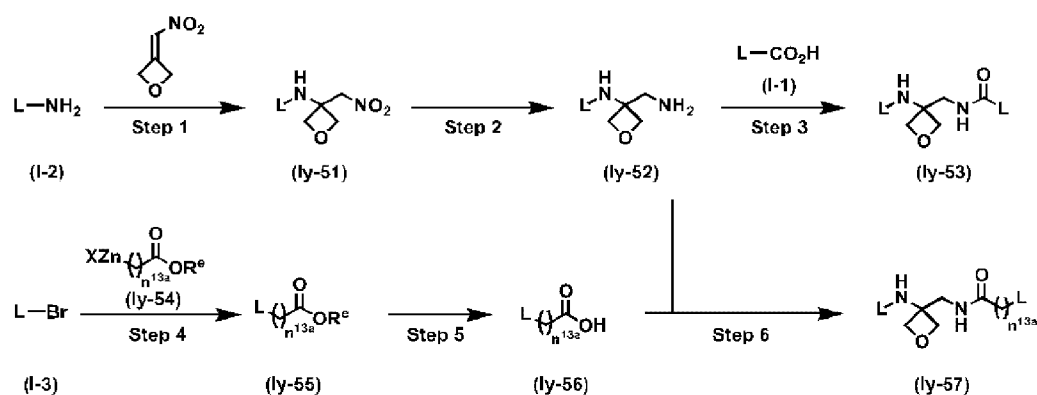
25 (Step 3)

Compound (I-53t) can be manufactured by using compound (I-52t) and 1 equivalent to 5 equivalents of compound (I-40t) in the same manner as in step 1 of manufacturing method 1-3.

[0816]

[Manufacturing method YS13]

Among compound (I) in which S is formula (S13), (i) compound (Iy-53) in which n^{13} is 0 and (ii) compound (Iy-57) in which n^{13} is n^{13a} can be
5 manufactured respectively according to the following steps:



wherein n^{13a} represents 1 or 2, L represents L^1 or L^2 , X represents a
10 halogen, and R^e represents lower alkyl.

[0817]

(Step 1)

Compound (Iy-51) can be manufactured by reacting compound (I-2) and 1 equivalent to 10 equivalents of 3-(nitromethylene)oxetane in the
15 presence of a large excess of base in a solvent at a temperature between -20°C and 150°C for 5 minutes to 120 hours.

[0818]

Examples of the base include triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, DBU, and the like.

20 [0819]

Examples of the solvent include toluene, diethyl ether, THF, DME, 1,4-dioxane, and the like, and these are used alone or as a mixture.

[0820]

(Step 2)

Compound (Iy-52) can be manufactured by using compound (Iy-51) in the same manner as in step 8 of manufacturing method 1.

[0821]

(Step 3)

5 Compound (Iy-53) can be manufactured by using compound (Iy-52) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0822]

(Step 4)

10 Compound (Iy-55) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-54) in the same manner as in step 2 of manufacturing method YS12-1.

[0823]

15 Compound (Iy-54) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.77, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0824]

(Step 5)

20 Compound (Iy-56) can be manufactured by using compound (Iy-55) in the same manner as in step 6 of manufacturing method 1.

[0825]

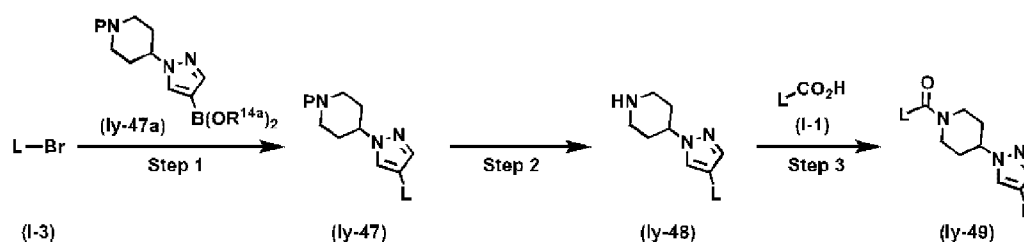
(Step 6)

25 Compound (Iy-57) can be manufactured by using compound (Iy-52) and 1 equivalent to 5 equivalents of compound (Iy-56) in the same manner as in step 2 of manufacturing method 2.

[0826]

[Manufacturing method YS14]

30 Among compound (I), compound (Iy-49) in which S is formula (S14) can be manufactured according to the following steps:



wherein L represents L¹ or L², R^{14a} represents a hydrogen atom or lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0827]

(Step 1)

Compound (Iy-47) can be manufactured by using compound (I-3) and 1 equivalent to 5 equivalents of compound (Iy-47a) in the same manner as in step 3 of manufacturing method 3.

[0828]

Compound (Iy-47a) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 18, p.95, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0829]

(Step 2)

Compound (Iy-48) can be manufactured by using compound (Iy-47) in the same manner as in step 4 of manufacturing method 1.

[0830]

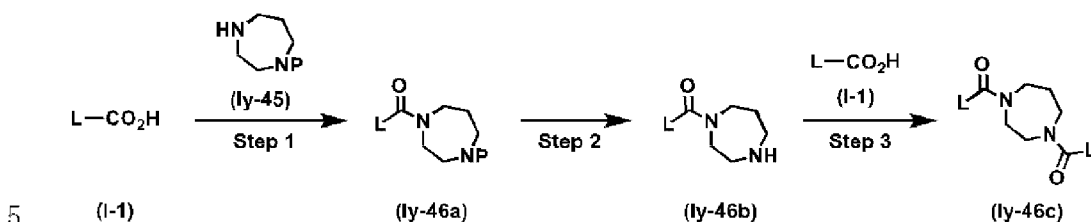
(Step 3)

Compound (Iy-49) can be manufactured by using compound (Iy-48) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0831]

[Manufacturing method YS15]

Among compound (I), compound (Iy-46c) in which S is represented by formula (S15) can be manufactured according to the following steps:



wherein L represents L¹ or L² and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0832]

10 (Step 1)

Compound (Iy-46a) can be manufactured by using compound (I-1) and 1 equivalent to 5 equivalents of compound (Iy-45) in the same manner as in step 2 of manufacturing method 2.

[0833]

15 Compound (Iy-45) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0834]

20 (Step 2)

Compound (Iy-46b) can be manufactured by using compound (Iy-46a) in the same manner as in step 4 of manufacturing method 1.

[0835]

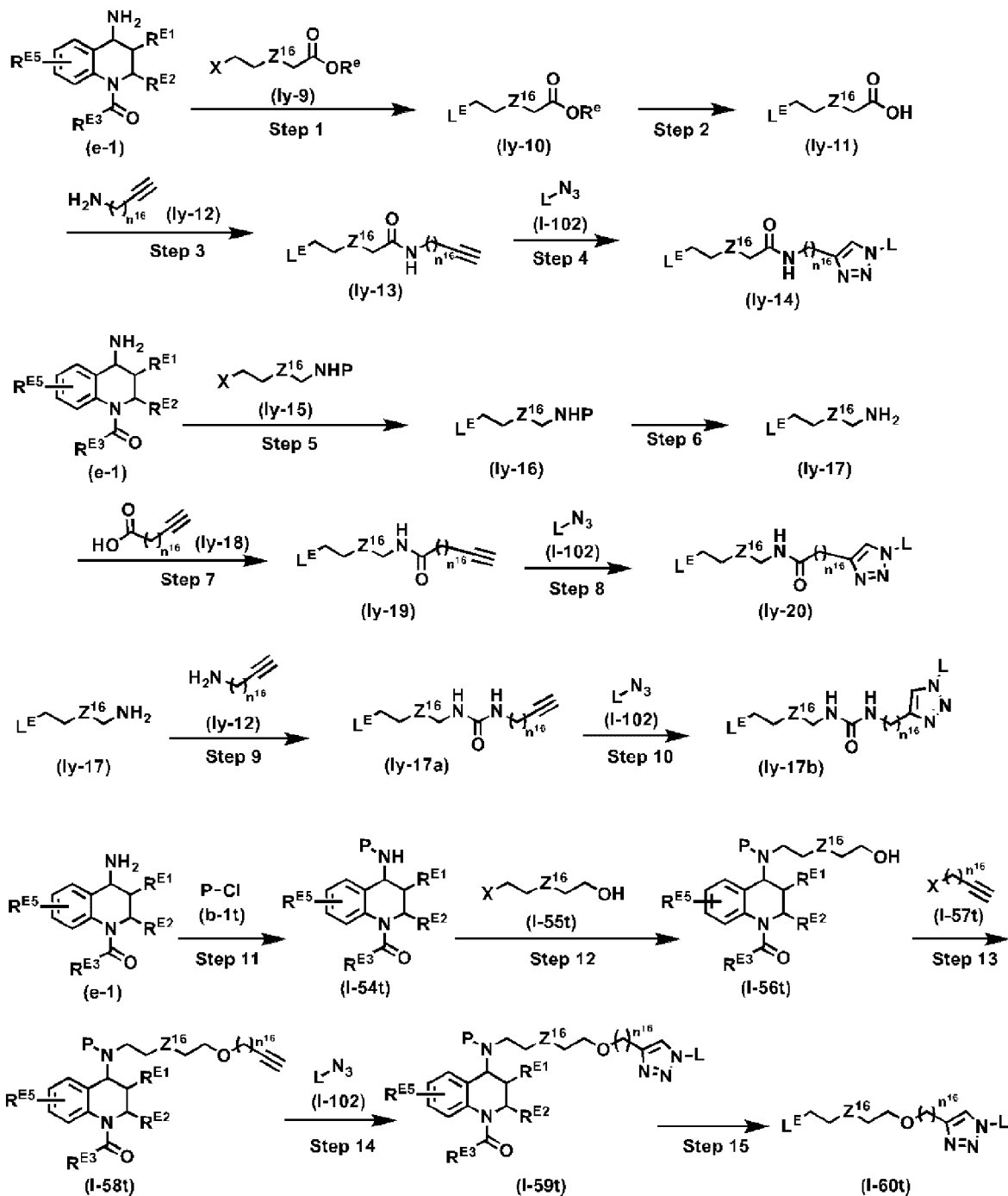
(Step 3)

25 Compound (Iy-46c) can be manufactured by using compound (Iy-46b) and 1 equivalent to 5 equivalents of compound (I-1) in the same manner as in step 2 of manufacturing method 2.

[0836]

[Manufacturing method YS16-1-2]

Among compound (I) in which L^1 is L^E and S is formula (S16), the following compounds in which Ar^{16} is triazolediyl: (i) compound (Iy-14) in
5 which X^{16} is $-C(=O)-NH-$, (ii) compound (Iy-20) in which X^{16} is $-NH-C(=O)-$, (iii) compound (Iy-17b) in which X^{16} is $-NH-C(=O)-NH-$, and (iv) compound (I-60t) in which X^{16} is $-CH_2-O-$ can be manufactured respectively according to the following steps:



wherein R^{E1} , R^{E2} , R^{E3} , R^{E5} , n^{16} , and Z^{16} are as defined above, L^E is a group represented by formula (E), L represents L^2 , X represents a halogen, R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, 2-nitrobenzenesulfonyl (Ns), and the like.

[0837]

(Step 1)

Compound (Iy-10) can be manufactured by using compound (e-1) and 1 equivalent to 5 equivalents of compound (Iy-9) in the same manner
5 as in step 1 of manufacturing method 1-2.

Compound (e-1) can be obtained in the same manner as in step 4 of manufacturing method 1.

[0838]

Compound (Iy-9) can be obtained as a commercially available
10 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0839]

(Step 2)

15 Compound (Iy-11) can be manufactured by using compound (Iy-10) in the same manner as in step 6 of manufacturing method 1.

[0840]

(Step 3)

Compound (Iy-13) can be manufactured by using compound (Iy-11)
20 and 1 equivalent to 5 equivalents of compound (Iy-12) in the same manner as in step 2 of manufacturing method 2.

[0841]

Compound (Iy-12) can be obtained as a commercially available
25 product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 14, p.351, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0842]

(Step 4)

Compound (Iy-14) can be manufactured by using compound (Iy-13)
30 and 1 equivalent to 5 equivalents of compound (I-102) in the same manner

as in step 6 of manufacturing method 17.

[0843]

(Step 5)

Compound (Iy-16) can be manufactured by using compound (e-1)
5 and 1 equivalent to 5 equivalents of compound (Iy-15) in the same manner
as in step 1 of manufacturing method 1-2.

[0844]

Compound (Iy-15) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
10 Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0845]

(Step 6)

Compound (Iy-17) can be manufactured by using compound (Iy-16)
15 in the same manner as in step 4 of manufacturing method 1.

[0846]

(Step 7)

Compound (Iy-19) can be manufactured by using compound (Iy-17)
and 1 equivalent to 5 equivalents of compound (Iy-18) in the same manner
20 as in step 2 of manufacturing method 2.

[0847]

Compound (Iy-18) can be obtained as a commercially available
product, or can be obtained by known methods [e.g., Experimental
Chemistry Lecture, 5th Edition, Volume 16, p.1, Maruzen Co., Ltd. (2004)
25 and the like] or methods based thereon.

[0848]

(Step 8)

Compound (Iy-20) can be manufactured by using compound (Iy-19)
and 1 equivalent to 5 equivalents of compound (I-102) in the same manner
30 as in step 6 of manufacturing method 17.

[0849]

(Step 9)

Compound (Iy-17a) can be manufactured by using compound (Iy-17) and 1 equivalent to 5 equivalents of compound (Iy-12) in the same manner as in step 9 of manufacturing method 5.

[0850]

(Step 10)

Compound (Iy-17b) can be manufactured by using compound (Iy-17a) and 1 equivalent to 5 equivalents of compound (I-102) in the same manner as in step 6 of manufacturing method 17.

[0851]

(Step 11)

Compound (I-54t) can be manufactured by using compound (e-1) and 1 equivalent to 5 equivalents of compound (b-1t) in the same manner as in step 6 of manufacturing method T2.

[0852]

(Step 12)

Compound (I-56t) can be manufactured by using compound (I-54t) and 1 equivalent to 10 equivalents of compound (I-55t) in the same manner as in step 1 of manufacturing method 1-2.

[0853]

Compound (I-55t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0854]

(Step 13)

Compound (I-58t) can be manufactured by using compound (I-56t) and 1 equivalent to 10 equivalents of compound (I-57t) in the same manner as in step 4 of manufacturing method YS12-1.

[0855]

Compound (I-57t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004)

5 and the like] or methods based thereon.

[0856]

(Step 14)

Compound (I-59t) can be manufactured by using compound (I-58t) and 1 equivalent to 5 equivalents of compound (I-102) in the same manner
10 as in step 6 of manufacturing method 17.

[0857]

(Step 15)

When P in compound (I-59t) is, for example, Ns, compound (I-60t) can be manufactured by reacting compound (I-59t) in the presence of 1
15 equivalent to 10 equivalents of thiol and 1 equivalent to a large excess of base in a solvent at a temperature between -20°C and the boiling point of the solvent used for 5 minutes to 120 hours.

[0858]

Examples of the thiol include thiophenol, mercaptoacetic acid, 2-
20 mercaptoethanol, and the like.

[0859]

Examples of the base include cesium carbonate, potassium carbonate, sodium carbonate, and the like.

[0860]

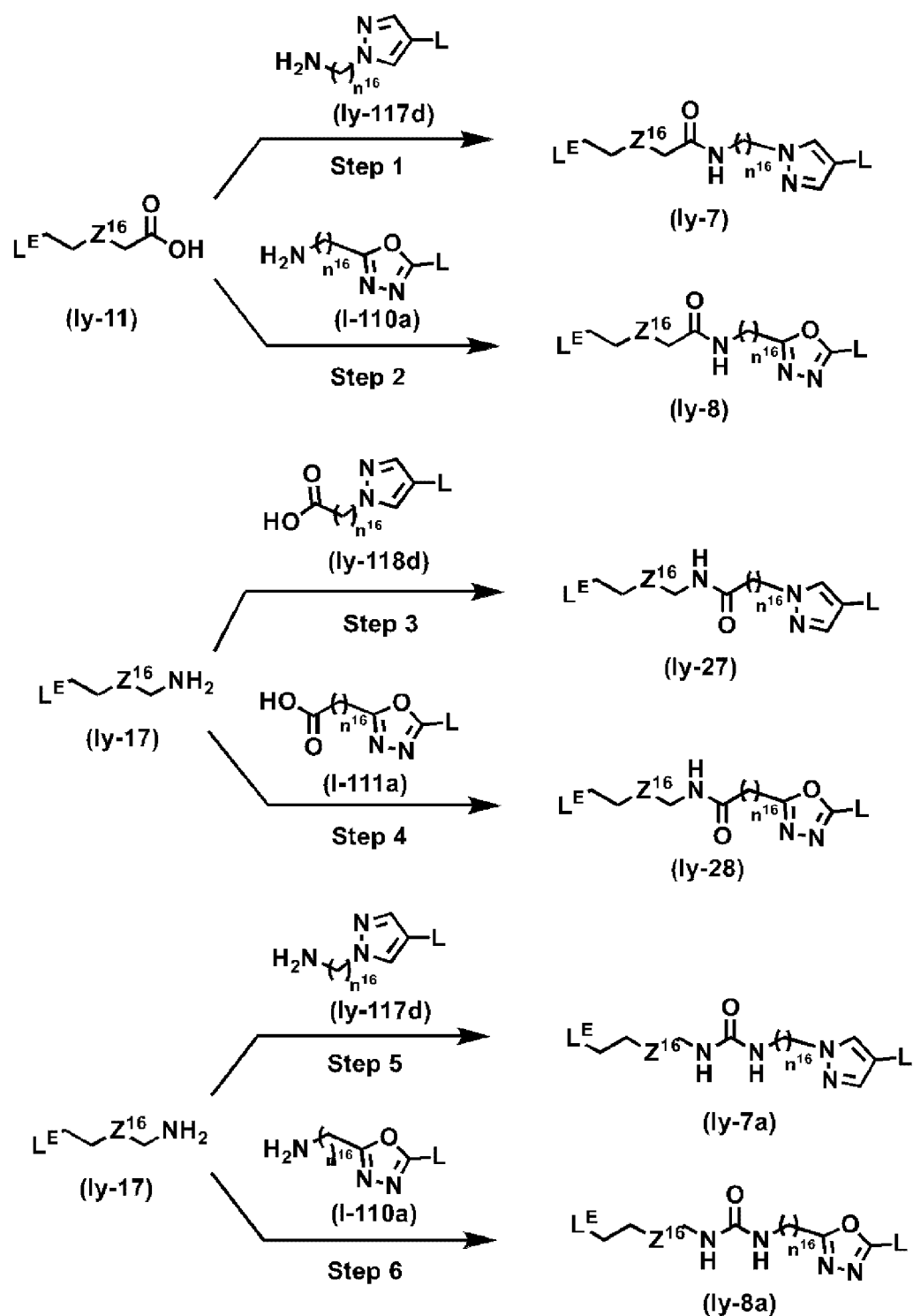
25 Examples of the solvent include acetonitrile, DMF, DMSO, and the like, and these can be used alone or as a mixture.

[0861]

[Manufacturing method YS16-2-2]

Among compound (I) in which S is formula (S16), the following
30 compounds in which Ar¹⁶ is pyrazolediyl: (i) compound (Iy-7) in which X¹⁶

is -C(=O)-NH-, (ii) compound (Iy-27) in which X^{16} is -NH-C(=O)-, and (iii) compound (Iy-7a) in which X^{16} is -NH-C(=O)-NH-; and the following compounds in which Ar^{16} is oxadiazolediyl: (i) compound (Iy-8) in which X^{16} is -C(=O)-NH-, (ii) compound (Iy-28) in which X^{16} is -NH-C(=O)-, and (iii) 5 compound (Iy-8a) in which X^{16} is -NH-C(=O)-NH- can be manufactured respectively according to the following steps:



wherein n^{16} and Z^{16} are as defined above, L^{E} is a group represented by formula (E), and L represents L^2 .

5 [0862]

(Step 1)

Compound (Iy-7) can be manufactured by using compound (Iy-11) and 1 equivalent to 5 equivalents of compound (Iy-117d) in the same manner as in step 2 of manufacturing method 2.

5 [0863]

Compound (Iy-117d) can be obtained in the same manner as in step 3 of manufacturing method YS6-1.

[0864]

(Step 2)

10 Compound (Iy-8) can be manufactured by using compound (Iy-11) and 1 equivalent to 5 equivalents of compound (I-110a) in the same manner as in step 2 of manufacturing method 2.

[0865]

Compound (I-110a) can be obtained in the same manner as in step 15 5 of manufacturing method 18.

[0866]

(Step 3)

Compound (Iy-27) can be manufactured by using compound (Iy-17) and 1 equivalent to 5 equivalents of compound (Iy-118d) in the same 20 manner as in step 2 of manufacturing method 2.

[0867]

Compound (Iy-118d) can be obtained in the same manner as in step 4 of manufacturing method YS6-1.

[0868]

25 (Step 4)

Compound (Iy-28) can be manufactured by using compound (Iy-17) and 1 equivalent to 5 equivalents of compound (I-111a) in the same manner as in step 2 of manufacturing method 2.

[0869]

30 Compound (I-111a) can be obtained in the same manner as in step

6 of manufacturing method 18.

[0870]

(Step 5)

- Compound (Iy-7a) can be manufactured by using compound (Iy-17) and 1 equivalent to 5 equivalents of compound (Iy-117d) in the same manner as in step 9 of manufacturing method 5.

[0871]

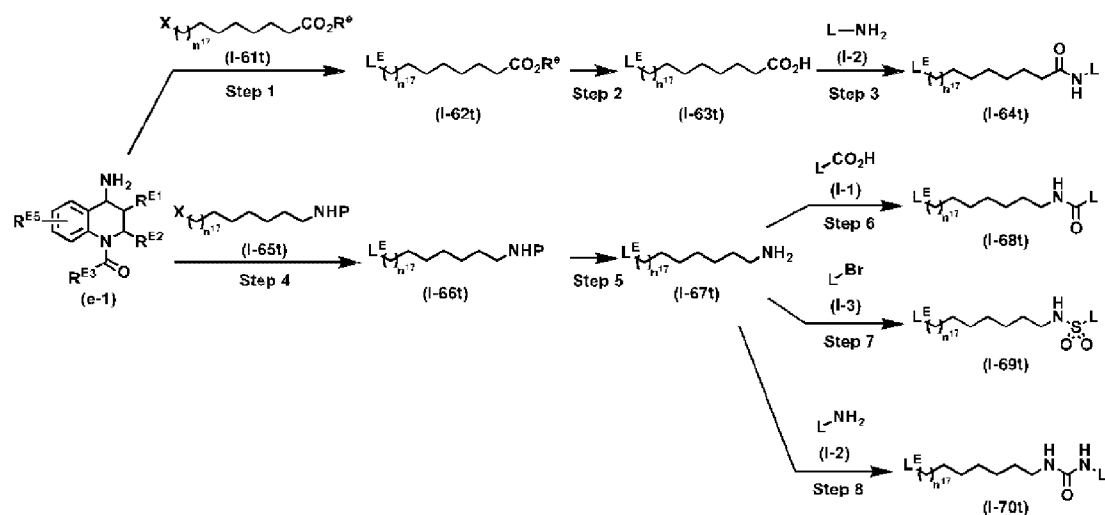
(Step 6)

- Compound (Iy-8a) can be manufactured by using compound (Iy-17) and 1 equivalent to 5 equivalents of compound (I-110a) in the same manner as in step 9 of manufacturing method 5.

[0872]

[Manufacturing method YS17]

- Among compound (I) in which L^1 is L^E and S is formula (S17), (i) compound (I-64t) in which X^{17} is $-C(=O)-NH-$, (ii) compound (I-68t) in which X^{17} is $-NH-C(=O)-$, (iii) compound (I-69t) in which X^{17} is $-NH-SO_2-$, and (iv) compound (I-70t) in which X^{17} is $-NH-C(=O)-NH-$ can be manufactured respectively according to the following steps:



wherein R^{E1} , R^{E2} , R^{E3} , R^{E5} , and n^{17} are as defined above, L^E is a group

represented by formula (E), L represents L^2 , X represents a halogen, R^e represents lower alkyl, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0873]

5 (Step 1)

Compound (I-62t) can be manufactured by using compound (e-1) and 1 equivalent to 10 equivalents of compound (I-61t) in the same manner as in step 1 of manufacturing method 1-2.

[0874]

10 Compound (I-61t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0875]

15 (Step 2)

Compound (I-63t) can be manufactured by using compound (I-62t) in the same manner as in step 6 of manufacturing method 1.

[0876]

(Step 3)

20 Compound (I-64t) can be manufactured by using compound (I-63t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner as in step 2 of manufacturing method 2.

[0877]

(Step 4)

25 Compound (I-66t) can be manufactured by using compound (e-1) and 1 equivalent to 10 equivalents of compound (I-65t) in the same manner as in step 1 of manufacturing method 1-2.

[0878]

30 Compound (I-65t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental

Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004)
and the like] or methods based thereon.

[0879]

(Step 5)

- 5 Compound (I-67t) can be manufactured by using compound (I-66t)
in the same manner as in step 4 of manufacturing method 1.

[0880]

(Step 6)

- 10 Compound (I-68t) can be manufactured by using compound (I-67t)
and 1 equivalent to 5 equivalents of compound (I-1) in the same manner
as in step 2 of manufacturing method 2.

[0881]

(Step 7)

- 15 Compound (I-69t) can be manufactured by using compound (I-67t)
and 1 equivalent to 5 equivalents of compound (I-3) in the same manner
as in step 4 of manufacturing method 5.

[0882]

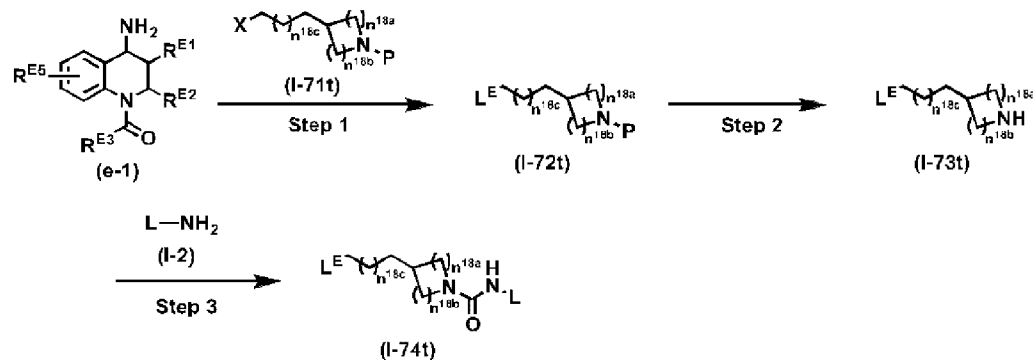
(Step 8)

- 20 Compound (I-70t) can be manufactured by using compound (I-67t)
and 1 equivalent to 5 equivalents of compound (I-2) in the same manner
as in step 9 of manufacturing method 5.

[0883]

[Manufacturing method YS18]

- 25 Compound (I) in which L^1 is L^E and S is formula (S18) can be
manufactured according to the following steps:



wherein R^{E1} , R^{E2} , R^{E3} , R^{E5} , n^{18a} , n^{18b} , and n^{18c} are as defined above, L^E is a group represented by formula (E), L represents L^2 , X represents a halogen, and P represents an amine protecting group such as Boc, Cbz, PMB, and the like.

[0884]

(Step 1)

Compound (I-72t) can be manufactured by using compound (e-1) and 1 equivalent to 10 equivalents of compound (I-71t) in the same manner as in step 1 of manufacturing method 1-2.

[0885]

Compound (I-71t) can be obtained as a commercially available product, or can be obtained by known methods [e.g., Experimental Chemistry Lecture, 5th Edition, Volume 13, p.374, Maruzen Co., Ltd. (2004) and the like] or methods based thereon.

[0886]

(Step 2)

Compound (I-73t) can be manufactured by using compound (I-72t) in the same manner as in step 4 of manufacturing method 1.

[0887]

(Step 3)

Compound (I-74t) can be manufactured by using compound (I-73t) and 1 equivalent to 5 equivalents of compound (I-2) in the same manner

as in step 9 of manufacturing method 5.

[0888]

Conversion of various functional groups in the manufacturing methods of compound (I) and compound (I)-1 can be conducted by known
5 methods [e.g., methods described in Comprehensive Organic Transformations, 2nd Edition, R. C. Larock, Vch. Verlagsgesellschaft MbH (1999) and the like] or methods based thereon.

[0889]

The intermediates and target compounds in each of the above-
10 mentioned manufacturing methods can be isolated and purified by subjecting them to isolation/purification methods commonly used in synthetic organic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, various chromatography, and the like. Furthermore, the intermediates can be supplied to the next reactions
15 without any particular purification.

[0890]

Among compound (I) and compound (I)-1, there are compounds for which there can be stereoisomers such as geometrical isomers, optical isomers, and the like, tautomers, and the like, but the present invention
20 includes all possible isomers including these and mixtures thereof. For example, compound numbers 2c and 2d in Table 2 below are optical isomers, and both of these are included in the scope of compound (I) and compound (I)-1 of the present invention.

[0891]

25 A part or all of atoms in each of compound (I) and compound (I)-1 may be substituted with corresponding isotope atoms, and the present invention also includes the compounds substituted with these isotope atoms. For example, a part or all of hydrogen atoms in each of compound (I) and compound (I)-1 may be hydrogen atoms having an atomic weight
30 of 2 (deuterium atoms).

[0892]

A compound obtained by substituting a part or all of atoms in each of compound (I) and compound (I)-1 with the corresponding isotope atom can be manufactured by a method similar to each of the above-mentioned
5 manufacturing methods by using commercially available building blocks. Furthermore, a compound obtained by substituting a part or all of hydrogen atoms in each of compound (I) and compound (I)-1 with deuterium atoms can also be synthesized, for example, by 1) a method of deuterating a carboxylic acid and the like by using deuterium peroxide under a basic
10 condition (see the description of U.S. Patent No. 3849458), 2) a method of deuterating an alcohol, a carboxylic acid, and the like by using an iridium complex as a catalyst and heavy water as a deuterium source [see J. Am. Chem. Soc., Vol. 124, No. 10, 2092 (2002)], 3) a method of deuterating an aliphatic acid by using palladium on carbon as a catalyst and using only
15 deuterium gas as a deuterium source [see LIPIDS, Vol. 9, No. 11, 913 (1974)], 4) a method of deuterating acrylic acid, methyl acrylate, methacrylic acid, methyl methacrylate, and the like by using a metal such as platinum, palladium, rhodium, ruthenium, iridium, and the like as a catalyst and using heavy water or heavy water and deuterium gas as a
20 deuterium source (see Japanese Examined Patent Application Publication No. H5-19536, Japanese Unexamined Patent Application Publication No. S61-277648, and Japanese Unexamined Patent Application Publication No. S61-275241), 5) a method of deuterating acrylic acid, methyl methacrylate, and the like by using a catalyst such as palladium, nickel, copper, copper
25 chromite, and the like, and heavy water as a deuterium source (see Japanese Unexamined Patent Application Publication No. S63-198638), and the like.

[0893]

When a salt of compound (I) or compound (I)-1 is desired, in the
30 case where compound (I) or compound (I)-1 is obtained in the form of a

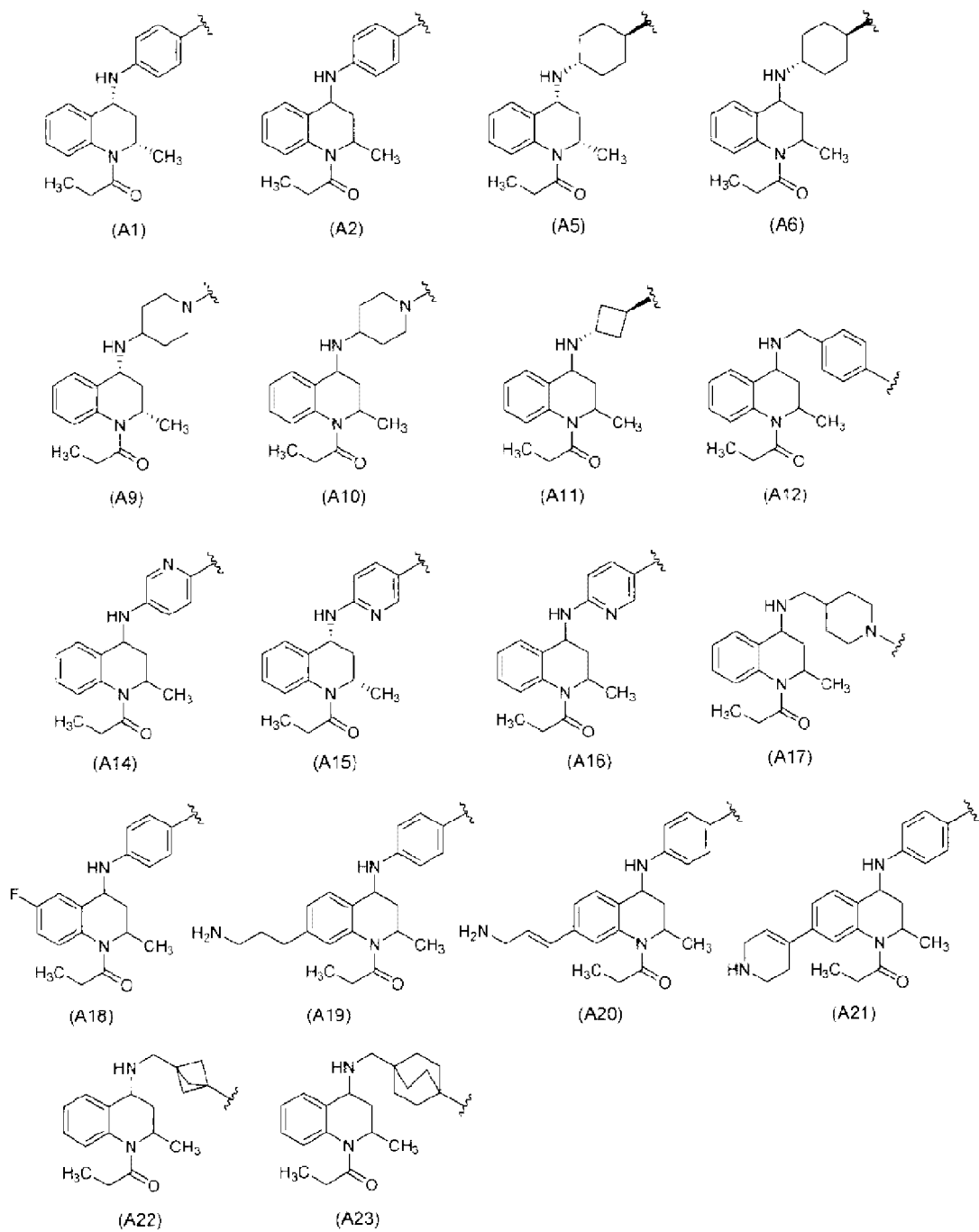
salt, it should be purified as it is, or in the case where compound (I) or compound (I)-1 is obtained in a free form, it should be dissolved or suspended in a suitable solvent and an acid or a base should be added to form a salt thereof, followed by isolation and purification.

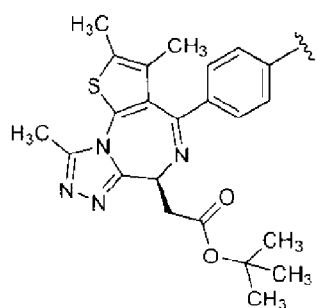
5 [0894]

Furthermore, compound (I), compound (I)-1 and a pharmaceutically acceptable salt thereof may sometimes be present in the form of an adduct with water or various solvents, but these adducts are also included in the present invention.

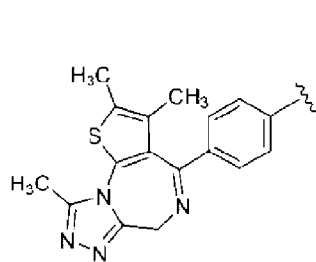
10 [0895]

Compound (I) and compound (I)-1 preferably includes compounds described in the following Tables 1 to 17. In addition, in the Tables, A1, A2, A5, A6, A9, A10, A11, A12, A14, A15, A16, A17, A18, A19, A20, A21, A22, A23, B1, B2, B3, B4, B5, B6, B7, B8, B9, C1, C2, C3, C4, D1, D2, D3,
15 D4, D5, E1, F1, F2, G1, H1, H2, H3, H4, H5, H6, J1, K1, K2, M1, M2 and N1, which are described as L¹ or L², have the following structures, respectively:

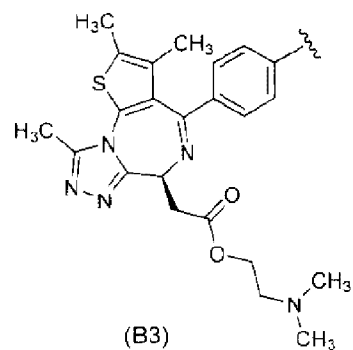




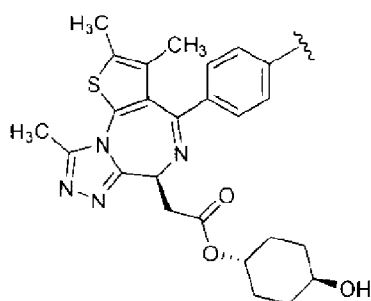
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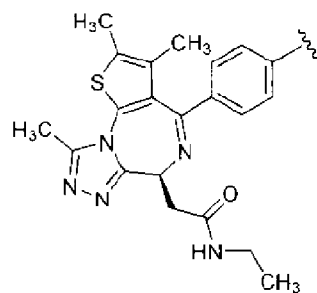
(B2)



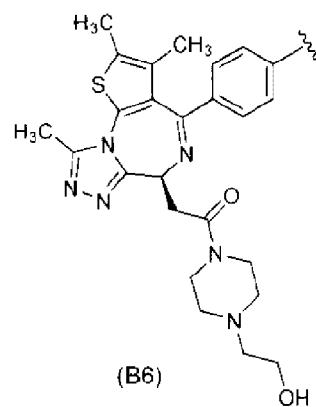
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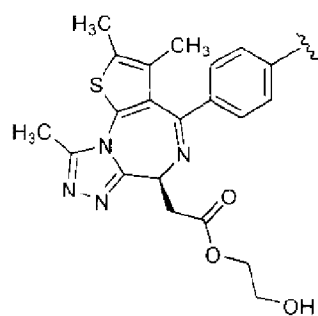
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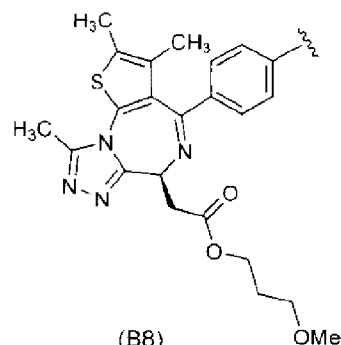
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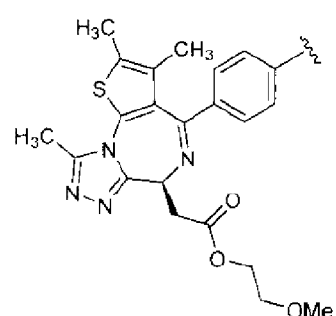
(B6)



(B7)



(B8)



(B9)

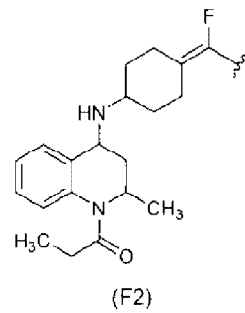
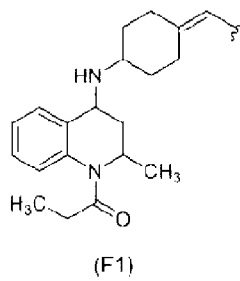
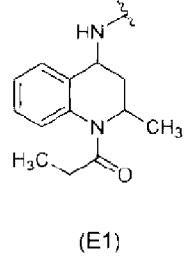
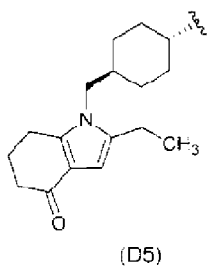
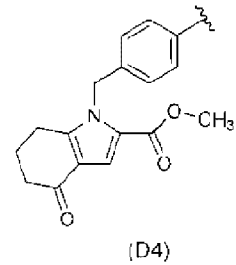
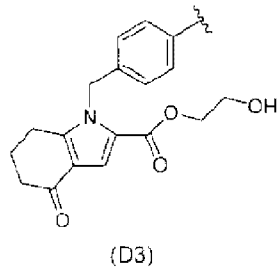
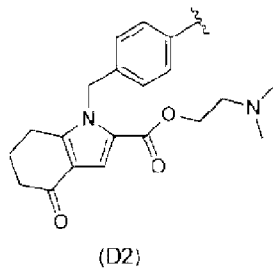
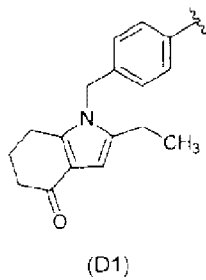
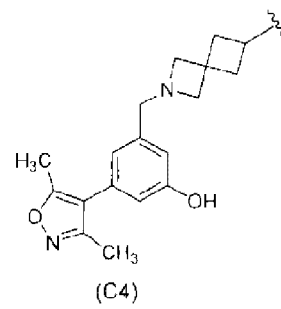
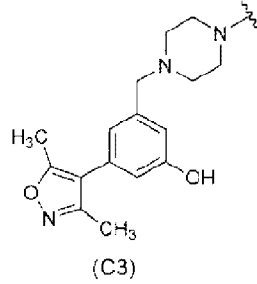
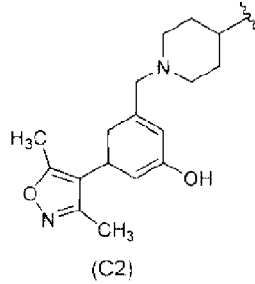
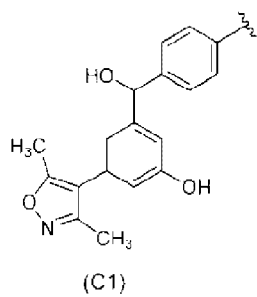


Table 1

Compound No	L ¹	L ²	S
1a	A1	A1	
1b	B1	B1	
1c	A2	A2	
1d	A2	C1	
1e	A2	D1	
1f	A2	B2	
1g	A2	A2	

Compound No	L ¹	L ²	S
1h	A1	B1	
1i	B1	B1	
1j	A1	A1	
1k	A1	A1	
1l	A1	A1	
1m	B2	A1	
1n	A1	B1	
1o	A1	B1	

[0897]

[Table 2]

Table 2

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
2a	A2	A2		2f	A2	A1	
2b	B1	B1		2g	A1	A2	
2c	A2	A1		2h	A1	A2	
2d	A2	A1		2i	A1	A2	
2e	A2	A1		2j	A1	A2	

[0898]

[Table 3]

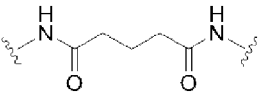
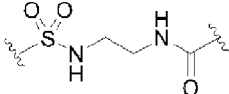
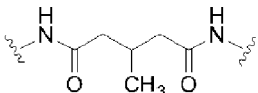
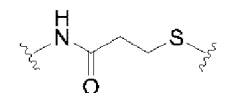
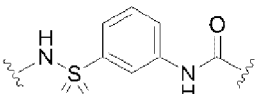
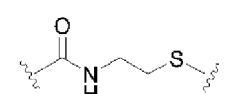
Table 3

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
3a	A1	A1		3d	A1	A1	
3b	B1	B1		3e	A1	A1	
3c	A1	A1		3f	A1	A1	

5 [0899]

[Table 4]

Table 4

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
4a	A2	A2		4d	A1	A1	
4b	A2	A2		4e	A2	A1	
4c	A2	A1		4f	A1	A1	

[0900]

[Table 5]

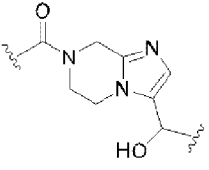
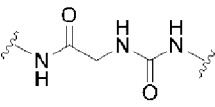
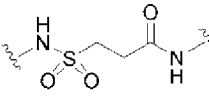
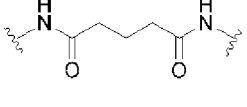
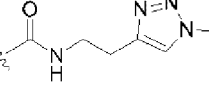
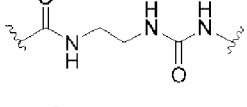
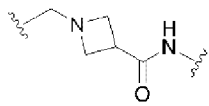
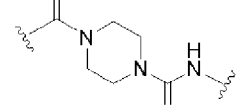
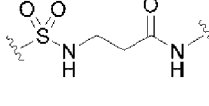
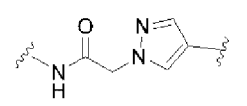
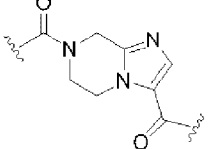
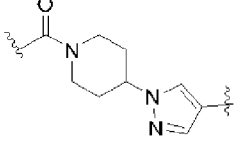
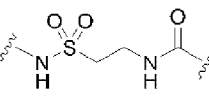
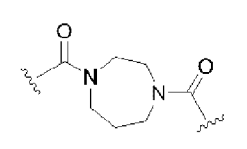
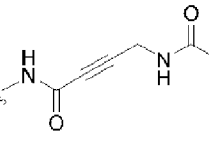
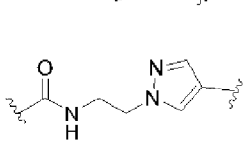
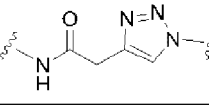
Table 5

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
5a	A1	A1		5j	A1	A1	
5b	A1	A1		5k	A1	A1	
5c	A1	A1		5l	A1	A1	
5d	A1	A1		5m	A1	A1	
5e	A1	A1		5n	A1	A1	
5f	A1	A1		5o	A1	A1	
5g	A1	A1		5p	A1	A1	
5h	A1	A1		5q	A1	A1	
5i	A1	A1		5r	A1	A1	

[0901]

[Table 6]

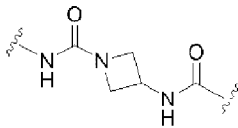
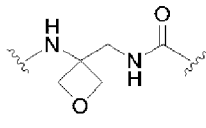
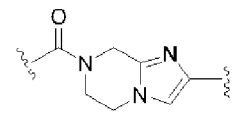
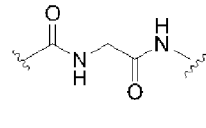
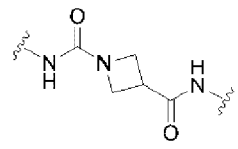
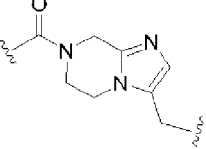
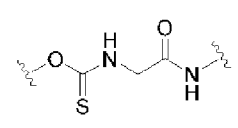
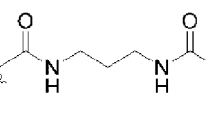
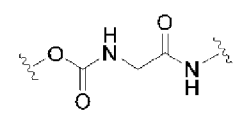
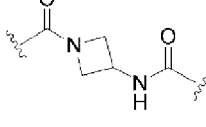
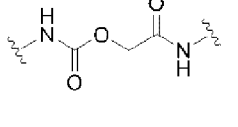
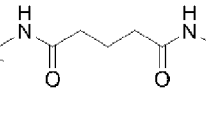
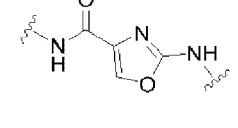
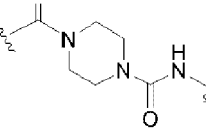
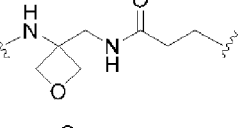
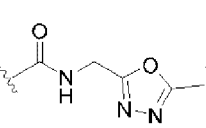
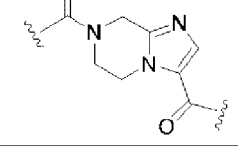
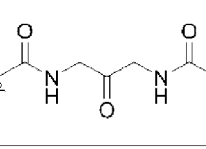
Table 6

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
6a	A1	A1		6j	A2	A2	
6b	A1	A1		6k	A1	A1	
6c	A1	A1		6l	A1	A2	
6d	A1	A1		6m	A1	A2	
6e	A1	A1		6n	A2	A1	
6f	A1	A1		6o	A1	A1	
6g	A1	A1		6p	A1	A1	
6h	A1	A1		6q	A1	A1	
6i	A2	A2					

[0902]

[Table 7]

Table 7

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
7a	A1	A5		7j	A5	A1	
7b	A6	A1		7k	A6	A1	
7c	A5	A1		7l	A6	A1	
7d	A6	A1		7m	A6	A1	
7e	A6	A1		7n	A6	A1	
7f	A5	A1		7o	A5	A1	
7g	A1	A5		7p	A5	A1	
7h	A5	A1		7q	A5	A1	
7i	A6	A1		7r	A6	A1	

[0903]

[Table 8]

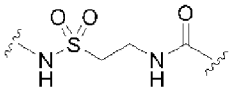
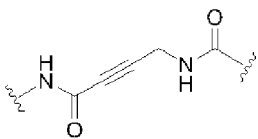
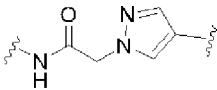
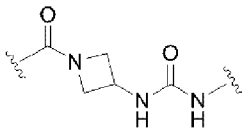
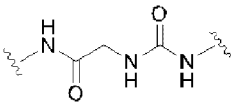
Table 8

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
8a	A5	A1		8j	A5	A1	
8b	A5	A1		8k	A6	A1	
8c	A5	A1		8l	A6	A1	
8d	A6	A1		8m	A5	A1	
8e	A6	A1		8n	A6	A1	
8f	A6	A1		8o	A6	A1	
8g	A1	A6		8p	A5	A1	
8h	A6	A1		8q	A6	A1	
8i	A6	A1		8r	A1	A5	

[0904]

[Table 9]

Table 9

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
9a	A6	A1		9d	A5	A6	
9b	A6	A1		9h	A5	A1	
9c	A6	A1					

[0905]

[Table 10]

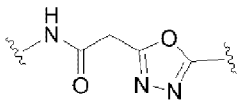
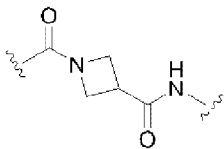
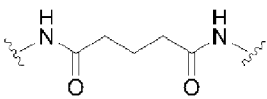
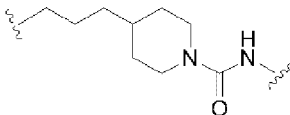
Table 10

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
10a	A9	A1		10l	A14	A1	
10b	A10	A1		10m	A1	A16	
10c	A9	A1		10n	A16	A1	
10d	A10	A1		10o	A16	A1	
10e	A10	A1		10p	A17	A1	
10f	A11	A1		10q	A18	A18	
10g	A12	A1		10r	A18	A18	
10h	A12	A1		10s	A19	A1	
10j	A1	A16		10t	A20	A1	
10k	A15	A1		10u	A21	A1	

[0906]

[Table 11]

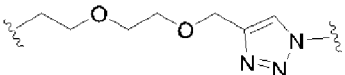
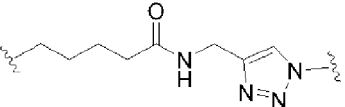
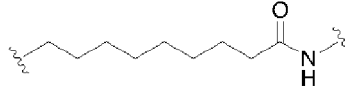
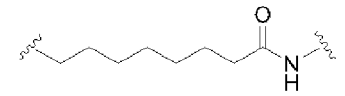
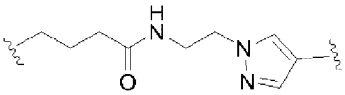
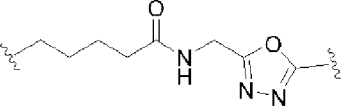
Table 11

Compound No	L ¹	L ²	S
12a	C2	A1	
12b	C2	A1	
12c	C2	A1	
12d	E1	A1	

[0907]

[Table 12]

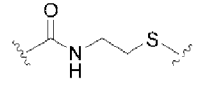
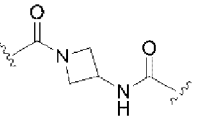
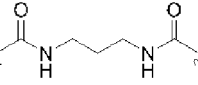
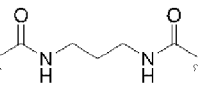
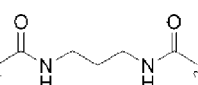
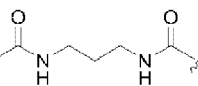
Table 12

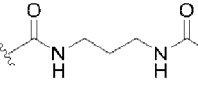
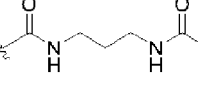
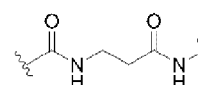
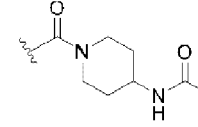
Compound No	L ¹	L ²	S
12e	E1	A1	
12f	E1	A1	
12g	E1	A1	
12h	E1	A1	
12i	E1	A1	
12j	E1	A1	

[0908]

[Table 13]

Table 13

Compound No	L ¹	L ²	S
13a	B3	A1	
13b	B3	A1	
13c	B3	A1	
13d	B4	A1	
13e	B5	A1	
13f	B6	A1	

Compound No	L ¹	L ²	S
13g	B7	A1	
13h	B8	A1	
13i	B1	A2	
13j	B1	A1	

[0909]

[Table 14]

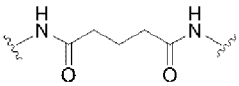
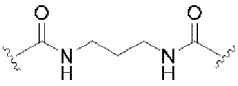
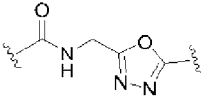
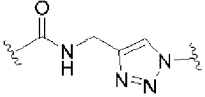
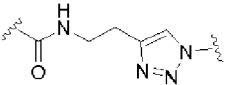
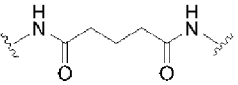
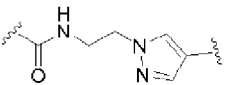
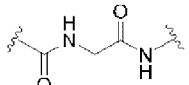
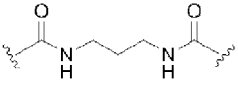
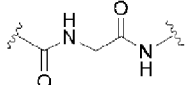
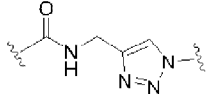
Table 14

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
14a	B2	A1		14j	A1	B2	
14b	B2	A1		14k	B2	A1	
14c	A6	B2		14l	B2	A1	
14d	B2	A1		14m	B2	A1	
14e	B2	B2		14n	B2	A1	
14f	A1	B2		14o	B2	B2	
14g	B2	A1		14p	B2	B1	
14h	B2	A1		14q	A1	B2	
14i	A1	B2		14r	B2	A1	
				14s	B2	A1	
				14t	B2	A2	

[0910]

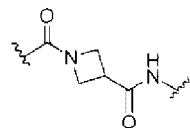
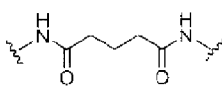
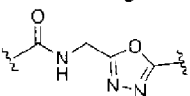
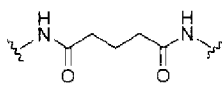
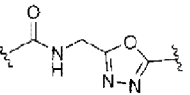
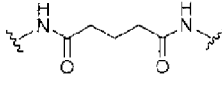
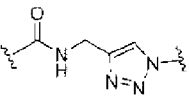
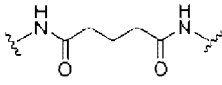
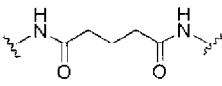
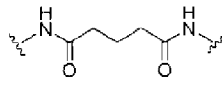
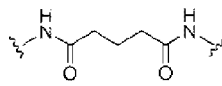
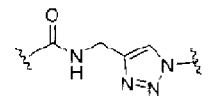
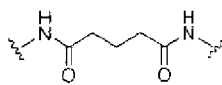
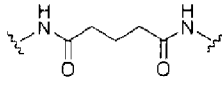
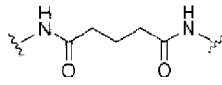
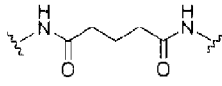
[Table 15]

Table 15

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
15a	D2	A1		15g	D4	A1	
15b	D2	A1		15h	A1	D1	
15c	D2	A1		15i	D1	A2	
15d	D2	A1		15j	F1	A1	
15e	D2	A1		15k	F2	A1	
15f	D1	A1					

[Table 16]

Table 16

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
16a	G1	A1		16i	A1	M1	
16b	G1	A1		16j	A1	H4	
16c	C3	A1		16k	A1	H6	
16d	C2	A1		16l	A1	H5	
16e	G1	A1		16m	A1	H3	
16f	A1	H2		16n	H4	A1	
16g	A1	C4		16o	A1	J1	
16h	A1	H1		16p	A1	K2	

[Table 17]

Table 17

Compound No	L ¹	L ²	S	Compound No	L ¹	L ²	S
17a	A1	K1		17i	C2	A1	
17b	A1	D5		17j	A1	C2	
17c	A1	M2		17k	C2	A1	
17d	H3	A1		17l	C2	A1	
17e	A1	A15		17m	A1	C2	
17g	A1	A16		17n	A22	A1	
17h	A5	A16		17o	A23	A1	
				17p	N1	A1	

[0911]

The BET degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof can be administered alone, but generally it is desirable to provide it as various pharmaceutical preparations. In addition, these pharmaceutical preparations are used for animals or humans, preferably humans.

[0912]

The pharmaceutical preparation related to the present invention can

contain as an active ingredient the BET degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof by itself, or as a mixture with any other active ingredients used for the treatment. Furthermore, those pharmaceutical preparations are
5 manufactured by a well-known method in the technical field of pharmaceuticals by mixing the active ingredient with one kind or more pharmaceutically acceptable carriers (e.g., an attenuant, a solvent, a diluent and the like).

[0913]

10 The most effective administration route is desirably used for the treatment. For example, it includes an oral or parental administration route such as intravenous injection and the like.

[0914]

Administration forms include, for example, tablets, injection and the
15 like.

[0915]

Suitable formulation for the oral administration, for example, such as tablets, can be manufactured using a diluent such as lactose, a disintegrant such as starch, a lubricant such as magnesium stearate, a
20 binder such as hydroxypropylcellulose, and the like.

[0916]

Suitable formulation for the parenteral administration, for example, such as injection, can be manufactured using an attenuant such as a salt solution, glucose solution or mixed solution of saline and glucose solutions;
25 a solvent or the like.

[0917]

Dose and frequency of administration of the BET degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof differ depending on administration form, age of the
30 patient, body weight or the nature of the symptoms to be treated or severity

of them or the like. Generally, they are administered for oral administration at a dosage of 0.01 to 1000 mg per adult, preferably at a dosage of 0.05 to 100 mg once daily or several times a day. In the case of parenteral administrations such as intravenous administration, they are administered
5 at a dosage of 0.001 to 1000 mg per adult, preferably at a dosage of 0.01 to 100 mg once daily or several times a day. However, the dose and frequency of the administration vary depending on the above-mentioned conditions.

[0918]

10 According to another embodiment of the present invention, provided is a pharmaceutical composition containing the BET degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof, which pharmaceutical composition may contain a carrier. The pharmaceutical composition of the present invention is used in
15 administration routes and dosage forms and the like similar to the pharmaceutical preparation mentioned above. Furthermore, the carrier that may be contained in the pharmaceutical composition of the present invention may be an attenuant, solvent, diluent, and the like that are similar to the case of the pharmaceutical preparation mentioned above.
20 Furthermore, the pharmaceutical composition of the present invention is used preferably for degrading BET protein, or for the treatment or prevention of cancer, more preferably for the treatment or prevention of cancer. Here, prevention means that the clinical condition of a disease, the outcome of biological symptoms or the severity of the disease is
25 substantially reduced, or that development of such condition or the biological symptoms is delayed, and the like. The situation is similar to the following prevention.

[0919]

According to another embodiment of the present invention, there is
30 provided a method for degrading BET (protein) (preferably a method for

inducing BET (protein) degradation), including administering compound (I) or compound (I)-1 or a pharmaceutically acceptable salt thereof (preferably a prophylactically or therapeutically safe and effective amount of compound (I) or compound (I)-1 or a pharmaceutically acceptable salt thereof) to a
5 subject (preferably a subject in need thereof). The subject includes an animal other than a human, but is preferably a human. This is also the same in the following subjects.

[0920]

According to another embodiment of the present invention, there is
10 provided a method for treatment or prevention, including administering the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof (preferably a prophylactically or therapeutically safe and effective amount of the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically
15 acceptable salt thereof) to a subject (preferably a subject in need thereof). The method for treatment or prevention of the present invention is preferably used for degrading BET protein or for the treatment or prevention of cancer, and more preferably for the treatment or prevention of cancer.

20 [0921]

According to another embodiment of the present invention, there is provided the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof for use as a medicament.

[0922]

25 According to another embodiment of the present invention, there is provided the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof for use for the degradation of BET protein (preferably for use for inducing degradation of BET protein), or for use in the treatment or prevention of cancer (preferably
30 for use in the treatment or prevention of cancer).

[0923]

According to another embodiment of the present invention, there is provided use of the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof for the manufacture of a drug for degradation of BET protein (preferably for inducing degradation of BET protein), or for the treatment or prevention of cancer (preferably for the treatment or prevention of cancer).

[0924]

According to another embodiment of the present invention, there is provided use of the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof for the degradation of BET protein (preferably for inducing degradation of BET protein), or for the treatment or prevention of cancer (preferably for the treatment or prevention of cancer).

[0925]

According to another embodiment of the present invention, there is provided a medicament containing as an active ingredient the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof.

[0926]

According to another embodiment of the present invention, there is provided a BET degrader or a prophylactic or therapeutic agent for cancer (preferably a prophylactic or therapeutic agent for cancer) containing as an active ingredient the degrader of the present invention or compound (I), compound (I)-1 or a pharmaceutically acceptable salt thereof.

EXAMPLES

[0927]

The present invention will be explained by examples more specifically below, but the scope of the present invention is not limited to

these examples.

[0928]

Among compounds (I) and compounds (I)-1, the pharmacological action of typical compounds will be specifically described with reference to
5 test examples.

[0929]

[Test Example 1]

Inhibitory effect on cell viability in SU-DHL-4 cell line

SU-DHL-4 cells (Code No. ACC 495, Deutsche Sammlung von
10 Mikroorganismen und Zellkulturen GmbH; DSMZ) were cultured at 37°C using a carbon dioxide incubator (95% air, 5% CO₂) in RPMI1640 medium (Code No. 11875-093, Thermo Fisher Scientific) in which inactivated fetal bovine serum (FBS: Code No. 10099-148, Thermo Fisher Scientific) in an amount to give a final concentration of 10 vol% and penicillin/streptomycin
15 solution (PS: Code No. 15140-122, Thermo Fisher Scientific) in an amount to give a final concentration of 1 vol% were added. The cells were passaged twice a week at a volume of 20-40 mL so as to maintain a cell concentration of 1×10⁶ cells/mL or less.

[0930]

20 The cultured SU-DHL-4 cells were seeded at 2000 cells/well in a transparent 384-well plate (Code No. 781182, Greiner bio-one). After seeding, the cells were precultured at 37°C in a carbon dioxide gas incubator for 18 to 25 hours. Next, 1, 0.1 or 0.01 mmol/L DMSO solution of the test compound was prepared and a 9-step dilution series were
25 prepared so that the concentration will be 200 times the final concentration in the RPMI1640 medium containing the above FBS and PS, and 1/200 volume of the dilution series were added to each well. At this time, the final concentration of DMSO was adjusted to be 0.1vol %. After adding the test compound, the cells were cultured at 37°C in a carbon dioxide gas
30 incubator for 72 hours. Next, 0.020 mL of Cell Counting Kit-8 (Code No.

CK04, DOJINDO) solution diluted 2-fold or 4-fold with phosphate buffered saline (PBS) was added to each well. Color reaction was carried out in a carbon dioxide gas incubator at 37°C for 2 to 3 hours, and the absorbance at a wavelength of 450 nm was measured using SpectraMax 340PC (Molecular Devices). The inhibition rate of cell viability was calculated by the following formula, and the concentration of the test compound (IC₉₀ value) showing a 90% inhibition rate of cell viability was calculated.

$$\text{Inhibition rate of cell viability (\%)} = 100 - (A - B) / (C - B) \times 100$$

A: Absorbance of a well containing test compound

B: Absorbance of a well without addition of cells

C: Absorbance of a well without addition of test compound

[0931]

The results are shown in Table 18.

[Table 18]

Compound No.	SU-DHL-4 Cell Viability Inhibition Rate IC ₉₀ (nmol/L)
1a	5.21
1b	1.78
1c	7.85
1d	38.0
1e	39.8
1f	4.78
1g	10.6
1h	0.27
1i	0.54
1j	33.1
1k	0.55
1l	0.04
1m	0.53
1n	0.49
1o	3.18
2a	2.12
2b	1.52
2c	29.1

2d	26.6
2e	16.3
2f	0.23
2g	0.63
2h	0.03
2i	1.84
2j	0.36
3a	0.04
3b	0.18
3c	0.11
3d	0.11
3e	0.12
3f	0.33
4a	0.45
4b	5.87
4c	4.03
4d	13.0
4e	0.34
4f	1.19
5a	2.15
5b	39.56
5c	63.60
5d	0.67
5e	5.93
5f	24.73
5g	2.53
5h	0.12
5i	4.49
5j	0.08
5k	7.48
5l	36.95
5m	0.59
5n	8.83
5o	0.14
5p	2.68
5q	0.11
5r	1.78
6a	0.89
6b	0.10

6c	0.83
6d	5.08
6e	4.31
6f	0.11
6g	0.31
6h	0.003
6i	0.11
6j	0.13
6k	0.15
6l	0.35
6m	0.12
6n	0.13
6o	0.14
6p	41.54
6q	0.45
7a	10.83
7b	1.51
7c	7.00
7d	25.87
7e	20.42
7f	3.20
7g	7.56
7h	5.47
7i	0.33
7j	63.96
7k	0.62
7l	0.28
7m	20.30
7n	13.86
7o	1.15
7p	0.79
7q	0.24
7r	0.38
8a	0.87
8b	13.90
8c	0.26
8d	0.14
8e	0.20
8f	1.14

8g	0.01
8h	1.14
8i	2.69
8j	0.50
8k	0.26
8l	0.04
8m	0.11
8n	1.17
8o	0.49
8p	14.99
8q	19.01
8r	0.47
9a	1.68
9b	3.18
9c	12.36
9d	0.93
9h	7.16
10a	2.40
10b	0.60
10c	0.13
10d	3.42
10e	3.59
10f	0.92
10g	1.15
10h	0.35
10j	1.73
10k	0.93
10l	1.08
10m	30.87
10n	0.01
10o	1.48
10p	47.49
10q	9.88
10r	9.16
10s	21.69
10t	26.33
10u	15.92
12a	1.01
12b	4.35

12c	0.56
12d	34.92
12e	73.65
12f	0.42
12g	31.08
12h	3.92
12i	3.68
12j	17.40
13a	0.49
13b	3.50
13c	7.36
13d	1.19
13e	3.33
13f	11.62
13g	1.70
13h	0.34
13i	3.37
13j	0.31
14a	0.04
14b	0.12
14c	0.34
14d	0.16
14e	0.26
14f	0.31
14g	0.03
14h	0.34
14i	0.03
14j	0.74
14k	1.80
14l	0.60
14m	1.45
14n	0.05
14o	30.87
14p	1.27
14q	0.17
14r	1.47
14s	2.20
14t	1.17
15a	0.34

15b	1.07
15c	0.30
15d	0.16
15e	33.97
15f	0.04
15g	5.03
15h	2.32
15i	0.88
15j	0.52
15k	0.32
16a	11.14
16b	2.05
16c	0.28
16d	0.17
16e	5.97
16f	24.56
16g	14.93
16h	68.44
16i	7.84
16j	3.09
16k	0.90
16l	89.83
16m	1.85
16n	0.48
16o	80.35
16p	0.63
17a	0.16
17b	1.74
17c	2.05
17d	0.13
17e	1.82
17g	32.68
17h	0.20
17i	1.45
17j	28.98
17k	43.66
17l	1.89
17m	74.08
17n	5.14

17o	2.18
17p	0.35
Comparative Compound 1	2557.75
Comparative Compound 2	>10000

[0932]

As described above, compound (I) and compound (I)-1 of the present invention represented by the test compound showed a strong inhibitory effect on cell viability in SU-DHL-4 cells. In addition, the inhibition rate was far stronger than that of the known comparative compounds 1 and 2. Therefore, compound (I) and compound (I)-1 of the present invention were found to be useful for preventing or treating cancer.

[0933]

The comparative compound 1 is described as example 14 (2,2'-((4S,4'S)-6,6'-((butane-1,4-diylbis(sulfanediy))bis(4,1-phenylene))bis(8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine-6,4-diyl))bis(N-ethylacetamide)) (corresponding to the compound represented by formula (P3) (compound P3)) in Patent Document 2 (WO 2015/081284). The comparative compound 2 is a compound described as MT1 (corresponding to the compound represented by formula (P5)) in Patent Document 3 (WO 2017/091673). The comparative compounds were synthesized according to the methods described in Patent Documents 2 and 3, respectively, and used in this test.

[0934]

[Test Example 2]

Suppressive effect on MYC mRNA expression

SU-DHL-4 cells were cultured at 37°C using a carbon dioxide gas incubator (95% air, 5% CO₂) in RPMI1640 medium in which FBS in an amount to give a final concentration of 10 vol% and PS in an amount to give a final concentration of 1 vol% were added. The cells were passaged twice a week at a volume of 20-40 mL so as to maintain a cell concentration

of 1×10^6 cells/mL or less.

The cultured SU-DHL-4 cells were seeded at 6×10^5 cells/well in a transparent 6-well plate (Code No. 140675, Thermo Fisher Scientific). After seeding, the cells were precultured at 37°C in a carbon dioxide gas incubator for 18 to 25 hours. Next, a 0.1 mmol/L DMSO solution of the test compound was prepared, diluted so that the concentration will be 200 times the final concentration in the RPMI1640 medium containing the above FBS and PS, and 1/200 volume of the diluted solution was added to each well. At this time, the final concentration of DMSO was adjusted to be 0.1 vol%. After adding the test compound, the cells were cultured at 37°C in a carbon dioxide gas incubator for 6 hours.

[0935]

Then, the cells were collected by centrifugation and used for extraction of mRNA. mRNA extraction from cells was performed using Maxwell^(R) 16 LEV simplyRNA Purification Kits (Code No. AS1270, Promega). The mRNA recovery protocol was performed according to the manufacturer's recommended protocol attached to the kit.

0.001 mg of the recovered mRNA was converted to cDNA by SuperScript IV VILO Master Mix with ezDNase Enzyme (Code No. 11766050, Thermo Fisher Scientific). The cDNA conversion was performed, according to the manufacturer's recommended protocol attached to the kit, in 0.020 mL of the reaction solution, and GeneAmp^(R) PCR System 9700 (Applied Biosystems) was used. The cDNA-converted sample was diluted 10-fold by adding 0.180 mL of RNase Free Water (Code No. 10977-023, Thermo Fisher Scientific) and used for quantitative real-time polymerase chain reaction (qRT-PCR). For the calibration curve of qRT-PCR, 0.08 mL of RNase Free Water was added to a cDNA sample using DMSO as a test compound for 5-fold dilution. Further, two 5-fold dilutions were prepared stepwise, and these three samples were used as the calibration curve samples.

[0936]

The following reagents were used for qRT-PCR: TaqMan Gene Expression Assays, Inventoried (Primer probe: Code No. 4331182, Thermo Fisher Scientific, Assay ID: (i) MYC: Hs00153408_m1, (ii) ACTB: Hs01060665_g1, (iii) GAPDH: Hs04420697_g1, (iv) HPRT1: Hs02800695_m1); 2X TaqManR Fast Universal PCR Master Mix, no AmpEraseR UNG (Master Mix: Code No. 4367846, Thermo Fisher Scientific).

[0937]

Primer probe (0.001 mL), Master Mix (0.010 mL), water (0.004 mL) and the diluted cDNA sample (0.005 mL) were mixed, and qRT-PCR analysis was performed. For qRT-PCR analysis, QuantStudio 7 Flex (Thermo Fisher Scientific) or 7500 Fast Real-Time PCR (Applied Biosystems) was used to measure in Fast mode and analyze. The expression level of the MYC gene was determined by quantifying ACTB, GAPDH, and HPRT1 as housekeeping genes and correcting by the following formula to calculate the suppression rate of (%) of MYC mRNA expression when the test compound was allowed to act at a concentration of 100 nmol/L.

Corrected MYC expression = A/B

A: MYC expression level

B: Geometric mean of expression levels of ACTB, GAPDH and HPRT1

Using the corrected values, the suppression rate of MYC expression for the wells to which the test compound was not added was calculated by the following formula.

Suppression rate of MYC expression (%) = $100 - C/D \times 100$

C: Corrected MYC expression level in a well containing test compound

D: Corrected MYC expression level in a well to which test compound was not added

[0938]

The results are shown in Table 19.

[Table 19]

Compound No.	Suppression Rate of MYC mRNA Expression (%)
1a	96.7
1b	98.4
1c	97.3
1k	98.6
1l	98.5
2d	80.0
2f	98.6
2h	98.2
3a	98.1
3e	98.3
4a	98.4
4d	98.3
4e	98.4
5d	97.5
5h	97.3
5j	96.8
5q	97.2
5r	96.7
6h	97.2
6k	97.0
6m	97.0
7h	97.5
7o	97.4
7p	97.9
7q	97.4
8g	96.6
8j	97.2
8r	96.7
9d	98.0
10b	96.6
10g	97.2
10k	97.0
12a	98.5
12b	97.8

12c	97.8
12f	97.9
12h	96.5
13a	97.6
13d	97.2
13h	97.4
14a	97.1
14d	97.4
14e	96.7
14f	97.3
14p	97.6
15a	97.6
15d	96.9
15f	97.2
15k	97.4
16j	92.4
16m	97.1
16o	79.1
16p	96.2
17a	96.2
17o	97.1
Comparative Compound 1	61.7
Comparative Compound 2	57.7

[0939]

As described above, compound (I) and compound (I)-1 of the present invention represented by the test compound strongly suppressed the expression of MYC mRNA. Further, the suppression rate was far stronger than that of the known comparative compounds 1 and 2. Therefore, the compound (I) and compound (I)-1 of the present invention were found to be useful for preventing or treating cancer.

[0940]

Comparative compound 1 is a compound described as example 14 in Patent Document 2 (WO 2015/081284), and comparative compound 2 is a compound described as MT1 in Patent Document 3 (WO 2017/091673). Each of comparative compounds was synthesized according to the method

described in Patent Document 2 or 3, and used in this test.

[0941]

[Test Example 3]

Antitumor effect on subcutaneous transplant model in SCID mouse DLBCL strain SU-DHL-4

1×10^7 cells of DLBCL strain SU-DHL-4 (Code No. ACC 495, Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) suspended in a 1:1 mixed solution of PBS and matrigel (CORNING Code No. 354234) were transplanted subcutaneously to the ventral side of a male SCID mouse.

Eighteen days after the transplantation, the body weight and the tumor diameter were measured, the tumor volume was calculated by the following formula, and the mice were divided into two groups (n=5) so that the average tumor volume of each group was equal.

$$[\text{Tumor volume (mm}^3\text{)}] = [\text{Tumor long diameter (mm)}] \times [\text{Tumor short diameter (mm)}]^2 \times 0.5$$

The test was conducted in two groups, a vehicle administration group and a compound 1a administration group (compound administration group). To the compound 1a administration group, a solution of compound 1a dissolved in 30% DMSO/3% Tween 80/physiological saline so as to give a final concentration of 0.6 mg/mL was administered intravenously (tail vein) at 5 mL/kg (3 mg/kg) 5 times a week for 2 weeks. To the vehicle administration group, 30% DMSO/3% Tween 80/physiological saline was administered intravenously (tail vein) at 5 mL/kg on the same schedule as the compound 1a administration group. After the start of the test, body weight and tumor diameter were measured twice a week. The tumor volume on each measurement day was calculated by the above formula. The tumor growth rate (hereinafter referred to as V/V₀) was calculated by dividing the tumor volume V on each measurement day by the tumor volume V₀ on the test start day (Day 0). The T/C was calculated by dividing the average value (T) of V/V₀ of each group by the average value (C) of

the vehicle administration group.

[0942]

The results are shown in Table 20 below (mean values of n=5 are shown).

5 [Table 20]

Measure- ment Day	Tumor Volume (mm ³)		V/V0	
	Vehicle Administration Group	Compound Administration Group	Vehicle Administration Group	Compound Administration Group
Day0	245.49	246.14	1.00	1.00
Day3	396.59	284.29	1.62	1.15
Day7	654.80	326.25	2.68	1.29
Day10	923.83	214.74	3.80	0.85
Day14	1288.10	224.55	5.30	0.89
Day18	1951.98	325.61	8.00	1.30

Measure- ment Day	T/C		Body Weight (g)	
	Vehicle Administration Group	Compound Administration Group	Vehicle Administration Group	Compound Administration Group
Day0	1.00	1.00	24.14	24.56
Day3	1.00	0.71	23.87	25.36
Day7	1.00	0.48	23.98	25.44
Day10	1.00	0.22	23.66	25.14
Day14	1.00	0.17	23.71	25.74
Day18	1.00	0.16	23.53	26.23

[0943]

10 As described above, the tumor volume, tumor growth rate and T/C of the compound 1a administration group were smaller than those of the vehicle administration group. On the other hand, no weight loss was observed by the compound 1a administration group. That is, compound 1a showed a potent antitumor effect on SU-DHL-4 subcutaneously transplanted tumor. Therefore, the compound (I) and compound (I)-1 of the present invention represented by the test compound were found to be useful as a therapeutic drug for cancer.

15

[0944]

[Test Example 4]

Evaluation of BET proteolysis in SU-DHL-4 cell line by Western blotting (WB)

(1) Reagents and media

The human DLBCL cell line SU-DHL-4 was purchased from DSMZ.

5 SU-DHL-4 was passaged using RPMI1640 medium containing 10 vol% FBS.

The culture conditions were 37°C and 5% CO₂.

[0945]

(2) The following antibodies were used for protein detection.

Primary antibody

10 Anti-BRD4 antibody: BRD4 (E2A7X) Rabbit mAb (Cell Signaling Technology, Cat No. #13440S)

Anti-BRD2 antibody: Brd2 (D89B4) Rabbit mAb (Cell Signaling Technology, Cat No. #5848S)

15 Anti-BRD3 antibody: Anti-BRD3 antibody (2088C3a) (Santa Cruz Biotechnology, Cat No. sc-81202)

Anti-beta actin antibody: Monoclonal Anti-β Actin antibody produced in mouse (SIGMA, Cat No. A5441)

Secondary antibody

20 Anti-Mouse IgG, HRP-Linked Whole Ab Sheep (GE Healthcare, Cat No. NA931-1ML)

Anti-Rabbit IgG, HRP-Linked Whole Ab Donkey (GE Healthcare, Cat No. NA934-1ML)

[0946]

(3) Evaluation of BET protein

25 Changes in the amount of BRD4, BRD2 and BRD3 proteins in the SU-DHL-4 cell line by the test compound (compound 1b, compound 1l or compound P3) were detected by WB. The compound P3 is a compound described as example 14 in the known Patent Document 2 (WO 2015/081284), which was synthesized according to the method described
30 in Patent Document 2 and used in this test.

The cultured SU-DHL-4 cells were seeded at 6×10^5 cells/well in a transparent 6-well plate (Code No. 140675, Thermo Fisher Scientific). After seeding, the cells were pre-cultured at 37°C in a carbon dioxide gas incubator for 18 to 25 hours. Next, a 0.1 mmol/L DMSO solution of the test compound was prepared, diluted so that the concentration was 200-fold of the final concentration in RPMI1640 medium containing the above FBS and PS, and 1/200 volume of the diluted solution was added to each well. At this time, the final concentration of DMSO was adjusted to be 0.1 vol%. After adding the test compound, the cells were cultured at 37°C in a carbon dioxide gas incubator for 24 hours.

[0947]

After collecting the cells, the supernatant was aspirated, and Lysis buffer 6 (R&D systems, Cat No. 895561) was added to the pellet at 0.1 mL/sample. After incubating on ice for 60 minutes, the supernatant was collected by centrifugation at 15000 rpm for 10 minutes at 4°C.

[0948]

Using Pierce BCA Protein Assay Kit (Thermo Fisher, Cat No.23225), the protein concentration of each sample was quantified according to the manual attached to the kit, and then was diluted and prepared with Lane Marker Reducing Sample Buffer (5x) (Thermo Fisher, Cat No. 39000) and Lysis buffer 6 to 1 mg/mL. The cells were incubated at 95°C for 5 minutes to prepare WB samples. WB samples were stored at -30°C until electrophoresis.

[0949]

The WB sample was thawed and used after vortex mixing and spin down. As a gel for electrophoresis, SuperSep Ace, 5-20% 17 well (Wako, Cat No. 194-15021) was used. Samples were added at 0.010 mL/well (protein content 0.01 mg/well) and proteins were separated by SDS-PAGE.

[0950]

Proteins were transferred from the electrophoresed gel to an

Immobilon-P Transfer membrane (Merck Millipore, Cat No. IPVH304F0) using a semi-dry transfer device (ATTO, Cat No. WSE-4020) (100 mA/gel, 60 minutes).

[0951]

5 The transfer membrane was soaked for blocking in 1X TBS TweenTM-20 (TBS-T, Thermo Scientific, Cat No.28360) containing 5 w/v% skim milk (nakarai, Cat No. 31149-75) (hereinafter, referred to as 5% skim milk -TBS-T) for 1 hour.

[0952]

10 As a primary antibody reaction, BRD4 and BRD2 antibodies were diluted 1000-fold with 5% skim milk-TBS-T and reacted overnight at 4°C. Beta actin antibody was diluted 2000-fold with 5% skim milk-TBS-T and reacted overnight at 4°C. BRD3 antibody was diluted 200-fold with Can Get Signal Solution 1 (TOYOBO, Cat No. NKB-201) and reacted at 4°C
15 overnight.

[0953]

 As a secondary antibody reaction for BRD4 and BRD2 antibodies, Anti-Rabbit IgG and HRP-Linked Whole Ab Donkey antibodies were diluted 5000-fold with 5% skim milk-TBS-T and reacted for 1 hour. As a secondary
20 antibody reaction for BRD3 and beta actin antibodies, Anti-Mouse IgG, HRP-Linked Whole Ab Sheep antibodies were diluted 5000-fold with 5% skim milk-TBS-T and reacted for 1 hour.

[0954]

 As a luminescent agent, SuperSignal West Femto Maximum
25 Sensitivity Substrate (Thermo Fisher, Cat No. #34096) was used to detect BRD4, BRD2 and BRD3, and SuperSignal West Pico Chemiluminescent Substrate (Thermo Fisher, Cat No. #34080) was used to detect beta actin, and the detection was performed using Amersham imager 600 imagers (AI600, GE Healthcare Life Sciences) . The results are shown in FIG. 1.

30 [0955]

As shown in FIG. 1, in the group to which compound 1b or compound 1l was added, the band became faint compared with that of control, and thus the compound of the present invention represented by the test compound was shown to induce degradation of BET proteins such as BRD2, BRD3 and BRD4 and the like. On the other hand, in the group to which compound P3 was added, the band was not faint compared with that of control, and known divalent BET inhibitors represented by compound P3 was shown not to degrade BET proteins such as BRD2, BRD3 and BRD4 and the like.

[0956]

[Test Example 5]

Evaluation of inhibition of BRD2, BRD3 and BRD4 degradation by ubiquitination pathway inhibitors (MLN-4924)

SU-DHL-4 cells were cultured in the same manner as in test example 4 and seeded in a 6-well plate, and MLN-4924 (Funakoshi Co., Ltd., Cat No. 15217) and the test compound (Compound 1b or Compound 1l) was diluted to 200-fold of the final concentration and 1/200 volume of the diluted solution was added to each well. MLN-4924 was added 1 hour before the addition of the test compound. At this time, the final concentration of DMSO was adjusted to be 0.1 vol%. After adding the test compound, the cells were cultured in a carbon dioxide gas incubator at 37°C for 16 hours. After collecting the cells, changes in the amount of BRD4, BRD2 and BRD3 proteins were detected by WB in the same manner as in test example 4. The results are shown in FIG. 2.

[0957]

As shown in FIG. 2, in the group to which MLN-4924 was added, the band became stronger, and thus the degradation of BET proteins such as BRD2, BRD3 and BRD4 by the compound of the present invention represented by the test compound was shown to be attenuated by the ubiquitin pathway inhibitor. That is, it was found that the degrading action

of BET proteins such as BRD2, BRD3 and BRD4 by the compound of the present invention depends on the ubiquitin pathway.

[0958]

[Test Example 6]

- 5 Inhibitory effect on cell viability using SU-DHL-4 DCAF16 knock out (KO) cell line

(1) Reagents and media

The human DLBCL cell line SU-DHL-4 was purchased from DSMZ. SU-DHL-4 was passaged using RPMI1640 medium containing 10 vol% FBS.

- 10 After the Cas9 gene was introduced, the cells were cultured in the above medium containing 0.01 mg/mL blasticidin (InvivoGen, Cat No. ant-bl-1). After introduction of sgRNA, the cells were cultured in the above medium containing 0.001 mg/mL puromycin dihydrochloride (SIGMA, Cat No. P9020-10 ML). The culture conditions were 37°C and 5% CO₂.

15 [0959]

(2) Lentivirus

Edit-R Lentiviral hEF1α-Blast -Cas9 Nuclease Particles (Cat No. VCAS10126) was used as a lentivirus for expressing Cas9 in human cell lines. Three types of Edit-R Human DCAF16 Lentiviral sgRNA (Cat
20 No.VSGH10142-246568260; DNA target sequence CGCCTCTTGAGAGTCTTGCC (SEQ ID NO: 1), Cat No. VSGH10142-246568262; DNA target sequence GTTGTATCATGCTAAACTGT (SEQ ID NO: 2) and Cat No. VSGH10142-246568263; DNA target sequence AGAGATCATGCCACTCTAAA (SEQ ID NO: 3)) were used as lentiviruses for
25 introducing DCAF16 sgRNA. As a control, Edit-R Lentiviral sgRNA Non-targeting Control #1 (Cat No. VSGC10215) was used. All lentiviruses were purchased from Dharmacon and stored at -80°C until use.

[0960]

(3) The following antibodies were used to detect DCAF16.

- 30 (i) Primary antibody: Anti-DCAF16 antibody (in-house monoclonal

antibody produced by immunizing mice with DCAF16 full-length protein denatured by SDS and heat)

(ii) Secondary antibody: Anti-Mouse IgG, HRP-Linked Whole Ab Sheep (GE Healthcare, Cat No. NA931-1ML)

5 [0961]

(4) The following antibodies were used to detect beta actin.

(i) Primary antibody: Monoclonal Anti- β Actin antibody produced in mouse (SIGMA, Cat No. A5441)

(ii) Secondary antibody: Anti-Mouse IgG, HRP-Linked Whole Ab Sheep (GE Healthcare, Cat No. NA931-1ML)

10 [0962]

(5) Introduction of Cas9 gene

SU-DHL-4 was suspended at 4×10^5 cells/mL in RPMI 1640 without FBS, 0.25 mL of the suspension was added to a 24-well plate, and the cells were cultured overnight. The next day, 0.003 mL of virus particles of Edit-R Lentiviral hEF1 α -Blast -Cas9 Nuclease Particles was added. After culturing in a CO₂ incubator for 4 hours, RPMI 1640 containing 0.75 mL of 10 vol% FBS was added. After culturing in a CO₂ incubator for about 48 hours, the medium was replaced with RPMI1640 containing 10 vol% FBS, and the cells were cultured in a CO₂ incubator. Four days after infection, the medium was replaced with a medium containing 0.01 mg/mL blasticidin (InvivoGen, Cat No. ant-bl-1). Then, the cells were passaged once every 2 to 3 days and thus twice in total (that is, cultured for 1 week) to obtain SU-DHL-4/Cas9, which is a Cas9-introduced SU-DHL-4 cell line.

25 [0963]

(6) sgRNA infection

SU-DHL-4/Cas9 was suspended at 4×10^5 cells/mL in RPMI 1640 without FBS, 0.25 mL of the suspension was added to a 24-well plate, and the cells were cultured overnight. The next day, a total of 4 types of sgRNA virus particles, 1 type of Control and 3 types targeting DCAF16 were added

to the respective wells by 0.03 mL. After culturing in a CO₂ incubator for 5 hours, RPMI 1640 containing 0.75 mL of 10 vol% FBS was added.

[0964]

After culturing in a CO₂ incubator for about 48 hours, the medium
5 was replaced with RPMI1640 containing 10 vol% FBS, and the cells were
cultured in a CO₂ incubator. Four days after infection, the medium was
replaced with a medium supplemented with 0.01 mg/mL puromycin
dihydrochloride (SIGMA, Cat No. P9020-10 ML). Then, the cells were
10 passaged once or twice a week for 2 weeks, and a cell stock was prepared
using CELLBANKER I plus (Takara Bio, Cat No. CB-021). Cell line stock was
stored at -80°C. Using Edit-R Lentiviral sgRNA Non-targeting Control #1,
the Negative Control sequence was introduced into the SU-DHL-4 cell line,
which was referred to as SU-DHL-4 NC strain, and using Edit-R Human
DCAF16 Lentiviral sgRNA, CGCCTCTTGAGAGTCTTGCC sequence (SEQ ID
15 NO: 1) was introduced into the SU-DHL-4 cell line, which was referred to
as SU-DHL-4 DCAF16 KO1 strain, GTTGTATCATGCTAAACTGT sequence
(SEQ ID NO: 2) was introduced into the SU-DHL-4 cell line, which was
referred to as SU-DHL-4 DCAF16 KO2 strain, and
AGAGATCATGCCACTCTAAA sequence (SEQ ID NO: 3) was introduced into
20 the SU-DHL-4 cell line, which was referred to as SU-DHL-4 DCAF16 KO 3
strain.

[0965]

(7) Confirmation of DCAF16 KO

The DCAF16 protein and beta actin protein of the cells obtained by
25 the above method were detected by Western blotting (WB).

The cells were seeded at 6×10^5 cells/well in each well on a 6-well
plate and incubated for 24 hours. After collecting the cells, the supernatant
was aspirated, and 0.1 mL/sample of Lysis buffer 6 (R&D systems, Cat No.
895561) was added to the pellet. After incubating on ice for 60 minutes,
30 the supernatant was collected by centrifugation at 15000 rpm for 10

minutes at 4°C.

[0966]

Using Pierce BCA Protein Assay Kit (Thermo Fisher, Cat No.23225), the protein concentration of each sample was quantified according to the manual attached to the kit, and then was diluted and prepared with Lane Marker Reducing Sample Buffer (5x) (Thermo Fisher, Cat No. 39000) and Lysis buffer 6 to 1 mg/mL. The cells were incubated at 95°C for 5 minutes to prepare WB samples. WB samples were stored at -30°C until electrophoresis.

10 [0967]

The WB sample was thawed and used after vortex mixing and spin down. As a gel for electrophoresis, SuperSep Ace, 5-20% 17 well (Wako, Cat No. 194-15021) was used. Samples were added at 0.010 mL/well (protein content 0.01 mg/well) and proteins were separated by SDS-PAGE.

15 [0968]

Proteins were transferred from the electrophoresed gel to an Immobilon-P Transfer membrane (Merck Millipore, Cat No. IPVH304F0) using a semi-dry transfer device (ATTO, Cat No. WSE-4020) (100 mA/gel, 60 minutes).

20 [0969]

The transfer membrane was soaked for blocking for 1 hour in PVDF Blocking Reagent for Can Get signal (TOYOBO, Cat No. NYPBR01) when detecting DCAF16, and in 1X TBS Tween™-20 (TBS-T, Thermo Scientific, Cat No.28360) containing 5 w/v% skim milk (nakarai, Cat No. 31149-75) (hereinafter, referred to as 5% skim milk -TBS-T) when detecting beta actin.

[0970]

As a primary antibody reaction, the DCAF16 antibody was diluted 30-fold with Can Get Signal Solution 1 (TOYOBO, Cat No. NKB-201) and reacted at 4°C overnight. Subsequently, beta actin antibody was diluted

30

2000-fold with 5% skim milk-TBS-T and reacted overnight at 4°C.

[0971]

As a secondary antibody reaction for DCAF16 antibody, Anti-Mouse IgG, HRP-Linked Whole Ab Sheep antibody was diluted 5000-fold with Can
5 Get Signal Solution 2 (TOYOBO, Cat No. NKB-301) and reacted for 1 hour.
As a secondary antibody reaction for beta actin antibody, Anti-Mouse IgG, HRP-Linked Whole Ab Sheep antibody was diluted 5000-fold with 5% skim milk-TBS-T and reacted for 1 hour.

[0972]

10 Detection was performed using Amersham imager 600 imagers (AI600, GE Healthcare Life Sciences), and luminescent reagents of Supersignal West Femto Maximum Sensitivity Substrate (Thermo Fisher, Cat No. #34096) for detection of DCAF16, and SuperSignal West Pico Chemiluminescent Substrate (Thermo Fisher, Cat No. #34080) for
15 detection of beta actin.

[0973]

DCAF16 and beta actin protein were detected by WB in cell strains (SU-DHL-4 DCAF16 KO1, 2, 3) into which three types of sgRNA targeting DCAF16 genes were introduced and cell strains (SU-DHL-4 NC) into which
20 control sgRNA was introduced. As a result, the DCAF16 band was detected in the parent strain of SU-DHL-4 and the SU-DHL-4 NC strain, but not detected in DCAF16 KO1, DCAF16 KO2 and DCAF16 KO3. Therefore, it was concluded that the DCAF16 gene was knocked out (KO) in DCAF16 KO1, DCAF16 KO2 and DCAF16 KO3.

25 [0974]

(8) Inhibitory effect on cell viability of DCAF16 KO Cell

The cultured DCAF16 KO SU-DHL-4 cells were seeded at 2000 cells/well in a transparent 384-well plate (Code No. 781182, Greiner bio-one). After seeding, the cells were pre-cultured at 37°C in a carbon dioxide
30 gas incubator for 18 to 25 hours. Next, a 1, 0.1 or 0.01 mmol/L DMSO

solution of the test compound was prepared, and a 9-step dilution series were prepared so that the concentration was 200-fold of the final concentration in the RPMI1640 medium containing the above FBS and PS, and 1/200 volume of the dilution series were added to each well. At this
5 time, the final concentration of DMSO was adjusted to be 0.1 vol%. After adding the test compound, the cells were cultured at 37°C in a carbon dioxide gas incubator for 72 hours. Next, 0.020 mL of Cell Counting Kit-8 (Code No. CK04, DOJINDO) solution diluted 2- or 4-fold with phosphate buffered saline (PBS) was added to each well. Color reaction was carried
10 out in a carbon dioxide gas incubator at 37°C for 2 to 3 hours, and the absorbance at a wavelength of 450 nm was measured using SpectraMax 340PC (Molecular Devices).

[0975]

The inhibition rate of cell viability was calculated by the following
15 formula, and the concentration of the test compound (SU-DHL-4 DCAF16 KO IC₅₀) showing a 50% inhibition rate of cell viability was calculated.

$$\text{Inhibition rate of cell viability (\%)} = 100 - (A - B) / (C - B) \times 100$$

A: Absorbance of a well containing test compound

B: Absorbance of a well without addition of cells

20 C: Absorbance of a well without addition of test compound

[0976]

Next, using the measurement results of test example 1, the concentration of the test compound (SU-DHL-4 WT IC₅₀) showing 50% inhibition rate of cell viability was calculated by the same method.

25 [0977]

Using these, the activity attenuation ratio (ratio of SU-DHL-4 DCAF16 KO IC₅₀ to SU-DHL-4 WT IC₅₀) for inhibitory activity of cell viability by DCAF16 KO in SU-DHL-4 was calculated by the following formula. The results are shown in Table 21 below.

30 Activity attenuation ratio = (SU-DHL-4 DCAF16 KO IC₅₀) / (SU-DHL-4 WT

IC₅₀)

[Table 21]

Compound No.	SU-DHL-4 DCAF16 KO IC ₅₀ (nmol/L)	SU-DHL-4 WT IC ₅₀ (nmol/L)	Activity Attenuation Ratio
1a	68.70	1.13	61
1b	36.70	0.65	56
1c	384.93	2.93	131
1k	7.42	0.22	34
1l	100.71	0.03	3357
2f	99.98	0.09	1111
2h	12.23	0.03	408
3a	6.58	0.025	263
3e	951.47	0.10	9515
4a	75.84	0.21	361
4d	1526.03	4.18	365
4e	75.00	0.30	250
5d	166.93	0.31	546
5h	58.39	0.06	942
5j	37.29	0.04	941
5q	621.66	0.09	7078
5r	15.73	0.53	30
6h	6.8	0.003	2250
6k	31.17	0.06	520
6m	90.32	0.08	1164
6r	74.42	0.45	164
7o	397	0.53	750
7p	293	0.38	766
7q	79.74	0.09	850
8g	26.00	0.008	3174
8j	228.23	0.29	767
8r	67.37	0.30	224
9d	262.55	0.75	348
10b	180.44	0.34	524
10g	141.87	0.91	154
10k	143.34	0.21	672
12a	354.14	0.51	693
12b	>10000	2.83	>3526
12c	>10000	0.22	>44436
12f	>10000	0.24	>40284
12h	595	3.11	191
13a	9.31	0.26	35
13d	27.76	0.53	52
13h	22.83	0.30	76
14a	4.00	0.017	228
14d	9.61	0.10	96
14e	68.32	0.21	332
14f	2.95	0.14	22
14p	407	1.00	408
15a	63.03	0.28	225

15d	858.20	0.11	7994
15f	28.31	0.03	902
16j	106.01	0.50	213
16m	208.31	0.62	338
16o	2396.16	24.84	96
16p	925.34	0.27	3390
17a	181.92	0.10	1895
17o	522.29	0.78	670
Comparative Compound 1	49.24	220.84	0.23
Comparative Compound 2	75.67	234.72	0.32

[0978]

As described above, the inhibitory action of cell viability by the compound of the present invention represented by the test compound in wild-type DCAF16 cells was 22 to 44436 times more potent than that in DCAF16 KO cells. That is, it was found that the inhibitory action of cell viability by the compound of the present invention potently depends on DCAF16. Comparative compound 1 is a compound described as example 14 in Patent Document 2 (WO 2015/081284), and comparative compound 2 is a compound described as MT1 in Patent Document 3 (WO 2017/091673). Each of the comparative compounds was synthesized according to the method described in Patent Document 2 or 3, and used in this test.

[0979]

[Test Example 7]

Verification of BET-DCAF16 interaction

HEK293 cells (ATCC^(R) CRL-1573TM) were cultured using a carbon dioxide gas incubator (95% air, 5% CO₂) at 37°C in DMEM, High Glucose, Pyruvate (DMEM: Code No. 11995073, Thermo Fisher Scientific) in which inactivated fetal bovine serum (FBS: Code No. 10099-148 (Thermo Fisher Scientific) was added in an amount to give a final concentration of 10 vol%. A Falcon^(R) 100 mm x 20 mm cell culture dish (Code No. 353003, CORNING) was used for cell culture.

[0980]

A sequence encoding BRD2 was cleaved from pFN21AB3863 (Code No. FHC01342, Kazusa Genome Technologies) using Flexi Enzyme Blend (SgfI and PmeI) (Code No. R1852, Promega) and recombined with pFN31A Nluc CMV-Hygro Flexi^(R) Vector (Code No. N131A, Promega) similarly
5 cleaved using Flexi Enzyme Blend (SgfI and PmeI) to prepare a plasmid pFN31A_BRD2 expressing BRD2 with an Nluc tag added to the N-terminal. A sequence encoding DCAF16 having sgfI and pmeI restriction enzyme sites at both ends was amplified and purified by polymerase chain reaction using
10 two primers, AAAGCGATCGCCATGGGTCCTAGAAATCCC (SEQ ID NO: 4) and AAAGTTAAACCAGTGATGCAGTTAGGAG (SEQ ID NO: 5) from cDNA derived from HEK293 cells. Cleavage was performed using Flexi Enzyme Blend (SgfI and PmeI), and pFC27K HaloTag^(R) CMV-neo Flexi^(R) Vector (Code No. G8431, Promega) cleaved using Carboxy Flexi Enzyme Blend (Sgf I and
15 EcoICR I) (Code No. R1901, Promega) was recombined to prepare a plasmid pFC27K_DCAF16 expressing DCAF16 with HaloTag added to the C-terminal. Sequencing was performed and confirmed that the sequence encoding DCAF16 matched NM_001345880.

[0981]

20 Cultured HEK293 cells were washed with DPBS, no calcium, no magnesium (DPBS: Code No. 14190144, Thermo Fisher Scientific) and harvested using TrypLETM Express Enzyme (1X), phenol red (TrypLE: Code No. 12605036, Thermo Fisher Scientific), and prepared to be 4.0×10^5 cells/mL in DMEM. A volume of 12 mL of the cell suspension was seeded in
25 a Falcon^(R) 100 mm x 20 mm cell culture dish and cultured in a carbon dioxide gas incubator at 37°C for 6 hours. For one dish, 12 µg of pFC27K_DCAF16, 0.12 µg of p FN31A_BRD2, 48 µL of FuGENE^(R) HD Transfection Reagent (Code No. E2312, Promega) were added to 600 µL of Opti-MEMTM I Reduced Serum Medium, no phenol red (Opti-MEM: Code No.
30 11058021, Thermo Fisher Scientific) and mixed. The mixture was allowed

to stand for 15 minutes and added to HEK293 cells. After 20 hours, the cells were washed with DPBS, no calcium, no magnesium, harvested from the dish using TrypLE, and then neutralized in DMEM. After centrifugation, the supernatant was discarded, and the cells were prepared to be 2.2×10^5 cells/mL using Opti-MEM containing 4% FBS. HaloTag^(R) NanoBRETTM 618 Ligand contained in NanoBRETTM Nano-Glo^(R) Detection System (Code No. N1662, Promega) and bortezomib as a proteasome inhibitor were added to be a 1000-fold dilution. In addition, a group was prepared to which DMSO was added instead of HaloTag^(R) NanoBRETTM 618 Ligand. 90 μ L of the cell suspension was seeded in CulturPlate-96 (Code No. 6005688, PerkinElmer), and allowed to stand in a carbon dioxide gas incubator at 37°C for 30 minutes. A volume of 10 mmol/L of a solution of the test compound in DMSO was adjusted to be 100 μ mol/L with Opti-MEM, 10 μ L of the solution was added to each well, and then the mixture was allowed to stand in a carbon dioxide gas incubator at 37°C for 2 hours. At this time, all the groups were prepared so that the final concentration of DMSO was 0.1 vol% including the group to which the test compound was not added. NanoBRETTM Nano-Glo^(R) Substrate included in the NanoBRETTM Nano-Glo^(R) Detection System was diluted 100-fold with Opti-MEM. After adding 25 μ L of the dilution each and stirring for 30 seconds, measurement was performed with an Emission Filter of 460 nm and 620 nm using EnVision (PerkinElmer). The BRET ratio of 10 μ mol/L for each test compound was calculated using the following formula. The experiment was performed by $n = 3$ and the average value was calculated.

$$\text{BRET ratio} = \{(A/B) - (C/D)\} \times 1000$$

A: value at 620 nm filter of the well with addition of test compound and 618 Ligand

B: value at 460 nm filter of the well with addition of test compound and 618 Ligand

C: value at 620 nm filter of the well without addition of test

compound or 618 Ligand

D: value at 460 nm filter of the well without addition of test compound or 618 Ligand

The results are shown in Table 22 below.

5 [Table 22]

Compound No.	BRET Ratio
DMSO	1.51
1h	6.84
1l	8.03
3a	8.51
3b	6.06
3e	5.96
6k	7.07
7o	6.69
7p	6.8
8a	7.27
8j	7.07
12c	7.6
15a	5.88
15f	5.99

As described above, it was found that the compound of the present invention represented by the test compound induced a proximity state because the chemiluminescence catalyzed by Nluc caused an energy transfer to 618 Ligand bonded to HaloTag. In this test, since Nluc was added to BRD2 and HaloTag was added to DCAF16, it was found that the compound of the present invention strongly promoted the interaction between the BET protein BRD2 and the E3 ligase DCAF16.

15 [0982]

[Test Example 8]

Verification of BET-DCAF16 interaction (comparative test with known

compounds)

For comparison with the known comparative compound 1, the enhancement of the BET-DCAF16 interaction was verified by the same method as in test example 7. However, for the purpose of system optimization, bortezomib was changed to Neddylation inhibitor MLN4924 (Code No. HY-10484, MedChem Express), and the dilution ratio of NanoBRET™ Nano-Glo^(R) Substrate was set to 200-fold. The BRET ratio of 1.0 μmol/L of each test compound was calculated, and the results are shown as in Table 23 below.

10 [Table 23]

Compound No.	BRET Ratio
DMSO	0.99
1h	10.95
1l	14.93
3a	14.46
3b	9.69
3e	9.58
6k	12.62
7o	13.00
7p	11.57
8a	12.45
8j	11.91
12c	13.16
15a	9.59
15f	12.43
Comparative Compound 1	1.93

As described above, it was found that the compound of the present invention represented by the test compound strongly promotes the interaction between BRD2 and E3 ligase DCAF16 as compared with comparative compound 1.

The comparative compound 1 is a compound described as example 14 in Patent Document 2 (WO 2015/081284), which was synthesized according to the method described in Patent Document 2, and used in this test.

5 [0983]

[Test Example 9]

Antitumor effect on subcutaneous transplant model in SCID mouse DLBCL strain SU-DHL-4

1 $\times 10^7$ cells of DLBCL strain SU-DHL-4 (Code No. ACC 495,
10 Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) suspended in a 1:1 mixed solution of PBS and matrigel (CORNING Code No. 354234) were transplanted subcutaneously on the ventral side of male SCID mouse. 14 days after the transplantation, the body weight and tumor diameter were measured, the tumor volume was calculated by the following
15 formula, and the mice were divided into two groups (n=5) so that the average tumor volume of each group was equal. E-workbook software (ID Business Solutions) was used for grouping and measurement.

[Tumor volume (mm³)] = [Tumor long diameter (mm)] x [Tumor short diameter (mm)]² x 0.5

20 As shown in Table 24 below, the test was conducted in two groups, a vehicle administration group and a compound 1b administration group (compound administration group). To the compound 1b administration group, a solution of compound 1b dissolved in 30% DMSO/3% Tween 80/physiological saline so as to give a final concentration of 2 mg/mL was
25 administered intravenously (tail vein) at 5 mL/kg (10 mg/kg) once on the test start day. To the vehicle administration group, 30% DMSO/3% Tween 80/physiological saline was administered intravenously (tail vein) at 5 mL/kg in the same schedule as in the compound 1b administration group. After the start of the test, body weight and tumor diameter were measured
30 twice a week. The tumor volume on each measurement day was calculated

by the above formula. The tumor growth rate (hereinafter referred to as V/V_0) was calculated by dividing the tumor volume V on each measurement day by the tumor volume V_0 on the test start date (Day 0). The T/C was calculated by dividing the average value (T) of V/V_0 of each group by the average value (C) of the vehicle administration group.

[0984]

The results are shown in Table 24 below (the average values of $n = 5$ are shown).

[Table 24]

10

Measure- ment Day	Tumor Volume (mm ³)		V/V ₀	
	Vehicle Administration Group	Compound Administration Group	Vehicle Administration Group	Compound Administration Group
Day0	210	208	1.00	1.00
Day4	333	101	1.60	0.49
Day7	416	49	2.00	0.24
Day10	589	66	2.85	0.32
Day14	736	87	3.60	0.42
Day17	943	122	4.59	0.59

Measure- ment Day	T/C		Body Weight (g)	
	Vehicle Administration Group	Compound Administration Group	Vehicle Administration Group	Compound Administration Group
Day0	1.00	1.00	26	25
Day4	1.00	0.31	26	25
Day7	1.00	0.12	26	25
Day10	1.00	0.11	26	26
Day14	1.00	0.12	26	26
Day17	1.00	0.13	27	27

As described above, the tumor volume, tumor growth rate and T/C of the compound 1b administration group were smaller than those of the vehicle administration group. On the other hand, no weight loss was observed due to the administration of compound 1b. That is, compound 1b showed a potent antitumor effect on SU-DHL-4 subcutaneously transplanted tumor. Therefore, compound (I) and compound (I)-1 of the present invention represented by the test compound were found to be

useful as a therapeutic drug for cancer.

[0985]

The proton nuclear magnetic resonance spectra (^1H NMR) used in the following reference examples and examples were measured at 300 MHz or 400 MHz, and exchangeable protons could not be clearly observed depending on the compound and the measurement conditions. Incidentally, the multiplicity of a signal was indicated with common term, while br indicated that the signal is apparently wide. In addition, ChemBioDraw Ultra version 14.0 was used as necessary for naming each compound synthesized.

[0986]

[Reference Example 1]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid

(Step 1)

Aniline (25.0 g, 268.82 mmol) was dissolved in acetonitrile (200 mL), then acetaldehyde (15 mL, 268.8 mmol), bismuth(III) chloride (8.5 g, 26.9 mmol) and N-vinylformamide (22.67 mL, 322.6 mmol) were added to the solution, and the mixture was stirred at room temperature for 36 hours. A saturated aqueous sodium carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to give N-[(2S*,4R*)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]formamide (18.0 g).

[0987]

(Step 2)

N-[(2S*,4R*)-2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl]formamide (18.0 g, 94.7 mmol) obtained in step 1 was dissolved in dichloromethane (100 mL), then pyridine (30.5 mL, 379.0 mmol) and propionyl chloride (8.3

mL, 94.7 mmol) were added to the solution, and the mixture was stirred at 0°C for 1 hour. Water was added to the reaction mixture, and the mixture was extracted twice with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

- 5 The obtained residue was purified by silica gel column chromatography (dichloromethane/methanol = 19/1) to give N-[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]formamide (15.0 g).

[0988]

(Step 3)

- 10 N-[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]formamide (15.0 g, 61.0 mmol) obtained in step 2 was dissolved in methanol (100 mL), then hydrochloric acid (5 mol/L, 18 mL) was added to the solution under ice cooling, and the mixture was stirred at 70°C for 3 hours. Water was added to the reaction mixture, and the mixture was
15 extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (dichloromethane/methanol = 19/1) to give 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (9.0 g, total yield of 3
20 steps 15%).

[0989]

(Step 4)

- 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (5.0 g, 22.9 mmol) obtained in step 3 was dissolved in
25 dichloromethane (100 mL), then [4-(methoxycarbonyl)phenyl]boronic acid (12.3 g, 68.8 mmol), triethylamine (12.9 mL, 91.7 mmol) and copper(II) acetate (6.2 g, 34.4 mmol) were added to the solution, and the mixture was stirred at room temperature for 24 hours under an oxygen atmosphere. The reaction mixture was concentrated under reduced pressure, and the
30 obtained residue was purified by silica gel column chromatography

(petroleum ether/ethyl acetate = 7/3) to give Methyl 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (2.1 g, 18%).

[0990]

5 (Step 5)

Methyl 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (2.1 g, 5.84 mmol) obtained in step 4 was purified by supercritical fluid chromatography (SFC) (Chiralcel OX-H (250×30 mm, 5 μ), CO₂/methanol = 60/40, flow rate 90.0 g/min, retention time (rt) = 7.5 min) to give Methyl 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (750 mg, 36%).

SFC (Chiralpak AD-H (250×4.6 mm, 5 μ), methanol/CO₂ = 25/75, flow rate 3.0 ml/min): rt = 5.38 min

15 [0991]

(Step 6)

Methyl 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (410 mg, 1.16 mmol) obtained in step 4 was dissolved in methanol (6.0 mL), then aqueous sodium hydroxide solution (4 mol/L, 1.45 mL) was added to the solution, and the mixture was stirred at 50°C overnight. Hydrochloric acid (1 mol/L) was added to the reaction mixture, and the mixture was extracted twice with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (390 mg, 99%).

[0992]

(Step 7)

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (1.92 g, 100%) was obtained from methyl 4-

{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (2.0 g, 5.67 mmol) obtained in step 5 in the same manner as in step 6.

ESI-MS m/z : 337 (M-H)⁻, ¹H-NMR (CDCl₃, δ): 1.08-1.23 (m, 6H), 1.23-1.40 (m, 1H), 2.32-2.46 (m, 1H), 2.52-2.77 (m, 2H), 4.21-4.46 (m, 2H), 4.87-5.03 (m, 1H), 6.56-6.66 (m, 2H), 7.09-7.34 (m, 4H), 7.88-7.99 (m, 2H).
[0993]

[Reference Example 2]

1-{{(2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one

1-{{(2S*,4R*)-4-[(4-bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (15.0 g) was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (15.0 g, 68.8 mmol) obtained in step 3 of reference example 1 and (4-bromophenyl) boronic acid (13.76 g, 68.81 mmol) in the same manner as in step 4 of reference example 1. The obtained 1-{{(2S*,4R*)-4-[(4-bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (15.0 g) was purified by SFC ((R, R) Whelk-01 (250×30 mm, 5 μ), CO₂/methanol = 80/20, flow rate 100 g/min, r_t = 10.63 min) to give 1-{{(2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (5.4 g, 21%).

ESI-MS (M+H)⁺: 373, ¹H NMR (DMSO-d₆, δ): 0.99-1.04 (m, 6H), 1.13-1.20 (m, 1H), 2.20-2.25 (m, 1H), 2.55-2.61 (m, 2H), 4.14 (ddd, J = 11.98, 7.71, 4.12 Hz, 1H), 4.70-4.75 (m, 1H), 6.28 (d, J = 7.63 Hz, 1H), 6.59-6.62 (m, 2H), 7.10 (d, J = 7.50 Hz, 1H), 7.16-7.23 (m, 3H), 7.25-7.30 (m, 2H).

SFC ((R, R) Whelk-01 (250×4.6 mm, 5 μ), methanol/CO₂ = 25/75, flow rate 3.0 ml/min): r_t = 7.29 min

[0994]

[Reference Example 3]

(S)-4-{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid
tert-Butyl 2-[4-(4-bromophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (5.0 g, 10.0 mmol) synthesized according to the method described in WO2017/030814 was
5 dissolved in a mixed solvent (70 mL) of DMF and water (5:2), then potassium carbonate (2.1 g, 15.0 mmol), palladium acetate (0.67 g, 1.0 mmol) and Bis(diphenylphosphino)propane (0.82 g, 2.0 mmol) were added to the solution, and the mixture was stirred at 100° C for 16 hours under a carbon monoxide atmosphere. The reaction mixture was filtered through
10 Celite, water was added to the filtrate, and the aqueous layer was washed with ethyl acetate. Citric acid was added to the aqueous layer, and the aqueous layer was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase column
15 chromatography (acetonitrile/0.1% formic acid aqueous solution = 1/1) to give 4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (2.75 g). The resulting 4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (2.75 g)
20 was purified by SFC (Chiralpak AD-H (250×30 mm, 5 μ), CO₂ /methanol = 70/30, flow rate 90 g/min, rt = 3.89 min) to give (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (1.68 g, 36%).
ESI-MS (M+H)⁺: 467, ¹H NMR (DMSO-d₆, δ): 1.43 (s, 9H), 1.60 (d, J = 0.61
25 Hz, 3H), 2.42 (d, J = 0.61 Hz, 3H), 2.61 (s, 3H), 3.34-3.40 (m, 2H), 4.46 (dd, J = 8.24, 6.41 Hz, 1H), 7.52 (d, J = 8.54 Hz, 2H), 7.97 (d, J = 8.85 Hz, 2H), 13.14 (brs, 1H).
SFC (Chiralpak AD-H (250×4.6mm, 5 μ), methanol/CO₂ = 25/75, flow rate 3.0 ml/min): rt = 3.62 min
30 [0995]

[Reference Example 4]

4-(2,3,9-Trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid

(Step 1)

5 (tert-Butoxycarbonyl)glycine (79 mg, 0.451 mmol) was dissolved in DMF (1.6 mL), then HATU (184 mg, 0.484 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.645 mmol) were added to the solution and the mixture was stirred at room temperature for 10 minutes. (2-Amino-4,5-dimethylthiophen-3-yl)(4-bromophenyl)methanone (100 mg,
10 0.322 mmol) synthesized by the method described in WO2017030814 was added to the reaction mixture, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous
15 magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 100/0-80/20) to give tert-butyl (2-{[3-(4-bromobenzoyl)-4,5-dimethylthiophen-2-yl]amino}-2-oxoethyl)carbamate (110 mg, 73%).

20 [0996]

(Step 2)

tert-Butyl (2-{[3-(4-bromobenzoyl)-4,5-dimethylthiophen-2-yl]amino}-2-oxoethyl)carbamate (110 mg, 0.235 mmol) obtained in step 1 was dissolved in dichloromethane (0.79 mL), then trifluoroacetic acid (0.54
25 mL) was added to the solution, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, the obtained residue (110 mg) was dissolved in toluene (2.0 mL), then pyridine (0.36 mL, 4.49 mmol) and molecular sieves 4A (300 mg) were added to the solution, and the mixture was refluxed overnight.
30 The reaction mixture was suction filtered, and water was added to the

obtained filtrate, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol = 100/0 to 90/10) to give 5-(4-bromophenyl)-6,7-dimethyl-1,3-dihydro-2H-thieno[2,3-e][1,4]diazepin-2-one (56 mg, 68%).

[0997]

(Step 3)

5-(4-Bromophenyl)-6,7-dimethyl-1,3-dihydro-2H-thieno[2,3-e][1,4]diazepin-2-one (55 mg, 0.157 mmol) obtained in step 2 was dissolved in THF (1.0 mL), the solution was refrigerated to -78°C, then potassium tert-butoxide (21 mg, 0.189 mmol) was added to the solution, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was refrigerated to -78°C and diethylphosphoryl chloride (0.027 mL, 0.189 mmol) was added to the mixture, and the mixture was stirred at -10°C for 45 minutes. Acetohydrazine (18 mg, 0.236 mmol) and 1-butanol (1.0 mL) were added to the reaction mixture, and the mixture was stirred at 90°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform/methanol = 100/0 to 90/10) to give 4-(4-bromophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (24 mg, 39%).

[0998]

(Step 4)

4-(4-Bromophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (160 mg, 0.413 mmol) obtained in step 3 was dissolved in a mixed solvent (2.2 mL) of DMF and water (10:1), then palladium acetate (9.3 mg, 0.041 mmol), 1,3-bis(diphenylphosphino)propane (34 mg, 0.083 mmol) and potassium carbonate (120 mg, 0.868 mmol) were added to the solution, and the

mixture was stirred at 80°C overnight under a carbon monoxide atmosphere. Hydrochloric acid (1 mol/L) was added to the reaction mixture, and the mixture was extracted twice with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was slurried with ethyl acetate to give 4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (170 mg, 100%).
ESI-MS m/z: 351 (M-H)⁻; ¹H-NMR (DMSO-d₆, δ): 2.40 (s, 3H), 2.63 (s, 3H), 2.90 (s, 3H), 4.17 -4.20 (m, 1H), 5.26-5.33 (m, 1H), 7.53-7.59 (m, 2H), 7.94-8.02 (m, 2H).

[0999]

[Reference Example 5]

4-[(2-Ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl]benzoic acid (Step 1)

2-(2-Oxobutyl)cyclohexane-1,3-dione (150 mg, 0.823 mmol) synthesized according to the method described in the literature (Eur. J. of Org. Chem. 2016, 5169-5179) was dissolved in toluene (1.2 ml), then methyl 4-(aminomethyl)benzoate hydrochloride (174 mg, 0.864 mmol) and triethylamine (0.23 ml, 1.65 mmol) were added to the solution, and the mixture was stirred at room temperature for 15 minutes and then refluxed for 7 hours. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol = 100/0 to 90/10) to give methyl 4-[(2-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl]benzoate (120 mg, 47%).

[1000]

(Step 2)

4-[(2-Ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl]benzoic acid (170 mg, 77%) was obtained from methyl 4-[(2-ethyl-4-oxo-4,5,6,7-

tetrahydro-1H-indol-1-yl)methyl]benzoate (230 mg, 0.739 mmol) obtained in step 1 in the same manner as in step 6 of reference example 1.

ESI-MS m/z : 296 (M-H)⁻; ¹H-NMR (CDCl₃, δ): 1.20 (t, J = 7.4 Hz, 3H), 2.06-2.18 (m, 2H), 2.41 (q, J = 7.4 Hz, 2H), 2.45-2.52 (m, 2H), 2.58-2.64 (m, 2H), 5.11 (s, 2H), 6.42 (s, 1H), 6.99 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.2 Hz, 2H).

[1001]

[Reference Example 6]

4-{[3-(3,5-Dimethylisoxazol-4-yl)-5-

hydroxyphenyl](hydroxy)methyl}benzoic acid
(Step 1)

3-Bromo-5-hydroxybenzaldehyde (3.7 g, 18.41 mmol) was dissolved in DMF (100 mL), then tert-butyldimethylchlorosilane (3.33 g, 22.09 mmol) and imidazole (1.38 g, 20.25 mmol) were added to the solution, and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 90/10) to give 3-bromo-5-[(tert-butyldimethylsilyl)oxy]benzaldehyde (4.6 g, 79%).

[1002]

(Step 2)

3-Bromo-5-[(tert-butyldimethylsilyl)oxy]benzaldehyde (800 mg, 2.54 mmol) obtained in step 1 were mixed with [4-(ethoxycarbonyl)phenyl](iodo)zinc (0.5 mol/L in THF, 30.4 mL, 15.20 mmol), and the mixture was stirred at room temperature for 24 hours. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated

under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 95/5 to 50/50) to give ethyl 4-({3-bromo-5-[(tert-butyldimethylsilyl)oxy]phenyl}(hydroxy)methyl)benzoate (570 mg, 45%).

5 [1003]

(Step 3)

Ethyl 4-({3-bromo-5-[(tert-butyldimethylsilyl)oxy]phenyl}(hydroxy)methyl)benzoate (550 mg, 1.18 mmol) obtained in step 2 was dissolved in a mixed solvent (24 mL) of 1,4-dioxane and water (5:1), then 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)isoxazole (343 mg, 1.54 mmol), potassium carbonate (490 mg, 3.54 mmol) and Pd(dppf)Cl₂ (87 mg, 0.12 mmol) were added to the solution, and the mixture was stirred at 80°C for 16 hours. Ethyl acetate was added to the reaction mixture, and the mixture was extracted with

15 ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by thin layer chromatography (petroleum ether/ethyl acetate = 67/33) to give ethyl 4-({3-[(tert-butyldimethylsilyl)oxy]-5-(3,5-dimethylisoxazol-4-yl)phenyl}(hydroxy)methyl)benzoate (570 mg, 95%).

20 [1004]

(Step 4)

4-{{3-[(3,5-Dimethylisoxazol-4-yl)-5-hydroxyphenyl]}(hydroxy)methyl}benzoic acid (400 mg, 98%) was obtained from ethyl 4-({3-[(tert-butyldimethylsilyl)oxy]-5-(3,5-dimethylisoxazol-4-yl)phenyl}(hydroxy)methyl)benzoate (570 mg, 1.18 mmol) obtained in step 3 in the same manner as in step 6 of reference example 1.

ESI-MS (M+H)⁺: 340, ¹H NMR (CD₃OD, δ): 2.20 (s, 3H), 2.36 (s, 3H), 5.80 (s, 1H), 6.65-6.61 (t, J = 1.6 Hz, 1H), 6.80 (d, J = 1.2 Hz, 1H), 6.84 (t, J = 1.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H).

30

[1005]

[Reference Example 7]

1-{{(2S,4R)-4-[(4-Aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}}propan-1-one

5 (Step 1)

1-[(2S*,4R*)-4-Amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (10.0 g, 45.87 mmol) obtained in step 3 of reference example 1 was dissolved in DMF (150 mL), then 1-fluoro-4-nitrobenzene (9.7 mL, 91.74 mmol), N,N-diisopropylethylamine (8.0 mL, 45.87 mmol) and potassium carbonate (19 g, 137.61 mmol) were added to the solution, and the mixture was stirred at 100°C for 48 hours. 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 sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 92/8 to 90/10) to give 1-[(2S*,4R*)-2-methyl-4-[(4-nitrophenyl)amino]-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (4.7 g, 30%).

ESI-MS (M+H)⁺: 340.

20 [1006]

(Step 2)

1-[(2S*,4R*)-2-Methyl-4-[(4-nitrophenyl)amino]-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (2.6 g, 7.66 mmol) obtained in step 1 was dissolved in a mixed solvent (45 mL) of ethanol, water and THF (1:1:1), then iron (2.13 g, 38.3 mmol) and ammonium chloride (0.6 g, 11.50 mmol) were added to the solution, and the mixture was stirred at 70°C for 2 hours. The reaction mixture was filtered, and water was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel

column chromatography (petroleum ether/ethyl acetate = 60/40 to 50/50) to give 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (1.65 g, 70%).

ESI-MS (M+H)⁺: 310: ¹H-NMR (DMSO-d₆, δ): 0.97-1.03 (m, 6H), 1.06-1.08 (m, 1H), 2.18-2.24 (m, 1H), 2.57-2.60 (m, 2H), 3.95-3.99 (m, 1H), 4.29 (brs, 2H), 4.68-4.70 (m, 1H), 5.17 (d, J = 8.4 Hz, 1H), 6.41- 6.46 (m, 4H), 7.14-7.18 (m, 1H), 7.22-7.28 (m, 3H)

[1007]

(Step 3)

1-{(2S*,4R*)-4-[(4-Aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (530 mg) obtained in step 2 was purified by SFC (Chiralcel OJ-H (250×21 mm, 5 μ), CO₂/methanol = 85/15, flow rate 70 g/min, rt = 6.36 min) to give 1-{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (180 mg, 34%).

ESI-MS (M+H)⁺: 310: ¹H-NMR (DMSO-d₆, δ): 1.12-1.19 (m, 7H), 2.32-2.37 (m, 1H), 2.52-2.67 (m, 2H), 3.49 (brs, 2H), 4.08 (dd, J = 12.0, 3.5 Hz, 1H), 4.89-4.90 (m, 1H), 6.53 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.18-7.21 (m, 1H), 7.24-7.25 (m, 1H), 7.36 (d, J = 7.5 Hz, 1H).

SFC (Chiralcel OJ-H (250×4.6 mm, 5 μ), methanol/CO₂ = 20/80, flow rate 3.0 ml/min): rt = 6.51 min

[1008]

[Reference Example 8]

tert-Butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate

(Step 1)

Methyl 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (0.5 g, 1.42 mmol) obtained in step 5 of reference example 1 was dissolved in tetrahydrofuran (10 mL),

then DMAP (0.693 g, 5.68 mmol) and di-tert-butyl dicarbonate (1.24 g, 5.68 mmol) were added to the solution, and the mixture was stirred at 70°C for 16 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 4/1) to give methyl 4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoate (0.5 g, 77%).

ESI-MS m/z: 453 (M+H)⁺

[1009]

(Step 2)

Methyl 4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoate (0.50 g, 1.1 mmol) obtained in step 1 was dissolved in methanol (10 mL), then 4 mol/L sodium hydroxide aqueous solution (10 mL) was added to the solution, and the mixture was stirred at 80°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and an aqueous citric acid solution was added to the obtained aqueous solution until pH approximately 5. The resulting solid was suction filtered to give 4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid (0.4 g, 83%).

ESI-MS m/z: 439 (M+H)⁺

[1010]

(Step 3)

4-((tert-Butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid (0.40 g, 0.91 mmol) obtained in step 2 was dissolved in dichloromethane (5 mL), then ethyl chloroformate (0.10 mL, 1.1 mmol) and triethylamine (0.38 mL, 2.74 mmol) were added to the solution, and the mixture was stirred at room temperature for 5

hours. Water was added to the reaction mixture, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was dissolved in methanol (5 mL), then sodium borohydride (0.069 g, 1.83 mmol) was added to the solution at 0°C, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction mixture, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to give tert-butyl (4-(hydroxymethyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.28 g, 72%).

ESI-MS m/z : 425 ($M+H$)⁺

[1011]

(Step 4)

tert-Butyl (4-(hydroxymethyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.400 g, 0.94 mmol) obtained in step 3 was dissolved in dichloromethane (5 mL), then DMP (0.480 g, 1.13 mmol) was added to the solution at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane and filtered through Celite. The obtained filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 9/1) to give tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.26 g, 65%).

ESI-MS m/z : 423 ($M+H$)⁺; ¹H-NMR(DMSO-d₆, δ): 0.92-0.99(m, 6H), 1.34(s, 9H), 2.10-2.18(m, 1H), 2.36 (brs, 1H), 2.47-2.48 (m, 1H), 2.51-2.52 (m, 1H), 4.63-4.68 (m, 1H), 4.86 (brs, 1H), 7.34 (brs, 4H), 7.44 (d, J = 8.0 Hz, 2H), 7.88-7.90 (m, 2H), 9.97 (s, 1H).

[1012]

[Reference Example 9]

1-((2S,4R)-4-(((1R,4R)-4-Aminocyclohexyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride

5 (Step 1)

1-[(2S*,4R*)-4-Amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (50.0 g, 230 mmol) obtained in step 3 of reference example 1 was dissolved in methanol (600 mL), then acetic acid (68.80 mL, 1147 mmol), tert-butyl (4-oxocyclohexyl)carbamate (68.4 g, 344 mmol) and sodium borohydride (26.0 g, 689 mmol) were added to the solution, and the mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the obtained residue, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/7) to give a crude product of tert-butyl (4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate (17 g). The resulting crude product was purified by SFC (Chiralpak IA (250×30 mm, 5 μ), CO₂/methanol = 85/15, flow rate 90.0 g/min, retention time (rt) = 6.7 min) to give tert-butyl ((1R,4r)-4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate (6.0 g, 6.2%). SFC (Chiralpak AD-H (250×4.6 mm, 5 μ), methanol/CO₂ = 15/85, flow rate 3.0 ml/min): rt = 6.7 min

25 ESI-MS m/z: 416.3 (M+H)⁺

[1013]

(Step 2)

1-((2S,4R)-4-(((1R,4R)-4-Aminocyclohexyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride (5.0 g, 89%) was obtained from tert-butyl ((1R,4r)-4-(((2S,4R)-2-methyl-1-propionyl-

30

1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate (6.0 g, 14 mmol) obtained in step 1 in the same manner as in step 2 of example 1a. ESIMS, (M+H)⁺, m/z: 316.41. ¹H NMR (DMSO-d₆, δ): 0.97 (t, J = 7.2 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 1.17-1.28 (m, 1H), 1.38-1.54 (m, 1H), 1.58-1.69 (m, 1H), 1.74-1.88 (m, 1H), 2.00-2.17 (m, 3H), 2.21-2.37 (m, 2H), 2.54-2.64 (m, 1H), 2.92-2.97 (m, 2H), 3.21-3.22 (m, 1H), 4.22-4.24 (m, 1H), 4.62-4.74 (m, 1H), 6.52 (brs, 1H), 7.31-7.41 (m, 3H), 7.56 (d, J = 7.67 Hz, 1H), 8.18 (brs, 3H), 9.63-9.93 (m, 2H).

[1014]

10 [Reference example 10]

1-((2S*,4R*)-4-(((1r,4R)-4-Aminocyclohexyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride
(Step 1)

The crude product (8.0 g) of tert-butyl (4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate obtained in step 1 of reference example 9 was purified by SFC (Chiralpak IA (250×30 mm, 5 μ), CO₂/methanol = 85/15, flow rate 90.0 g/min, retention time (rt) = 7.62, 11.0 min) to give tert-butyl ((1R,4r)-4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate (3.0 g, total yield of 2 steps 6.7%).

20 SFC (Chiralpak AD-H (250×4.6 mm, 5 μ), Methanol/CO₂ = 15/85, Flow rate 3.0 ml/min): rt = 7.62, 11.0 min

¹H NMR (CDCl₃, δ): 0.88-0.91 (m, 1H), 1.07-1.12 (m, 6H), 1.16-1.40 (m, 4H), 1.44 (s, 9H), 2.01-2.06 (m, 4H), 2.24-2.28 (m, 1H), 2.48-2.61 (m, 2H), 2.63-2.66 (m, 1H), 3.46-3.60 (m, 2H), 4.36 (brs, 1H), 4.85 (brs, 1H), 7.09 (d, J = 7.0 Hz, 1H), 7.22-7.25 (m, 2H), 7.45-7.47 (m, 1H).

[1015]

(Step 2)

1-((2S*,4R*)-4-(((1r,4R)-4-Aminocyclohexyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride (2.5 g, 90%) was

obtained from tert-butyl ((1R,4r)-4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexyl)carbamate (3.0 g, 7.23 mmol) obtained in step 1 in the same manner as in step 2 of example 1a. ESIMS, (M+H)⁺, m/z: 316.3. ¹H NMR (DMSO-d₆, δ): 0.98 (t, J = 7.6 Hz, 3H), 1.04 (d, J = 6.4 Hz, 3H), 1.23-1.25 (m, 2H), 1.44-1.51 (m, 2H), 1.61-1.69 (m, 1H), 1.81-1.89 (m, 1H), 2.05-2.14 (m, 3H), 2.25-2.33 (m, 2H), 2.51-2.62 (m, 1H), 2.93-2.98 (m, 2H), 4.18-4.28 (m, 1H), 4.68-4.70 (m, 1H), 7.30-7.41 (m, 3H), 7.57 (d, J = 7.6 Hz, 1H), 8.21 (brs, 3H), 9.82-9.88 (m, 2H).

[1016]
[Reference Example 11]
(1R,4r)-4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylic acid
(Step 1)

A crude product of methyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylate was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (2.0 g, 9.2 mmol) obtained in step 3 of reference example 1 and methyl 4-oxocyclohexane-1-carboxylate (2.86 g, 18.35 mmol) in the same manner as in step 1 of reference example 9. The crude product was purified by SFC (Chiralpak IA (250×30 mm, 5 μm), CO₂/methanol = 90/10, flow rate 90.0 g/min) to give methyl (1R,4r)-4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylate (0.240 g, 7.3%).

SFC (Chiralpak IA (250×4.6 mm, 5 μm), CO₂ /methanol = 90/10, flow rate 3 mL/min, retention time (rt) = 8.0 min)
¹H NMR (CD₃OD, δ): 0.89-1.01 (m, 1H), 1.03-1.10 (m, 6H), 1.21-1.36 (m, 2H), 1.39-1.57 (m, 2H), 1.93-2.14 (m, 4H), 2.15-2.22 (m, 1H), 2.24-2.38 (m, 2H), 2.49-2.60 (m, 1H), 2.62-2.70 (m, 1H), 2.72-2.83 (m, 1H), 3.63-3.70 (m, 3H), 4.76-4.79 (m, 1H), 7.21-7.46 (m, 4H).

[1017]

(Step 2)

(1R,4r)-4-(((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylic acid (0.040 g, 83%) was obtained from methyl (1R,4r)-4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylate (0.05 g, 0.14 mmol) obtained in step 1 in the same manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 345.60.

10 [1018]

(Step 3)

(1R,4r)-4-(((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylic acid (250 mg, 0.725 mmol) obtained in step 2 was purified by SFC (Lux Cellulose-2 (250×30 mm, 5 μm), CO₂/methanol = 75/25, flow rate 90.0 g/min, retention time (rt) = 2.3 min) to give (1R,4r)-4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclohexane-1-carboxylic acid (65 mg, 26%).

SFC (Lux Cellulose-2 (250×4.6 mm, 5 μm), CO₂/methanol = 55/45, flow rate 3.0 mL/min, retention time (rt) = 2.3 min)

ESIMS, (M+H)⁺, m/z: 345.35. ¹H NMR (DMSO-d₆, δ): 0.81-0.84 (m, 1H), 0.92-1.01 (m, 6H), 1.03-1.26 (m, 2H), 1.34 (qd, J = 12.72, 2.75 Hz, 2H), 1.85-2.02 (m, 4H), 2.09-2.19 (m, 2H), 2.53 (brs, 1H), 2.54-2.62 (m, 2H), 3.45 (dd, J = 11.90, 3.97 Hz, 1H), 4.56-4.68 (m, 1H), 7.19-7.25 (m, 3H), 7.47-7.51 (m, 1H).

[1019]

[Reference Example 12]

1-((2S,4R)-2-Methyl-4-(piperidin-4-ylamino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride

30 (Step 1)

tert-Butyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)piperidine-1-carboxylate (2.4 g, 87%) was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (1.5 g, 6.9 mmol) obtained in step 3 of reference example 1 and tert-butyl 4-oxopiperidine-1-carboxylate (2.73 g, 13.76 mmol) in the same manner as in step 1 of reference example 9.

ESI-MS m/z: 402 (M+H)⁺

[1020]

(Step 2)

1-((2S,4R)-2-Methyl-4-(piperidin-4-ylamino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride (1.9 g, 86%) was obtained from tert-butyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)piperidine-1-carboxylate (2.4 g, 5.98 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESI-MS m/z: 302.23 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.99 (t, J = 7.34 Hz, 3H), 1.05 (d, J = 6.36 Hz, 3H), 1.20-1.32 (m, 1H), 2.01-2.23 (m, 3H), 2.39 (t, J = 15.16 Hz, 2H), 2.55-2.62 (m, 1H), 2.82-3.02 (m, 3H), 3.37-3.39 (m, 2H), 3.64-3.68 (m, 1H), 4.28-4.32 (m, 1H), 4.67-4.70 (m, 1H), 7.30-7.41 (m, 3H), 7.57 (d, J = 7.83 Hz, 1H), 9.07-9.09 (m, 1H), 9.30 (d, J = 9.29 Hz, 1H), 10.16-10.21 (m, 2H).

[1021]

[Reference Example 13]

1-((2S,4R)-2-Methyl-4-(piperidin-4-ylamino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride
(Step 1)

tert-butyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)piperidine-1-carboxylate (3.0 g, 7.47 mmol) obtained in step 1 of reference example 12 was purified by SFC (Chiralpak IG (30×250 mm), 5 μ, CO₂/methanol = 75/25, flow rate 90 g/min, rt = 2.4) to give tert-butyl 4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-

tetrahydroquinolin-4-yl)amino)piperidine-1-carboxylate (0.900 g, 30%).
SFC (Chiralpak IC-3 (150×4.6 mm, 3 μm), methanol/CO₂ = 35/65, flow
rate 3.0 ml/min): rt = 2.4 min

ESI-MS m/z: 402.35 (M+H)⁺: ¹H-NMR (DMSO-d₆, δ): 0.98 (t, J = 7.3 Hz,
5 3H), 1.05 (d, J = 6.4 Hz, 3H), 1.17-1.25 (m, 1H), 1.38 (s, 9H), 1.52-1.60
(m, 1H), 1.70-1.75 (m, 1H), 2.09-2.23 (m, 3H), 2.54-2.67 (m, 1H), 2.79-
2.95 (m, 3H), 3.55-3.61 (m, 1H), 4.03 (d, J = 8.8 Hz, 2H), 4.27-4.31 (m,
1H), 4.64-4.72 (m, 1H), 7.35-7.39 (m, 3H), 7.50 (d, J = 7.6 Hz, 1H), 9.58
(brs, 1H).

10 [1022]

(Step 2)

1-((2S,4R)-2-Methyl-4-(piperidin-4-ylamino)-3,4-dihydroquinolin-
1(2H)-yl)propan-1-one dihydrochloride (0.4 g, 53%) was obtained from
tert-butyl 4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
15 yl)amino)piperidine-1-carboxylate (0.800 g, 1.99 mmol) obtained in step 1
in the same manner as in step 2 of example 1a.

ESI-MS m/z: 302 (M+H)⁺: ¹H-NMR (DMSO-d₆, δ): 0.99 (t, J = 7.34 Hz,
3H), 1.05 (d, J = 6.14 Hz, 3H), 1.20-1.35 (m, 1H), 1.96-2.25 (m, 3H), 2.39
(t, J = 15.13 Hz, 2H), 2.54-2.67 (m, 1H), 2.85-3.04 (m, 3H), 3.32-3.34
20 (m, 2H), 3.66-3.69 (m, 1H), 4.26-4.32 (m, 1H), 4.68-4.72 (m, 1H), 7.26-
7.43 (m, 3H), 7.58 (d, J = 7.45 Hz, 1H), 9.08 (d, J = 8.99 Hz, 1H), 9.27
(d, J = 8.4 Hz, 1H), 10.13-10.18 (m, 2H).

[1023]

[Reference Example 14]

25 1-((2S*,4R*)-4-(((1r,3R)-3-Aminocyclobutyl)amino)-2-methyl-3,4-
dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride
(Step 1)

The crude product of tert-butyl (3-(((2S*,4R*)-2-methyl-1-
propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclobutyl)carbamate
30 was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-

1(2H)-yl]propan-1-one (0.5 g, 2.29 mmol) obtained in step 3 of reference example 1 and tert-butyl (3-oxocyclobutyl)carbamate (0.678 g, 3.66 mmol) in the same manner as in step 1 of reference example 9. The resulting crude product was purified by SFC (Chiralpak IG (30×250 mm), 5 μm, CO₂ /ethanol = 75/25, flow rate 90 g/min) to give tert-butyl ((1R,3r)-3-
5 (((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclobutyl)carbamate (120 mg, 13%).

ESI-MS m/z: 388 (M+H)⁺: ¹H-NMR (DMSO-d₆, δ): 0.79-0.84 (m, 1H), 0.92-0.99 (m, 6H), 1.37 (s, 9H), 1.99-2.04 (m, 3H), 2.06-2.33 (m, 3H), 2.54-
10 2.61 (m, 2H), 3.23-3.25 (m, 1H), 3.46-3.49 (m, 1H), 4.02- 4.05 (m, 1H), 4.57-4.63 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.23-7.25 (m, 3H), 7.42-7.47 (m, 1H).

[1024]

(Step 2)

15 1-((2S*,4R*)-4-(((1r,3R)-3-Aminocyclobutyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride (0.21 g, 90%) was obtained from tert-butyl ((1R,3r)-3-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)cyclobutyl)carbamate (0.25 g, 0.64 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

20 ESI-MS m/z: 288 (M+H)⁺: ¹H-NMR (DMSO-d₆, δ): 0.98 (t, J = 7.5 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 1.10-1.23 (m, 1H), 2.10-2.14 (m, 1H), 2.51-2.60 (m, 3H), 2.74-2.79 (m, 1H), 2.84-2.88 (m, 1H), 2.91-2.99 (m, 1H), 3.91-3.98 (m, 1H), 4.11-4.19 (m, 1H), 4.29-4.34 (m, 1H), 4.62-4.72 (m, 1H), 7.32-7.41 (m, 3H), 7.57 (d, J = 8.0 Hz, 1H), 8.42 (brs, 3H), 10.36 (brs,
25 1H), 10.44 (brs, 1H).

[1025]

[Reference example 15]

4-((((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)benzoic acid
30 (Step 1)

1-[(2S*,4R*)-4-Amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (1.0 g, 4.6 mmol) obtained in step 3 of reference example 1 was dissolved in DMF (3 mL), then methyl 4-(bromomethyl)benzoate (1.56 g, 6.88 mmol) and potassium carbonate (1.89 g, 13.8 mmol) were added to the solution, and the mixture was stirred at 80°C for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase column chromatography (acetonitrile/water = 1/1) to give methyl 4-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)benzoate (1.0 g, 60%).

ESI-MS m/z: 367 (M+H)⁺

[1026]

(Step 2)

4-((((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)benzoic acid (0.6 g, 62%) was obtained from methyl 4-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)benzoate (1.0 g, 2.73 mmol) obtained in step 1 in the same manner as in step 2 of example 2f.

ESI-MS m/z: 353.34 (M+H)⁺

[1027]

[Reference Example 16]

1-((2S*,4R*)-4-((5-aminopyridin-2-yl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one
(Step 1)

1-[(2S*,4R*)-4-Amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (1.0 g, 4.6 mmol) obtained in step 3 of reference example 1 was dissolved in DMF (5 mL), then 2-fluoro-5-nitropyridine (0.488 g, 3.44 mmol) and potassium carbonate (0.94 g, 6.88 mmol) were added to the solution, and the mixture was stirred at 70°C for 1 hour. Water was added

to the reaction mixture, and the resulting solid was suction filtered to give 1-((2S*,4R*)-2-methyl-4-((5-nitropyridin-2-yl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.55 g, 71%).

ESI-MS m/z: 341 (M+H)⁺

5 [1028]

(Step 2)

1-((2S*,4R*)-2-Methyl-4-((5-nitropyridin-2-yl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.55 g, 1.61 mmol) obtained in step 1 was dissolved in a mixed solvent of THF (3 mL), ethanol (3 mL) and
10 water (3 mL), then iron powder (0.452 g, 8.08 mmol) and ammonium chloride (0.128 g, 2.42 mmol) were added to the solution, and the mixture was stirred at 60°C for 1 hour. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was
15 dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 1-((2S*,4R*)-4-((5-aminopyridin-2-yl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.45 g, 90%).

ESI-MS m/z: 311 (M+H)⁺

[1029]

20 [Reference Example 17]

1-((2S,4R)-4-((5-Aminopyridin-2-yl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one

(Step 1)

1-((2S*,4R*)-2-Methyl-4-((5-nitropyridin-2-yl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (940 mg, 2.76 mmol) obtained in
25 step 1 of reference example 16 was purified by SFC (CHIRALPAK IB, CO₂/methanol = 94/6, 30 mL/min, rt = 12.38 min) to give 1-((2S,4R)-2-methyl-4-((5-nitropyridin-2-yl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (230 mg, 24%).

30 ESI-MS, (M+H)⁺, m/z: 341. ¹H-NMR (CDCl₃, δ): 1.10-1.20 (m, 6H), 1.33-

1.44 (m, 1H), 2.29-2.43 (m, 1H), 2.53-2.64 (m, 1H), 2.66-2.76 (m, 1H), 4.90-5.04 (m, 1H), 5.69-5.96 (m, 1H), 6.48-6.59 (m, 1H), 7.16-7.25 (m, 3H), 7.29-7.36 (m, 1H), 8.21-8.27 (m, 1H), 9.00-9.04 (m, 1H).

[1030]

5 (Step 2)

1-((2S,4R)-2-Methyl-4-((5-nitropyridin-2-yl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (90 mg, 0.264 mmol) obtained in step 1 was dissolved in a mixed solvent of ethanol (2 mL) and water (2 mL), then zinc powder (173 mg, 2.64 mmol) and sodium chloride (141 mg, 10 2.64 mmol) were added to the solution, and the mixture was stirred for 1 hour under reflux. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, and the filtrate was extracted twice with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The obtained residue was 15 purified by silica gel column chromatography (heptane/ethyl acetate = 4/6 to 0/10) to give 1-((2S,4R)-4-((5-aminopyridin-2-yl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (52 mg, 63%).

ESI-MS, (M+H)⁺, m/z: 311. ¹H-NMR (CDCl₃, δ): 1.12-1.17 (m, 6H), 2.27-2.39 (m, 1H), 2.51-2.61 (m, 1H), 2.62-2.71 (m, 1H), 3.27 (brs, 2H), 4.26 20 (d, J = 9.1 Hz, 1H), 4.46-4.54 (m, 1H), 4.87-4.95 (m, 1H), 6.35 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 8.6, 2.7 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.17-7.22 (m, 1H), 7.24 -7.29 (m, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 3.2 Hz, 1H).

[1031]

25 [Reference Example 18]

1-((2S*,4R*)-2-Methyl-4-((piperidin-4-ylmethyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride
(Step 1)

1-[(2S*,4R*)-4-Amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.26 g, 1.0 mmol) obtained in step 3 of reference example 30

1 was dissolved in dichloroethane (5 mL), then tert-butyl 4-formylpiperidine-1-carboxylate (0.239 g, 1.12 mmol), acetic acid (0.029 mL, 0.510 mmol) and sodium triacetoxyborohydride (0.433 g, 2.04 mmol) were added to the solution, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to give tert-butyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)piperidine-1-carboxylate (0.41 g, 98%).

ESI-MS m/z: 416 (M+H)⁺

[1032]

(Step 2)

tert-Butyl 4-(((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)piperidine-1-carboxylate (0.41 g, 0.98 mmol) obtained in step 1 was dissolved in ethyl acetate (5 mL), then hydrogen chloride/ethyl acetate solution (4 mol/L, 2.5 mL, 9.9 mmol) was added to the solution, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was suction filtered, and the obtained solid was dissolved in methanol and concentrated under reduced pressure to give 1-((2S*,4R*)-2-methyl-4-((piperidin-4-ylmethyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one dihydrochloride (0.43 g, quantitative).

ESI-MS m/z: 316 (M+H)⁺

[1033]

[Reference Example 19]

4-(((2S*,4R*)-6-Fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid

(Step 1)

N-((2S*,4R*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (0.3 g, 16%) was obtained from 4-fluoroaniline (1.0 g, 9.0 mmol) in the same manner as in step 1 of reference example 1.

ESI-MS m/z: 209 (M+H)⁺

5 [1034]

(Step 2)

N-((2S*,4R*)-6-Fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (1.0 g, 79%) was obtained from N-((2S*,4R*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (1.0 g, 4.81 mmol) obtained in step 1 in the same manner as in step 2 of reference example 1.

ESI-MS m/z: 265 (M+H)⁺

[1035]

(Step 3)

15 1-((2S*,4R*)-4-Amino-6-fluoro-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.5 g, 56%) was obtained from N-((2S*,4R*)-6-fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (1.0 g, 3.79 mmol) obtained in step 2 in the same manner as in step 3 of reference example 1.

20 ESI-MS m/z: 237 (M+H)⁺

[1036]

(Step 4)

Methyl 4-(((2S*,4R*)-6-fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoate (0.08 g, 10%) was obtained from 1-((2S*,4R*)-4-amino-6-fluoro-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.3 g, 1.3 mmol) obtained in step 3 in the same manner as in step 4 of reference example 1.

ESI-MS m/z: 371 (M+H)⁺

[1037]

30 (Step 5)

4-(((2S*,4R*)-6-Fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid (0.65 g, 75%) was obtained from methyl 4-(((2S*,4R*)-6-fluoro-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoate (0.9 g, 2.4 mmol) obtained in step 4 in the same manner as in step 6 of reference example 1.

ESI-MS m/z: 357 (M+H)⁺; ¹H-NMR (CDCl₃, δ): 1.14-1.22 (m, 6H), 1.25-1.34 (m, 1H), 2.32-2.38 (m, 1H), 2.53-2.59 (m, 1H), 2.66-2.73 (m, 1H), 4.24-4.31 (m, 2H), 4.96 (brs, 1H), 6.61 (d, J = 8.80 Hz, 2H), 6.93 -7.02 (m, 2H), 7.15 (brs, 1H), 7.95 (d, J = 8.80 Hz, 2H).

[1038]
[Reference Example 20]
tert-Butyl ((E)-3-(((2S*,4R*)-4-((4-aminophenyl)amino)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-7-yl)allyl)carbamate (Step 1)

N-((2S*,4R*)-7-Bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (24 g, 62%) was obtained in the same manner as in step 1 of reference example 1 using 3-bromoaniline (25.0 g, 145 mmol).
ESI-MS m/z: 269 (M+H)⁺
[1039]
(Step 2)

N-((2S*,4R*)-7-Bromo-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (5.5 g, 19%) was obtained from N-((2S*,4R*)-7-bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (24 g, 89 mmol) obtained in step 1 in the same manner as in step 2 of reference example 1.

ESI-MS m/z: 325 (M+H)⁺
[1040]
(Step 3)

1-((2S*,4R*)-4-Amino-7-bromo-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (2.0 g, 74%) was obtained from N-((2S*,4R*)-7-

bromo-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)formamide (3.0 g, 9.2 mmol) obtained in step 2 in the same manner as in step 3 of reference example 1.

ESI-MS m/z: 297 (M+H)⁺

5 [1041]

(Step 4)

1-((2S*,4R*)-7-Bromo-2-methyl-4-((4-nitrophenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one. (0.18 g, 25%) was obtained from 1-((2S*,4R*)-4-amino-7-bromo-2-methyl-3,4-dihydroquinolin-1(2H)-
10 yl)propan-1-one (500 mg, 1.69 mmol) obtained in step 3 and (4-nitrophenyl)boronic acid (422 mg, 2.53 mmol) in the same manner as in Reference example 1 Step 4.

ESI-MS m/z: 418 (M+H)⁺

[1042]

15 (Step 5)

1-((2S*,4R*)-7-Bromo-2-methyl-4-((4-nitrophenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.33 g, 0.79 mmol) obtained in step 4 was dissolved in toluene (5 mL), then tert-butyl (E)-(3-(tributylstannyl)allyl)carbamate (0.422 g, 0.95 mmol) and Pd(PPh₃)₄
20 (0.091 g, 0.08 mmol) were added to the solution, and the mixture was stirred at 110°C for 5 hours under an argon atmosphere. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified
25 by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to give tert-butyl (E)-3-((2S*,4R*)-2-methyl-4-((4-nitrophenyl)amino)-1-propionyl-1,2,3,4-tetrahydroquinolin-7-yl)allyl)carbamate (0.3 g, 77%).

ESI-MS m/z: 495 (M+H)⁺

[1043]

30 (Step 6)

tert-Butyl ((E)-3-((2S*,4R*)-4-((4-aminophenyl)amino)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-7-yl)allyl)carbamate (0.25 g, 88%) was obtained from tert-butyl (E)-(3-((2S*,4R*)-2-methyl-4-((4-nitrophenyl)amino)-1-propionyl-1,2,3,4-tetrahydroquinolin-7-

5 yl)allyl)carbamate (0.3 g, 0.61 mmol) obtained in step 5 in the same manner as in step 2 of reference example 16.

ESI-MS m/z: 465 (M+H)⁺

[1044]

[Reference Example 21]

10 tert-Butyl 4-((2S*,4R*)-4-((4-aminophenyl)amino)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (Step 1)

1-((2S*,4R*)-7-Bromo-2-methyl-4-((4-nitrophenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.18 g, 25%) obtained in step 4 of
15 reference example 20 was dissolved in a mixed solvent (6 mL) of 1,2-dimethoxyethane and water (5:1), then tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.388 g, 1.25 mmol), lithium chloride (0.052 g, 1.25 mmol), sodium carbonate (0.177 g, 1.67 mmol) and Pd(PPh₃)₄ (0.096 g, 0.08 mmol) were added to
20 the solution and the mixture was stirred at 100°C for 2 hours under an argon atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to give tert-butyl 4-((2S*,4R*)-2-methyl-4-((4-
25 nitrophenyl)amino)-1-propionyl-1,2,3,4-tetrahydroquinolin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.3 g, 68%).

ESI-MS m/z: 521 (M+H)⁺

[1045]

(Step 2)

30 tert-Butyl 4-((2S*,4R*)-4-((4-aminophenyl)amino)-2-methyl-1-

propionyl-1,2,3,4-tetrahydroquinolin-7-yl)-3,6-dihydropyridine-1(2H)-
carboxylate (0.25 g, 88%) was obtained from tert-butyl 4-((2S*,4R*)-2-
methyl-4-((4-nitrophenyl)amino)-1-propionyl-1,2,3,4-tetrahydroquinolin-
7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.3 g, 0.57 mmol) obtained
5 in step 1 in the same manner as in step 2 of reference example 16.

[1046]

[Reference Example 22]

4-(2,3,9-Trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-
yl)aniline
10 4-(4-Bromophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-
a][1,4]diazepine (2.0 g, 5.17 mmol) obtained in step 3 of reference
example 4 was dissolved in DMSO (30 mL), then copper iodide (0.196 g,
1.03 mmol), 1,2-dimethylethylenediamine (0.136 g, 1.55 mmol) and 28%
aqueous ammonia (150 mL) were added to the solution, and the mixture
15 was stirred at 130°C for 16 hours. A saturated aqueous sodium sulfate
solution was added to the reaction mixture, and the mixture was extracted
twice with ethyl acetate. The organic layer was dried over anhydrous
sodium sulfate and concentrated under reduced pressure. The obtained
residue was purified by reverse phase HPLC (10 mmol/L aqueous
20 ammonium bicarbonate solution/acetonitrile) to give 4-(2,3,9-trimethyl-
6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)aniline (0.850 g,
19%).

ESI-MS m/z: 324 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 1.71 (s, 3H), 2.40 (s,
3H), 2.57 (s, 3H), 4.00 (d, J = 12.47 Hz, 1H), 5.09 (d, J = 12.72 Hz, 1H),
25 5.57 (s, 2H), 6.52 (d, J = 8.80 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H).

[1047]

[Reference Example 23]

1-(4-Aminobenzyl)-2-ethyl-1,5,6,7-tetrahydro-4H-indol-4-one
(Step 1)
30 2-(2-Oxobutyl)cyclohexane-1,3-dione (1.7 g, 9.34 mmol)

synthesized according to the method described in the literature (Eur. J. of Org. Chem. 2016, 5169-5179) was dissolved in toluene (20 ml), then tert-butyl (4-(aminomethyl)phenyl)carbamate (2.49 g, 11.21 mmol) was added to the solution, and the mixture was stirred at room temperature for 10 minutes, then refluxed for 4 hours, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/4 to 1/2) to give tert-butyl (4-((2-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)phenyl)carbamate (0.550 g, 16%).

ESI-MS m/z: 369 (M+H)⁺
[1048]
(Step 2)

1-(4-Aminobenzyl)-2-ethyl-1,5,6,7-tetrahydro-4H-indol-4-one (0.350 g, 87%) was obtained from tert-butyl (4-((2-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)phenyl)carbamate (0.550 g, 1.49 mmol) obtained in step 1 in the same manner as in step 1 of example 8h.

ESI-MS m/z: 269 (M+H)⁺
[1049]
[Reference Example 24]

1-(3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidine-4-carboxylic acid
(Step 1)

Commercially available ethyl 3-bromo-5-hydroxybenzaldehyde (0.25 g, 1.24 mmol) was dissolved in a mixed solvent (3 mL) of 1,4-dioxane and water (2:1), then commercially available 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (0.332 g, 1.49 mmol), tripotassium phosphate (0.791 g, 3.73 mmol) and Pd(dppf)Cl₂ (0.09 g, 0.12 mmol) were added to the solution, and the mixture was stirred at 100°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by column chromatography

(ethyl acetate/petroleum ether = 30/70) to give 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (0.17 g, 63%).

ESI-MS m/z : 218 (M+H)⁺

[1050]

5 (Step 2)

Ethyl 1-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidine-4-carboxylate (0.75 g, 23%) was obtained from 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (2.0 g, 9.22 mmol) obtained in step 1 and commercially available ethyl piperidine-4-carboxylate (1.73 g, 11.06 mmol)

10 in the same manner as in step 1 of example 7d.

ESI-MS m/z : 359 (M+H)⁺

[1051]

(Step 3)

15 1-(3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidine-4-carboxylic acid (0.295 g, 58%) was obtained from ethyl 1-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidine-4-carboxylate (0.55 g, 1.54 mmol) obtained in step 2 in the same manner as in step 2 of example 3d.

ESI-MS m/z : 331 (M+H)⁺

20 [1052]

[Reference Example 25]

3-((4-Aminopiperidin-1-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol dihydrochloride

(Step 1)

25 tert-Butyl (1-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidin-4-yl)carbamate (0.76 g, 21%) was obtained from 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (2.0 g, 9.22 mmol) obtained in step 1 of reference example 24 and commercially available tert-butyl piperidin-4-ylcarbamate (1.84 g, 9.22 mmol) in the same manner as
30 in step 1 of example 7d.

ESIMS, (M+H)⁺, m/z: 402.35.

[1053]

(Step 2)

3-((4-Aminopiperidin-1-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol dihydrochloride (0.23 g, 7%) was obtained from tert-butyl (1-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperidin-4-yl)carbamate (0.740 g, 1.84 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 302.27. ¹H NMR (DMSO-d₆, δ): 1.91-2.07 (m, 4H), 2.25 (s, 3H), 2.43 (s, 3H), 2.73-2.89 (m, 2H), 3.19-3.25 (m, 3H), 3.96-4.11 (m, 2H), 6.81-7.03 (m, 3H), 8.14 (s, 1H), 8.24-8.29 (m, 3H), 9.89 (brs, 1H).

[1054]

[Reference Example 26]

(S)-4-(6-(2-(2-(Dimethylamino)ethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (Step 1)

(S)-4-{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (1.0 g, 2.14 mmol) obtained in reference example 3 was dissolved in DMF (5 mL), then potassium carbonate (0.88 g, 6.44 mmol) and benzyl bromide (0.55 g, 3.22 mmol) were added to the solution. The mixture was stirred at 100°C for 2 hours. Water was added to the reaction mixture, and the precipitated solid was collected by filtration and dried under reduced pressure to give benzyl (S)-4-(6-(2-(tert-butoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (1.1 g, 92%).

ESI-MS m/z: 557 (M+H)⁺

[1055]

(Step 2)

Benzy (S)-4-(6-(2-(tert-butoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (1.1 g, 1.98 mmol) obtained in step 1 was dissolved in 1,4-dioxane (5 mL), then hydrogen chloride/1,4-dioxane solution (4 mol/L, 5.0 mL, 20 mmol) was added to the solution and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture, and the aqueous layer was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (methylene chloride/methanol = 95/5) to give (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.8 g, 80%).

ESI-MS m/z: 501 (M+H)⁺

[1056]

(Step 3)

A crude product of benzy (S)-4-(6-(2-(2-(dimethylamino)ethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.165 g) was obtained from (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.250 g, 0.5 mmol) obtained in step 2 and 2-(dimethylamino)ethan-1-ol (0.044 g, 0.5 mmol) in the same manner as in step 1 of example 1a.

ESI-MS m/z: 572 (M+H)⁺

[1057]

(Step 4)

The crude product of benzy (S)-4-(6-(2-(2-(dimethylamino)ethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate obtained in step 3 (0.165 g) was dissolved in methanol (5 mL), then palladium on carbon (0.05 g, 10 wt%) was added to the solution, and the mixture was stirred at

room temperature for 2 hours under a hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to obtain a crude product of (S)-4-(6-(2-(2-(dimethylamino)ethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.300 g).

ESI-MS m/z : 482 (M+H)⁺

[1058]

[Reference Example 27]

4-((S)-6-(2-(((1r,4S)-4-Hydroxycyclohexyl)oxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid

(Step 1)

(S)-2-(4-(4-((Benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.250 g, 0.5 mmol) obtained in step 2 of reference example 26 was dissolved in chloroform (5 mL), then p-toluenesulfonic acid (0.019 g, 0.1 mmol) and trans-1,4-cyclohexanediol (0.290 g, 2.5 mmol) were added to the solution and the mixture was stirred at 70°C for 36 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by reverse phase column chromatography (acetonitrile/0.1% formic acid aqueous solution = 45/55) to give benzyl 4-((S)-6-(2-(((1r,4S)-4-hydroxycyclohexyl)oxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.110 g, 37%).

ESIMS, (M+H)⁺, m/z : 599.23.

[1059]

(Step 2)

4-((S)-6-(2-(((1r,4S)-4-Hydroxycyclohexyl)oxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.115 g, 90%) was obtained from benzyl 4-((S)-6-(2-(((1r,4S)-4-hydroxycyclohexyl)oxy)-2-oxoethyl)-2,3,9-trimethyl-6H-

thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.150 g, 0.25 mmol) obtained in step 1 in the same manner as in step 4 of reference example 26.

ESIMS, (M+H)⁺, m/z: 509.34: ¹H NMR (DMSO-d₆, δ) 1.23-1.32 (m, 2H), 1.37-1.45 (m, 2H), 1.60 (s, 3H), 1.75-1.78 (m, 2H), 1.85-1.91 (m, 2H), 2.42 (s, 3H), 2.61 (s, 3H), 3.17 (d, J = 5.38 Hz, 1H), 3.40 (dd, J = 8.80, 6.36 Hz, 1H), 3.46-3.55 (m, 1H), 4.49-4.56 (m, 2H), 4.70-4.74 (m, 1H), 7.51 (d, J = 8.31 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 13.17 (brs, 1H).

[1060]

10 [Reference Example 28]

(S)-4-(6-(2-(Ethylamino)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid
(Step 1)

15 Benzyl (S)-4-(6-(2-(ethylamino)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.180 g, 86%) was obtained from (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.200 g, 0.4 mmol) obtained in step 2 of reference example 26 and ethylamine (2 mol/L THF solution, 0.6 ml, 1.2 mmol) in the same manner
20 as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 528.24.

[1061]

(Step 2)

25 (S)-4-(6-(2-(Ethylamino)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.135 g, 90%) was obtained from benzyl (S)-4-(6-(2-(ethylamino)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.180 g, 0.34 mmol) obtained in step 1 in the same manner as in step 4 of reference example 26.

30 ESIMS, (M+H)⁺, m/z: 438.

[1062]

[Reference Example 29]

(S)-4-(6-(2-(4-(2-Hydroxyethyl)piperazin-1-yl)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid

(Step 1)

A crude product (0.140 g) of benzyl (S)-4-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate was obtained from (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.150 g, 0.3 mmol) obtained in step 2 of reference example 26, and 2-(piperazin-1-yl)ethan-1-ol (0.039 g, 0.3 mmol) in the same manner as in step 3 of example 1b. ESIMS, (M+H)⁺, m/z: 613.27.

[1063]

(Step 2)

(S)-4-(6-(2-(4-(2-Hydroxyethyl)piperazin-1-yl)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.062 g, 80%) was obtained from the crude product (0.140 g) of benzyl (S)-4-(6-(2-(4-(2-hydroxyethyl)piperazin-1-yl)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate obtained in step 1 in the same manner as in step 4 of reference example 26.

ESIMS, (M+H)⁺, m/z: 523.

[1064]

[Reference Example 30]

(S)-4-(6-(2-(3-Methoxypropoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid

(Step 1)

Benzyl (S)-4-(6-(2-(3-methoxypropoxy)-2-oxoethyl)-2,3,9-

trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.192 g, 56%) was obtained from (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.3 g, 0.6 mmol) obtained in step 2 of reference example 26 and 3-methoxypropan-1-ol (0.540 g, 6 mmol) in the same manner as in step 1 of reference example 27.

ESIMS, (M+H)⁺, m/z: 573.31.

[1065]

10 (Step 2)

(S)-4-(6-(2-(3-Methoxypropoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.130 g, 80%) was obtained from benzyl (S)-4-(6-(2-(3-methoxypropoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.192 g, 0.33 mmol) obtained in step 1 in the same manner as in step 4 of reference example 26.

ESIMS, (M+H)⁺, m/z: 483.

[1066]

[Reference Example 31]

20 (S)-4-(6-(2-(2-Methoxyethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (Step 1)

Benzyl (S)-4-(6-(2-(2-methoxyethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.2 g, 59%) was obtained from (S)-2-(4-(4-((benzyloxy)carbonyl)phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (0.3 g, 0.6 mmol) obtained in step 2 of reference example 26, and 2-methoxyethan-1-ol (0.456 g, 6 mmol) in the same manner as in step 1 of reference example 27.

ESIMS, (M+H)⁺, m/z: 559.29.

[1067]

(Step 2)

(S)-4-(6-(2-(2-Methoxyethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (0.125 g, 75%) was obtained from benzyl (S)-4-(6-(2-(2-methoxyethoxy)-2-oxoethyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoate (0.2 g, 0.36 mmol) obtained in step 1 in the same manner as in step 4 of reference example 26.

ESIMS, (M+H)⁺, m/z: 469.

[1068]

[Reference Example 32]

4-((2-((2-(Dimethylamino)ethoxy)carbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid

(Step 1)

Aluminum chloride (4.73 g, 35.6 mmol) was dissolved in dichloromethane (25 mL), then 1,5,6,7-tetrahydro-4H-indol-4-one (2.0 g, 14.9 mmol) was added to the solution, and the mixture was stirred at -40°C for 5 minutes. Trichloroacetyl chloride (2.02 mL, 17.8 mmol) was added to the reaction mixture, and the mixture was stirred at -40°C for 5 minutes and then at room temperature for 16 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the aqueous layer was extracted twice with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (petroleum ether/ethyl acetate = 7/3 to 6/4) to give 2-(2,2,2-trichloroacetyl)-1,5,6,7-tetrahydro-4H-indol-4-one (2.0 g, 48%).

ESIMS, (M+H)⁺, m/z: 280.03.

[1069]

(Step 2)

2-(2,2,2-Trichloroacetyl)-1,5,6,7-tetrahydro-4H-indol-4-one (2.0 g, 7.17 mmol) obtained in step 1 was dissolved in methanol (15 mL), then sodium methoxide (0.425 g, 7.88 mmol) was added to the solution, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with hydrochloric acid (1 mol/L), and the aqueous layer was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give methyl 4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (1.0 g, 72%). ESIMS, (M+H)⁺, m/z: 194.11.

[1070]
(Step 3)

Methyl 4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (1.0 g, 5.18 mmol) obtained in step 2 was dissolved in acetonitrile (10 mL), then potassium carbonate (1.43 g, 10.36 mmol) was added to the solution, and the mixture was stirred at room temperature for 5 minutes. tert-Butyl 4-(bromomethyl)benzoate (1.4 g, 5.18 mmol) was added to the reaction mixture, and the mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated under reduced pressure, then water was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate/petroleum ether = 1/4) to give methyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (1.45 g, 73%).

ESIMS, (M+H)⁺, m/z: 384.21.

[1071]
(Step 4)

1-(4-(tert-Butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (0.900 g, 64%) was obtained from methyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-

carboxylate (1.45 g, 3.78 mmol) obtained in step 3 in the same manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 370.22.

[1072]

5 (Step 5)

2-(Dimethylamino)ethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (0.280 g, 81%) was obtained from 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (0.3 g, 0.81 mmol) obtained in step 4 and 2-
10 (dimethylamino)ethan-1-ol (0.12 mL, 1.22 mmol) in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 441.46.

[1073]

(Step 6)

15 4-((2-((2-(Dimethylamino)ethoxy)carbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid (0.150 g, 61%) was obtained from 2-(dimethylamino)ethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (0.280 g, 0.64 mmol) obtained in step 5 in the same manner as in step 2 of example 1k.

20 ESIMS, (M+H)⁺, m/z: 385: ¹H NMR (DMSO-d₆, δ) δ 2.04 (t, J = 6.0 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 2.45 (s, 6H), 2.75 (t, J = 6.0 Hz, 2H), 2.90-2.92 (m, 2H), 4.32 (t, J = 5.2 Hz, 2H), 5.69 (s, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H).

[1074]

25 [Reference Example 33]

4-((2-((2-Hydroxyethoxy)carbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid

(Step 1)

The mixture of 2-((tert-butyldimethylsilyl)oxy)ethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate
30

and 2-hydroxyethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate was obtained as a crude product (0.350 g) from 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (0.3 g, 0.81 mmol) obtained in step 4 of reference example 32 and 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol (0.19 mL, 0.97 mmol) in the same manner as in step 1 of example 1a..

ESIMS, (M+H)⁺, m/z: 528.36.

[1075]

(Step 2)

10 A crude product (0.3 g) of 4-((2-((2-hydroxyethoxy)carbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid was obtained from the crude products (0.350 g) of 2-((tert-butyldimethylsilyl)oxy)ethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate and 2-hydroxyethyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate obtained in step 1 in the same manner as in step 2 of example 1k.

ESIMS, (M+H)⁺, m/z: 358.35.

[1076]

[Reference Example 34]

20 4-((2-(Methoxycarbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid

4-((2-(Methoxycarbonyl)-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)benzoic acid (0.1 g, 81%) was obtained from methyl 1-(4-(tert-butoxycarbonyl)benzyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (0.145 g, 0.37 mmol) obtained in step 3 of reference example 32 in the same manner as in step 2 of example 1k.

ESIMS, (M+H)⁺, m/z: 328: ¹H NMR (CDCl₃, δ) δ 2.13-2.18 (m, 2H), 2.53 (t, J = 6.5 Hz, 2H), 2.69 (t, J = 6.10 Hz, 2H), 3.78 (s, 3H), 5.69 (s, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.44 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H).

30 [1077]

[Reference Example 35]

3-((((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid

(Step 1)

5 Methyl 3-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylate (0.110 g, 67%) was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.100 g, 0.46 mmol) obtained in step 3 of reference example 1 and methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (0.085 g, 0.55 mmol) in the
10 same manner as in step 3 of example 5b.

ESIMS, (M + H)⁺, m/z: 357.

[1078]

(Step 2)

15 3-((((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (0.09 g, 86%) was obtained from methyl 3-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[1.1.1]pentane-1-carboxylate (0.110 g, 0.31 mmol) obtained in step 1 in the same manner
20 as in step 2 of example 2f.

ESIMS, (M + H)⁺, m/z: 343.

[1079]

[Reference Example 36]

4-((((2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[2.2.2]octane-1-carboxylic acid
25

(Step 1)

 Methyl 4-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[2.2.2]octane-1-carboxylate (0.280 g, 77%) was obtained from 1-[(2S*,4R*)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.200 g, 0.91 mmol) obtained in
30

step 3 of reference example 1 and 4-formylbicyclo[2.2.2]octane-1-carboxylate (0.180 g, 0.91 mmol) in the same manner as in step 3 of example 5b.

ESIMS, (M + H)⁺, m/z: 399

5 [1080]

(Step 2)

A crude product (0.160 g) of 4-((((2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)methyl)bicyclo[2.2.2]octane-1-

10 propionyl-1,2,3,4-tetrahydroquinolin-4-

yl)amino)methyl)bicyclo[2.2.2]octane-1-carboxylate (0.106 g, 0.53 mmol) obtained in step 1 in the same manner as in step 2 of example 2f.

ESIMS, (M + H)⁺, m/z: 385.

[1081]

15 [Reference Example 37]

3-(3,5-Dimethylisoxazol-4-yl)-5-(piperazin-1-ylmethyl)phenol
trifluoroacetate

(Step 1)

tert-Butyl

4-(3-(3,5-dimethylisoxazol-4-yl)-5-

20 hydroxybenzyl)piperazine-1-carboxylate (0.500 g, 56%) was obtained from 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (0.500 g, 2.30 mmol) obtained in step 1 of reference example 24 and tert-butyl piperazine-1-carboxylate (0.429 g, 2.30 mmol) in the same manner as in step 3 of example 5b.

25 ESIMS, (M + H)⁺, m/z: 388.

[1082]

(Step 2)

A crude product (0.500 g) of 3-(3,5-dimethylisoxazol-4-yl)-5-(piperazin-1-ylmethyl)phenol trifluoroacetate was obtained from tert-butyl

30 4-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)piperazine-1-

carboxylate (0.480 g, 1.24 mmol) obtained in step 1 in the same manner as in step 2 of example 1k.

ESIMS, (M + H - TFA)⁺, m/z: 288.

[Reference Example 38]

- 5 3-((6-Amino-2-azaspiro[3.3]heptan-2-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol trifluoroacetate
(Step 1)

tert-Butyl (2-(3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)-2-azaspiro[3.3]heptan-6-yl)carbamate (0.230 g, 61%) was obtained from 3-
10 (3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (0.200 g, 0.92 mmol) obtained in step 1 of reference example 24 and tert-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate (0.234 g, 1.10 mmol) in the same manner as in step 3 of example 5b.

ESIMS, (M + H)⁺, m/z: 415.

- 15 [1083]
(Step 2)

A crude product (0.200 g) of 3-((6-amino-2-azaspiro[3.3]heptan-2-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol trifluoroacetate was obtained from tert-butyl (2-(3-(3,5-dimethylisoxazol-4-yl)-5-
20 hydroxybenzyl)-2-azaspiro[3.3]heptan-6-yl)carbamate (0.200 g, 0.47 mmol) obtained in step 1 in the same manner as in step 2 of example 1k.

ESIMS, (M + H - TFA)⁺, m/z: 314.

[1084]

[Reference Example 39]

- 25 1-(((1r,4r)-4-Aminocyclohexyl)methyl)-2-ethyl-1,5,6,7-tetrahydro-4H-indol-4-one hydrochloride
(Step 1)

tert-Butyl ((1r,4r)-4-((2-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl)cyclohexyl)carbamate (0.110 g, 27%) was obtained from 2-(2-
30 oxobutyl)cyclohexane-1,3-dione (0.2 g, 1.09 mmol) synthesized according

to the method described in the literature (Eur. J. of Org. Chem. 2016, 5169-5179) and tert-butyl ((1*r*,4*r*)-4-(aminomethyl)cyclohexyl)carbamate (0.498 g, 2.18 mmol) in the same manner as in step 1 of reference example 5.

5 ESIMS, (M + H)⁺, m/z: 376.

[1085]

(Step 2)

A crude product of 1-(((1*r*,4*r*)-4-aminocyclohexyl)methyl)-2-ethyl-1,5,6,7-tetrahydro-4*H*-indol-4-one hydrochloride (0.080 g, 64%) was
10 obtained from tert-butyl ((1*r*,4*r*)-4-((2-ethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)methyl)cyclohexyl)carbamate (0.110 g, 0.40 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M + H - HCl)⁺, m/z: 276.

[1086]

15 [Reference Example 40]

(*R*)-4-(2-(4-Aminophenoxy)ethyl)-1,3-dimethylpiperazin-2-one

(Step 1)

tert-Butyl (4-(2-chloroethoxy)phenyl)carbamate (137 mg, 87%)
was obtained from commercially available (4-(2-
20 chloroethoxy)phenyl)carbamate (100 mg, 0.583 mmol) in the same
manner as in step 1 of reference example 8.

¹H-NMR (CDCl₃, δ): 1.53 (s, 9H), 3.80 (d, J = 6.0 Hz, 2H), 4.20 (d, J = 6.0 Hz, 2H), 6.36 (brs, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.25-7.30 (m, 2H).

[1087]

25 (Step 2)

tert-Butyl (4-(2-chloroethoxy)phenyl)carbamate (47.8 mg, 0.176 mmol) obtained in step 1 was dissolved in DMA (1.0 ml), and commercially available (*R*)-1,3-dimethylpiperazin-2-one (31.5 mg, 0.246 mmol), *N,N*-diisopropylethylamine (0.138 ml, 0.792 mmol) and potassium iodide (35.0
30 mg, 0.211 mmol) were added to the solution, and the mixture was stirred

at 100°C for 17 hours. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted 3 times with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was
5 purified by silica gel column chromatography (chloroform/methanol = 100/0 to 98/2) to give tert-butyl (R)-(4-(2-(2,4-dimethyl-3-oxopiperazin-1-yl)ethoxy)phenyl)carbamate (27.9 mg, 44%).

ESIMS, (M + H)⁺, m/z: 364.

[1088]

10 (Step 3)

A crude product (27.9 mg) of (R)-4-(2-(4-aminophenoxy)ethyl)-1,3-dimethylpiperazin-2-one trifluoroacetate was obtained from tert-butyl (R)-(4-(2-(2,4-dimethyl-3-oxopiperazin-1-yl)ethoxy)phenyl)carbamate (27.4 mg, 0.075 mmol) obtained in step 2 in the same manner as in step 2 of
15 example 1k.

ESIMS, (M + H - TFA)⁺, m/z: 264.

[1089]

[Reference Example 41]

Methyl (R)-4-(2-(2,4-dimethyl-3-oxopiperazin-1-yl)ethoxy)benzoate

20 Methyl (R)-4-(2-(2,4-dimethyl-3-oxopiperazin-1-yl)ethoxy)benzoate (63.1 mg, 89%) was obtained from commercially available (R)-1,3-dimethylpiperazin-2-one (41.6 mg, 0.325 mmol) and methyl 4-(2-bromoethoxy)benzoate (60.0 mg, 0.232 mmol) in the same manner as in step 2 of reference example 40.

25 ESIMS, (M + H)⁺, m/z: 307.

[1090]

[Reference Example 42]

5-(2-((4-Aminopiperidin-1-yl)methyl)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one dihydrochloride

30 (Step 1)

Commercially available 5-bromo-4-chloropyridin-2-amine (10.0 g, 48.31 mmol) was dissolved in sulfuric acid (200 ml), an aqueous solution (100 mL) of sodium nitrite (3.66 g, 53.14 mmol) was added to the solution at 0°C, and the mixture was stirred at room temperature for 2 hours. Ice water was added to the reaction mixture, and the precipitated solid was collected by filtration and washed with diethyl ether to give 5-bromo-4-chloropyridin-2(1H)-one (7.5 g, 75%).

ESIMS, (M + H)⁺, m/z: 208.

[1091]

10 (Step 2)

5-Bromo-4-chloropyridin-2(1H)-one (18.0 g, 86.99 mmol) obtained in step 1 was dissolved in DMF (200 ml), then cesium carbonate (31.18 g, 95.70 mmol) was added to the solution, and the mixture was stirred at room temperature for 15 minutes. Subsequently, methyl iodide (6.5 mL, 104.40 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and extracted 3 times with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was washed with n-pentane to give 5-bromo-4-chloro-1-methylpyridin-2(1H)-one (11.3 g, 59%).

ESIMS, (M + H)⁺, m/z: 222.

[1092]

(Step 3)

5-Bromo-4-chloro-1-methylpyridin-2(1H)-one (10.0 g, 45.25 mmol) obtained in step 2 was dissolved in methanol (100 ml), then a solution of 25% sodium methoxide in methanol (39.09 mL, 180.99 mmol) was added to the solution, and the mixture was stirred at 70°C for 5 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was diluted with water and extracted 3 times with ethyl acetate. The organic layer was dried over

anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was washed with diethyl ether to give 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (7.0 g, 71%).

ESIMS, (M + H)⁺, m/z: 218.

5 [1093]

(Step 4)

2-(4-Methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzaldehyde (0.220 g, 79%) was obtained from 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (0.250 g, 1.15 mmol) obtained in step 3 and
10 commercially available (2-formylphenyl)boronic acid (0.206 g, 1.38 mmol) in the same manner as in step 1 of reference example 21.

ESIMS, (M + H)⁺, m/z: 244.

[1094]

(Step 5)

15 tert-Butyl (1-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-4-yl)carbamate (0.240 g, 62%) was obtained from 2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzaldehyde (0.220 g, 0.90 mmol) obtained in step 4 and tert-butyl piperidin-4-ylcarbamate (0.181 g, 0.90 mmol) in the same manner as in step 3 of example 6d.

20 ESIMS, (M + H)⁺, m/z: 428.

[1095]

(Step 6)

5-(2-((4-Aminopiperidin-1-yl)methyl)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one dihydrochloride (0.180 g, 80%) was obtained
25 from tert-butyl (1-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-4-yl)carbamate (0.240 g, 0.56 mmol) obtained in step 5 in the same manner as in step 2 of example 1a.

ESIMS, (M + H)⁺, m/z: 328.

[1096]

30 [Reference example 43]

N-(4-((3-Aminopiperidin-1-yl)methyl)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide

(Step 1)

5 A crude product (3.2 g) of 4-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde was obtained from commercially available 2-bromo-4-nitrobenzaldehyde (4.0 g, 17.47 mmol) in the same manner as in step 1 of example 5n.

¹H-NMR (CDCl₃, δ): 1.27 (s, 12H), 8.20-8.23 (m, 2H), 8.53 (dd, J = 8.5, 2.5 Hz, 1H), 9.95 (s, 1H).

10 [1097]

(Step 2)

The crude product (3.57 g) of 4-nitro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde obtained in step 1 and 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (1.0 g, 4.61 mmol) obtained in step 3
15 of reference example 42 were dissolved in a mixed solvent of 1,4-dioxane and water (75 mL, 2:1), then tripotassium phosphate (2.93 g, 13.82 mmol), Pd₂(dba)₃ (0.422 g, 0.46 mmol), and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.148 g, 0.50 mmol) were added to the solution, and the mixture was stirred at 90°C for 2 hours. The
20 reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol = 95/5) to give 2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-nitrobenzaldehyde (0.7 g, total yield of 2 steps 53%).

25 ESIMS, (M + H)⁺, m/z: 289.

[1098]

(Step 3)

tert-Butyl (1-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-nitrobenzyl)piperidin-3-yl)carbamate (0.400 g, 35%) was obtained
30 from 2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-

nitrobenzaldehyde (0.7 g, 2.43 mmol) obtained in step 2 and tert-butyl piperidin-3-ylcarbamate (0.486 g, 2.43 mmol) in the same manner as in step 3 of example 6d.

ESIMS, (M + H)⁺, m/z: 474.

5 [1099]

(Step 4)

tert-Butyl (1-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.340 g, 90%) was obtained from tert-butyl (1-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-nitrobenzyl)piperidin-3-yl)carbamate (0.400 g, 0.84 mmol) obtained in step 3 in the same manner as in step 2 of reference example 7.

ESIMS, (M + H)⁺, m/z: 444.

[1100]

15 (Step 5)

tert-Butyl (1-(4-(N-(ethylsulfonyl)ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.250 g, 52%) was obtained from tert-butyl (1-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.340 g, 0.77 mmol) obtained in step 4 and ethanesulfonyl chloride (0.146 mL, 1.54 mmol) in the same manner as in step 1 of example 4c.

ESIMS, (M + H)⁺, m/z: 628.

[1101]

(Step 6)

25 tert-Butyl (1-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.200 g, 94%) was obtained from tert-butyl (1-(4-(N-(ethylsulfonyl)ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.250 g, 0.40 mmol) obtained in step 5 in the same manner as in step 6 of reference example 46.

30

ESIMS, (M + H)⁺, m/z: 535.

[1102]

(Step 7)

A crude product (0.180 g) of N-(4-((3-aminopiperidin-1-yl)methyl)-
5 3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-
yl)phenyl)ethanesulfonamide hydrochloride was obtained from tert-butyl
(1-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-
dihydropyridin-3-yl)benzyl)piperidin-3-yl)carbamate (0.200 g, 0.37 mmol)
obtained in step 5 in the same manner as in step 2 of example 1a.

10 ESIMS, (M + H - HCl)⁺, m/z: 435.

[1103]

[Reference Example 44]

5-(2-(3-Aminophenoxy)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one
(Step 1)

15 tert-Butyl (3-(2-bromophenoxy)phenyl)carbamate (0.800 g, 38%)
was obtained from commercially available 2-bromophenol (1.0 g, 5.81
mmol) and commercially available (3-((tert-
butoxycarbonyl)amino)phenyl)boronic acid (1.79 g, 7.56 mmol) in the
same manner as in step 1 of reference example 45.

20 ESIMS, (M + H)⁺, m/z: 364.

[1104]

(Step 2)

A crude product (2.8 g) of tert-butyl (3-(2-(4,4,5,5-tetramethyl-
1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)carbamate was obtained from
25 tert-butyl (3-(2-bromophenoxy)phenyl)carbamate (10.0 g, 27.55 mmol)
obtained in step 1 in the same manner as in step 1 of example 5n.

ESIMS, (M + H)⁺, m/z: 413.

[1105]

(Step 3)

30 tert-Butyl (3-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-

yl)phenoxy)phenyl)carbamate (0.800 g, total yield of 2 steps 41%) was obtained from the crude product (4.73 g) of tert-butyl (3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)carbamate obtained in step 2 and 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (1.0 g, 4.61 mmol) obtained in step 3 of reference example 42 in the same manner as in step 1 of reference example 21.

ESIMS, (M + H)⁺, m/z: 423.

[1106]

(Step 4)

A crude product (0.540 g) of 5-(2-(3-aminophenoxy)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one hydrochloride was obtained from tert-butyl (3-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate (0.80 g, 1.89 mmol) obtained in step 3 in the same manner as in step 2 of example 1a.

ESIMS, (M + H - HCl)⁺, m/z: 323.

[1107]

[Reference Example 45]

3-(2-(4-Methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzoic acid

(Step 1)

Commercially available 2-bromophenol (10.0 g, 57.80 mmol) was dissolved in dichloromethane (150 mL), then commercially available (3-(ethoxycarbonyl)phenyl)boronic acid (16.82 g, 86.70 mmol), copper(II) acetate (15.69 g, 86.70 mmol) and pyridine (23.3 mL, 289.01 mmol) were added to the solution, and the mixture was stirred at room temperature for 48 hours under an oxygen atmosphere. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 98/2) to give ethyl 3-(2-bromophenoxy)benzoate (3.5 g, 21%).

ESIMS, (M + H)⁺, m/z: 321.

[1108]

(Step 2)

5 Ethyl 3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzoate (7.0 g, 85%) was obtained from ethyl 3-(2-bromophenoxy)benzoate (7.2 g, 22.5 mmol) obtained in step 1 in the same manner as in step 1 of example 5n.

ESIMS, (M + H)⁺, m/z: 369.

[1109]

10 (Step 3)

Ethyl 3-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzoate (2.0 g, 57%) was obtained from ethyl 3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzoate (6.78 g, 18.43 mmol) obtained in step 2 and 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (2.0 g, 9.21 mmol) obtained in step 3 of reference example 42 in the same manner as in step 1 of reference example 21.

ESIMS, (M + H)⁺, m/z: 380.

[1110]

(Step 4)

20 3-(2-(4-Methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzoic acid (0.71 g, 77%) was obtained from ethyl 3-(2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzoate (1.0 g, 2.63 mmol) obtained in step 3 in the same manner as in step 2 of example 2f.

25 ESIMS, (M + H)⁺, m/z: 352.

[1111]

[Reference Example 46]

N-(4-(3-Aminophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide

30 (Step 1)

tert-Butyl (3-(2-bromo-4-nitrophenoxy)phenyl)carbamate (8.0 g, 86%) was obtained from commercially available 2-bromo-1-fluoro-4-nitrobenzene (5.0 g, 22.73 mmol) and commercially available tert-butyl (3-hydroxyphenyl)carbamate (5.22 g, 25.00 mmol) in the same manner as in
5 step 2 of reference example 48.

ESIMS, (M + H)⁺, m/z: 409.

[1112]

(Step 2)

tert-Butyl (3-(4-amino-2-bromophenoxy)phenyl)carbamate (7.0 g, 95%) was obtained from tert-butyl (3-(2-bromo-4-nitrophenoxy)phenyl)carbamate (5.0 g, 22.73 mmol) obtained in step 1 in
10 the same manner as in step 2 of reference example 7.

ESIMS, (M + H)⁺, m/z: 381.

[1113]

15 (Step 3)

A crude product (8.5 g) of tert-butyl (3-(4-amino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)carbamate was obtained from tert-butyl (3-(4-amino-2-bromophenoxy)phenyl)carbamate (5.0 g, 13.18 mmol) obtained in step 2 in the same manner as in step 1 of
20 example 5n.

ESIMS, (M + H)⁺, m/z: 428.

[1114]

(Step 4)

tert-Butyl (3-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate (1.0 g, total yield of 2 steps 25%) was obtained from the crude product (7.82 g) of (3-(4-amino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)carbamate obtained in step 3 and 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (2.0 g, 9.17 mmol) obtained in step 3 of
30 reference example 42 in the same manner as in step 2 of reference example

43.

ESIMS, (M + H)⁺, m/z: 438.

[1115]

(Step 5)

5 A crude product (1.1 g) of tert-butyl (3-(4-(N-(ethylsulfonyl)ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate was obtained from tert-butyl (3-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate (1.0 g, 2.28 mmol) obtained in step 4 and
10 ethanesulfonyl chloride (0.26 mL, 2.74 mmol) in the same manner as in step 1 of example 4c.

ESIMS, (M + H)⁺, m/z: 622.

[1116]

(Step 6)

15 The crude product (1.6 g) of tert-butyl (3-(4-(N-(ethylsulfonyl)ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate obtained in step 5 was dissolved in a mixed solvent of THF and water (30 mL, 2:1), then lithium hydroxide monohydrate (0.433 g, 10.30 mmol) was added to the solution,
20 and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ice water and the aqueous layer was extracted 3 times with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (acetonitrile/0.1% formic acid
25 aqueous solution = 50/50) to give tert-butyl (3-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)phenyl)carbamate (0.750 g, total yield of 2 steps 55%).

ESIMS, (M + H)⁺, m/z: 530.

[1117]

30 (Step 7)

N-(4-(3-Aminophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide hydrochloride (1.06 g, 65%) was obtained from tert-butyl (3-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-

5 yl)phenoxy)phenyl)carbamate (1.25 g, 2.36 mmol) obtained in step 6 in the same manner as in step 2 of example 1a.

ESIMS, (M + H - HCl)⁺, m/z: 430.

[1118]

[Reference Example 47]

10 3-(4-(Ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzoic acid
(Step 1)

Ethyl 3-(2-bromo-4-nitrophenoxy)benzoate (13.0 g, 78%) was obtained from commercially available 2-bromo-1-fluoro-4-nitrobenzene
15 (10.0 g, 45.45 mmol) and commercially available ethyl 3-hydroxybenzoate (8.29 g, 49.99 mmol) in the same manner as in step 2 of reference example 48.

ESIMS, (M + H)⁺, m/z: 366.

[1119]

20 (Step 2)

Ethyl 3-(4-amino-2-bromophenoxy)benzoate (10 g, 83%) was obtained from ethyl 3-(2-bromo-4-nitrophenoxy)benzoate (13.0 g, 35.61 mmol) obtained in step 1 in the same manner as in step 2 of reference example 7.

25 ESIMS, (M + H)⁺, m/z: 336.

[1120]

(Step 3)

A crude product (14.0 g) of ethyl 3-(4-amino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzoate was obtained from
30 ethyl 3-(4-amino-2-bromophenoxy)benzoate (10 g, 29.85 mmol) obtained

ESIMS, (M + H)⁺, m/z: 434.

[1127]

(Step 4)

tert-Butyl ((1r,4r)-4-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)cyclohexyl)carbamate (0.3 g, total yield of 2 steps 74%) was obtained from the crude product (0.792 g) of tert-butyl ((1r,4r)-4-(4-amino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)cyclohexyl)carbamate obtained in step 3 and 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one (0.2 g, 0.92 mmol) obtained in step 3 of reference example 42 in the same manner as in step 1 of reference example 21.

ESIMS, (M + H)⁺, m/z: 445.

[1128]

(Step 5)

tert-Butyl ((1r,4r)-4-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)cyclohexyl)carbamate (0.090 g, 75%) was obtained from tert-butyl ((1r,4r)-4-(4-amino-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)cyclohexyl)carbamate (0.100 g, 0.22 mmol) obtained in step 4 and ethanesulfonyl chloride (0.021 mL, 0.22 mmol) in the same manner as in step 1 of example 4c.

ESIMS, (M + H)⁺, m/z: 537

[1129]

(Step 6)

A crude product (0.080 g) of N-(4-(((1r,4r)-4-aminocyclohexyl)oxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide hydrochloride was obtained from tert-butyl ((1r,4r)-4-(4-(ethylsulfonamide)-2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)cyclohexyl)carbamate (0.090 g, 0.17 mmol) obtained in step 5 in the same manner as in step 3 of reference example

46.

ESIMS, (M + H - HCl)⁺, m/z: 436.

[1130]

[Reference Example 49]

- 5 5-(2-(4-Aminophenoxy)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one
(Step 1)

1-Bromo-2-(4-nitrophenoxy)benzene (1.3 g, 76%) was obtained from commercially available 2-bromophenol (1.0 g, 5.78 mmol) and commercially available 1-fluoro-4-nitrobenzene (0.897 g, 6.36 mmol) in the
10 same manner as in step 2 of reference example 48.

ESIMS, (M + H)⁺, m/z: 294.

[1131]

(Step 2)

- 4-(2-Bromophenoxy)aniline (0.950 g, 81%) was obtained from 1-
15 bromo-2-(4-nitrophenoxy)benzene (1.3 g, 4.42 mmol) obtained in step 1
in the same manner as in step 2 of reference example 7.

ESIMS, (M + H)⁺, m/z: 264.

[1132]

(Step 3)

- 20 A crude product (1.5 g) of 4-(2-(4,4,5,5-tetramethyl-1,3,2-
dioxaborolan-2-yl)phenoxy)aniline was obtained from 4-(2-
bromophenoxy)aniline (0.950 g, 3.59 mmol) obtained in step 2 in the same
manner as in step 1 of example 5n.

ESIMS, (M + H)⁺, m/z: 312.

- 25 [1133]

(Step 4)

- 5-(2-(4-Aminophenoxy)phenyl)-4-methoxy-1-methylpyridin-2(1H)-
one (0.3 g, total yield of 2 steps 81%) was obtained from the crude product
(0.716 g) of 4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
30 yl)phenoxy)aniline obtained in step 3 and 5-bromo-4-methoxy-1-

methylpyridin-2(1H)-one (0.250 g, 1.15 mmol) obtained in step 3 of reference example 42 in the same manner as in step 1 of reference example 21.

ESIMS, (M + H)⁺, m/z: 323.

5 [1134]

[Reference Example 50]

1-(4-Aminobenzyl)-5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one
hydrochloride

(Step 1)

10 4-(6-Methoxypyridin-3-yl)-3,5-dimethylisoxazole (3.6 g, 66%) was obtained from commercially available 5-bromo-2-methoxypyridine (5.0 g, 26.59 mmol) and commercially available 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (5.93 g, 26.59 mmol) in the same manner as in step 1 of reference example 21.

15 ESIMS, (M + H)⁺, m/z: 205.

[1135]

(Step 2)

4-(6-Methoxypyridin-3-yl)-3,5-dimethylisoxazole (3.6 g, 17.65 mmol) obtained in step 1 was dissolved in ethanol (10 mL), then a 47%
20 hydrogen bromide aqueous solution (36 mL) was added to the solution, and the mixture was stirred at 90°C for 8 hours. The reaction mixture was diluted with water and the aqueous layer was extracted with 5% methanol/dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained
25 residue was washed with diethyl ether to give 5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one (2.7 g, 80%).

ESIMS, (M + H)⁺, m/z: 191.

[1136]

(Step 3)

30 5-(3,5-Dimethylisoxazol-4-yl)pyridin-2(1H)-one (0.3 g, 1.58 mmol)

obtained in step 2 was dissolved in DMF (5 mL), then commercially available tert-butyl (4-(bromomethyl)phenyl)carbamate (0.452 g, 1.58 mmol) and potassium carbonate (0.654 g, 4.73 mmol) were added to the solution, and the mixture was stirred at 70°C for 16 hours. The reaction mixture was
5 diluted with water and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/50) to give tert-butyl (4-((5-(3,5-dimethylisoxazol-4-yl)-2-oxopyridin-
10 1(2H)-yl)methyl)phenyl)carbamate (0.210 g, 34%).

ESIMS, (M + H)⁺, m/z: 397.

[1137]

(Step 4)

A crude product (0.180 g) of 1-(4-aminobenzyl)-5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one hydrochloride was obtained from
15 tert-butyl (4-((5-(3,5-dimethylisoxazol-4-yl)-2-oxopyridin-1(2H)-yl)methyl)phenyl)carbamate (0.210 g, 0.53 mmol) obtained in step 3 in the same manner as in step 2 of example 1a.

ESIMS, (M + H - HCl)⁺, m/z: 296.

20 [1138]

[Reference Example 51]

1-(((1r,4r)-4-Aminocyclohexyl)methyl)-5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one hydrochloride

(Step 1)

25 tert-Butyl ((1r,4r)-4-((5-(3,5-dimethylisoxazol-4-yl)-2-oxopyridin-1(2H)-yl)methyl)cyclohexyl)carbamate (0.180 g, 43%) was obtained from 5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one (0.20 g, 1.05 mmol) obtained in step 2 of reference example 50 and tert-butyl ((1r,4r)-4-(bromomethyl)cyclohexyl)carbamate (0.307 g, 1.05 mmol) in the same
30 manner as in step 3 of reference example 50.

ESIMS, (M + H)⁺, m/z: 403.

[1139]

(Step 2)

A crude product (0.160 g) of 1-(((1r,4r)-4-aminocyclohexyl)methyl)-5-(3,5-dimethylisoxazol-4-yl)pyridin-2(1H)-one hydrochloride was obtained from tert-butyl ((1r,4r)-4-((5-(3,5-dimethylisoxazol-4-yl)-2-oxopyridin-1(2H)-yl)methyl)cyclohexyl)carbamate (0.180 g, 0.45 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M + H - HCl)⁺, m/z: 303.

[1140]

[Reference Example 52]

3-(((3-Aminobicyclo[1.1.1]pentan-1-yl)amino)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol hydrochloride

(Step 1)

tert-Butyl (3-((3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (0.160 g, 43%) was obtained from 3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzaldehyde (0.2 g, 0.92 mmol) obtained in step 1 of reference example 24 and commercially available tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (0.182 g, 0.92 mmol) in the same manner as in step 3 of example 5b.

ESIMS, (M + H)⁺, m/z: 400.

[1141]

(Step 2)

A crude product (0.150 g) of 3-(((3-aminobicyclo[1.1.1]pentan-1-yl)amino)methyl)-5-(3,5-dimethylisoxazol-4-yl)phenol hydrochloride was obtained from tert-butyl (3-((3-(3,5-dimethylisoxazol-4-yl)-5-hydroxybenzyl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (0.160 g, 0.40 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M + H)⁺, m/z: 301.

[1142]

[Example 1a]

N,N'-(Propane-1,3-diyl)bis(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide}) (Compound 1a)
(Step 1)

4-{{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (200 mg, 0.89 mmol) obtained in step 6 of reference example 1 was dissolved in DMF (6.0 mL), then HATU (337 mg, 0.89 mmol),
tert-butyl (3-aminopropyl)carbamate (155 mg, 0.89 mmol) and N,N-diisopropylethylamine (0.21 mL, 1.18 mmol) were added to the solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The
organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol = 100/0 to 90/10) to give tert-butyl [3-(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]carbamate (330 mg, 75%).

ESIMS, (M+H)⁺, m/z: 495.

[1143]

(Step 2)

tert-Butyl [3-(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]carbamate (330 mg, 0.67 mmol) obtained in step 1 was dissolved in ethyl acetate (20 mL), then hydrogen chloride/1,4-dioxane solution (4 mol/L, 5.0 mL, 20 mmol) was added to the solution. The mixture was stirred at room temperature for 24 hours. The resulting solid was collected by filtration and washed with ethyl acetate to give N-(3-aminopropyl)-4-{{[(2S*,4R*)-2-methyl-1-propionyl-

1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (260 mg, 89%).

ESIMS, (M+H)⁺, m/z: 395.

[1144]

5 (Step 3)

A crude product of compound 1a (360 mg) was obtained from N-(3-aminopropyl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (543 mg, 1.38 mmol) obtained in step 2 and 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (466 mg, 1.38 mmol) obtained in step 6 of reference example 1 in the same manner as in step 1. The obtained crude product was purified by reverse phase high performance liquid chromatography (reverse phase HPLC) (Column: CHIRALART Cellulose-SB S-5 μm, methyl tert-butyl ether (MtBE)/methanol = 80/20, flow rate 1 mL/min, rt = 3.9 min) to give compound 1a (34 mg, 3.4%).

ESIMS, (M+H)⁺, m/z: 715. ¹H NMR (CDCl₃, δ): 1.08-1.20 (m, 12H), 1.21-1.38 (m, 4H), 1.70-1.90 (m, 2H), 2.30-2.44 (m, 2H), 2.50-2.71 (m, 4H), 3.40-3.75 (m, 4H), 4.19-4.29 (m, 2H), 4.88-5.01 (m, 2H), 6.63 (d, J = 8.4 Hz, 4H), 7.11-7.31 (m, 8H), 7.76 (d, J = 8.7 Hz, 4H).

20 HPLC (CHIRAL Cellulose-SB (0.46x15 cm, 3 μm), MtBE (0.1%DEA)/methanol = 80/20, flow rate 1.0 ml/min): rt = 7.9 min

[1145]

[Example 1b]

Di-tert-butyl 2,2'-[(6S,6'S)-({[propane-1,3-diylbis(azanediyl)]bis(carbonyl)}bis(4,1-phenylene))bis(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine-4,6-diyl)]diacetate (Compound 1b)

(Step 1)

(S)-4-{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (800

mg, 1.71 mmol) obtained in reference example 3 was dissolved in DMF (10 mL), then HATU (744 mg, 1.71 mmol), N,N-diisopropylethylamine (5 mL, 28.1 mmol) and benzyl N-(3-aminopropyl)carbamate (464 mg, 2.23 mmol) were added to the solution, and the mixture was stirred at room temperature for 25 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 90/10 to 50/50) to give tert-butyl (S)-2-(4-{4-[(3-
5 {[(benzyloxy)carbonyl]amino}propyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (910 mg).

ESIMS, (M+H)⁺, m/z: 657.

[1146]

(Step 2)

15 tert-Butyl (S)-2-(4-{4-[(3-
{[(benzyloxy)carbonyl]amino}propyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (900 mg, 1.37 mmol) obtained in step 1 was dissolved in methanol (20 mL), then 10% palladium on carbon (0.20 g, 10 wt%) was added to the solution, and the mixture was stirred at room temperature for 5 hours under a hydrogen atmosphere. The reaction mixture was suction filtered, and the filtrate was concentrated under reduced pressure to give a crude product (0.72 g) of tert-butyl (S)-2-(4-{4-[(3-aminopropyl)carbamoyl]phenyl}-2,3,9-
20 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate.

ESIMS, (M+H)⁺, m/z: 523.

[1147]

(Step 3)

(S)-4-{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-
30 thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (500

mg, 1.07 mmol) obtained in reference example 3 was dissolved in DMF (45 mL), then COMU (2 g, 4.62 mmol) and N,N-diisopropylethylamine (5 mL, 28.0 mmol) were added to the solution, and the mixture was stirred at room temperature for 5 minutes. The crude product (700 mg, 1.34 mmol) of
 5 tert-butyl (S)-2-(4-{4-[(3-aminopropyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate obtained in step 2 was added to the reaction mixture, and the mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was
 10 purified by reverse phase HPLC (0.1% formic acid/acetonitrile = 53/47 to 43/57) to give compound 1b (285 mg, total yield of 3 steps 18%).
 ESIMS, (M+H)⁺, m/z: 971. ¹H NMR (DMSO-d₆, δ): 1.58 (s, 18H), 1.75 (s, 6H), 1.70-1.90 (m, 2H), 2.41 (s, 6H), 2.61 (s, 6H), 3.20-3.40 (m, 8H), 4.44 (t, J = 7.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 4H), 7.87 (d, J = 8.4 Hz, 4H),
 15 8.60 (t, J = 5.6 Hz, 2H).

[1148]

[Example 1c]

4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-[1-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
 20 tetrahydroquinolin-4-yl]amino}benzoyl)piperidin-4-yl]benzamide
 (Compound 1c)
 (Step 1)

tert-Butyl 4-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)piperidine-1-carboxylate (62
 25 mg, 80%) was obtained from 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 6 of reference example 1 and tert-butyl 4-aminopiperidine-1-carboxylate (30 mg, 0.148 mmol) in the same manner as in step 1 of example 1a.

30 ESIMS, (M+H)⁺, m/z: 521.

[1149]

(Step 2)

4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-(piperidin-4-yl)benzamide hydrochloride (55 mg, 92%) was
5 obtained from tert-butyl 4-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)piperidine-1-carboxylate (66 mg, 0.127 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 421.

10 [1150]

(Step 3)

Compound 1c (30 mg, 28%) was obtained from 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-(piperidin-4-yl)benzamide hydrochloride (49 mg, 0.144 mmol) obtained in step 2 in
15 the same manner as in step 3 of example 1a.

ESIMS, (M+H)⁺, m/z: 741. ¹H NMR (DMSO-d₆, δ): 1.10-1.20 (m, 12H), 1.24-1.36 (m, 2H), 2.03-2.17 (m, 2H), 2.31-2.44 (m, 2H), 2.51-2.75 (m, 4H), 2.93-3.19 (m, 5H), 4.18-4.32 (m, 4H), 4.87-5.02 (m, 2H), 5.91 -5.99 (m, 1H), 6.56-6.64 (m, 5H), 7.14-7.35 (m, 11H), 7.58-7.68 (m, 2H).

20 [1151]

[Example 1d]

4-{[3-(3,5-Dimethylisoxazol-4-yl)-5-hydroxyphenyl](hydroxy)methyl}-N-[3-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]benzamide (Compound 1d)

25 N-(3-Aminopropyl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (123 mg, 0.32 mmol) obtained in step 2 of example 1a was dissolved in DMF (6.0 mL), then
4-{[3-(3,5-dimethylisoxazol-4-yl)-5-hydroxyphenyl](hydroxy)methyl}benzoic acid (110 mg, 0.32 mmol)
30 obtained in reference example 6, EDCI (124 mg, 0.65 mmol), HOBT (88 mg,

0.65 mmol) and N,N-diisopropylethylamine (0.23 mL, 1.30 mmol) were added to the solution, and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 63/37 to 59/41) to give compound 1d (39 mg, 17%).

ESIMS, (M+H)⁺, m/z: 716. ¹H NMR (CD₃OD, δ): 1.08-1.19 (m, 6H), 1.23-1.38 (m, 1H), 1.80-1.91 (m, 2H), 2.19 (s, 3H), 2.34 (s, 3H), 2.38-2.49 (m, 1H), 2.54-2.72 (m, 2H), 3.29-3.32 (m, 1H), 3.39-3.50 (m, 4H), 4.25 (dd, J = 12.3, 4.2 Hz, 1H), 5.79 (s, 1H), 6.61-6.70 (m, 3H), 6.79 (s, 1H), 6.84 (s, 1H), 7.18-7.30 (m, 4H), 7.50 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H).

[1152]

[Example 1e]

4-[(2-Ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl]-N-[3-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]benzamide (Compound 1e)

Compound 1e (15 mg, 24%) was obtained from N-(3-aminopropyl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (40 mg, 0.093 mmol) obtained in step 2 of example 1a and 4-[(2-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)methyl]benzoic acid (28 mg, 0.093 mmol) obtained in reference example 5 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 674. ¹H NMR (CDCl₃, δ): 1.10-1.22 (m, 9H), 1.27-1.35 (m, 1H), 1.79-1.89 (m, 2H), 2.06-2.18 (m, 2H), 2.37-2.48 (m, 3H), 2.51-2.72 (m, 6H), 3.44-3.59 (m, 4H), 4.22-4.32 (m, 1H), 4.92-5.04 (m, 1H), 5.11 (s, 2H), 6.40 (s, 1H), 6.60-6.66 (m, 2H), 6.96-7.01 (m, 2H), 7.11-7.17 (m, 1H), 7.19-7.24 (m, 2H), 7.28-7.35 (m, 1H), 7.68-7.72 (m,

2H), 7.72-7.78 (m, 1H), 7.82-7.88 (m, 2H).

[1153]

[Example 1f]

4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{3-[4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzamide]propyl}benzamide (Compound 1f)

Compound 1f (20 mg, 34%) was obtained from N-(3-aminopropyl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (35 mg, 0.081 mmol) obtained in step 2 of example 1a and 4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (29 mg, 0.081 mmol) obtained in reference example 4 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 729. ¹H NMR (CDCl₃, δ): 1.11-1.21 (m, 6H), 1.28-1.37 (m, 1H), 1.66 (s, 3H), 2.42 (s, 3H), 2.53-2.74 (m, 6H), 3.48-3.61 (m, 4H), 4.11-4.18 (m, 1H), 4.19-4.33 (m, 2H), 4.89-5.01 (m, 1H), 5.47-5.55 (m, 1H), 6.58-6.65 (m, 2H), 6.84-6.91 (m, 1H), 7.14-7.25 (m, 3H), 7.28-7.33 (m, 1H), 7.55-7.61 (m, 2H), 7.68-7.73 (m, 2H), 7.75-7.83 (m, 1H), 7.92-7.96 (m, 2H).

[1154]

[Example 1g]

4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-[1-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)azetidin-3-yl]benzamide (Compound 1g) (Step 1)

tert-Butyl 3-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)azetidine-1-carboxylate (47 mg, 80%) was obtained from 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (40 mg, 0.118 mmol) obtained

in step 6 of reference example 1 and tert-butyl 4-aminoazetidine-1-carboxylate (20 mg, 0.118 mmol) in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 493.

5 [1155]

(Step 2)

N-(Azetidin-3-yl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (34 mg, 100%) was obtained from tert-butyl 3-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)azetidine-1-carboxylate (39 mg, 0.079 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 393.

[1156]

15 (Step 3)

Compound 1g (12 mg, 21%) was obtained from N-(azetidin-3-yl)-4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (34 mg, 0.079 mmol) obtained in step 2 in the same manner as in step 3 of example 1a.

20 ESIMS, (M+H)⁺, m/z: 713. ¹H NMR (CDCl₃, δ): 1.09-1.19 (m, 12H), 1.23-1.35 (m, 2H), 2.32-2.46 (m, 2H), 2.51-2.72 (m, 4H), 4.16-4.29 (m, 4H), 4.58-4.72 (m, 2H), 4.82-5.03 (m, 3H), 6.49-6.63 (m, 4H), 7.14-7.25 (m, 8H), 7.25-7.33 (m, 2H), 7.43-7.54 (m, 2H), 7.67-7.76 (m, 2H).

[1157]

25 [Example 1h]

tert-Butyl 2-[(S)-2,3,9-trimethyl-4-(4-{[3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]carbamoyl}phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (Compound 1h)

30 (Step 1)

tert-Butyl [3-(4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]carbamate (512 mg, 100%) was obtained from 4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (350 mg, 1.03 mmol) obtained
5 in step 7 of reference example 1 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 495.

[1158]

(Step 2)

10 N-(3-Aminopropyl)-4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (279 mg, 100%) was obtained from tert-butyl [3-(4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propyl]carbamate (320 mg, 0.647 mmol) obtained in step 1 in the same manner as in step 2 of
15 example 1a.

ESIMS, (M+H)⁺, m/z: 395.

[1159]

(Step 3)

Compound 1h (35 mg, 36%) was obtained from N-(3-aminopropyl)-
20 4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (50 mg, 0.116 mmol) obtained in step 2 and (S)-4-{{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (54 mg, 0.116 mmol) obtained in reference example 3 in the same manner as in
25 step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 843. ¹H NMR (CDCl₃, δ): 1.10-1.18 (m, 6H), 1.25-1.35 (m, 1H), 1.50 (s, 9H), 1.97-2.10 (m, 2H), 2.19 (s, 3H), 2.30-2.46 (m, 4H), 2.52-2.73 (m, 5H), 3.45-3.59 (m, 6H), 4.16-4.28 (m, 1H), 4.37-4.44 (m, 1H), 4.56-4.64 (m, 1H), 4.83-5.01 (m, 1H), 6.51-6.66 (m, 2H), 6.99-
30 7.10 (m, 1H), 7.10-7.23 (m, 3H), 7.50-7.59 (m, 2H), 7.67-7.77 (m, 2H),

7.84-7.98 (m, 3H).

[1160]

[Example 1i]

tert-Butyl 2-((S)-4-{4-[4-(4-{(S)-6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-
5 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-
yl}benzamide)piperidine-1-carbonyl]phenyl}-2,3,9-trimethyl-6H-
thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (Compound
1i)

(Step 1)

10 tert-Butyl 4-aminopiperidine-1-carboxylate (1.0 g, 5.0 mmol) was
dissolved in dichloromethane (15 mL), then N,N-diisopropylethylamine
(2.61 mL, 15 mmol) and benzyl chloroformate (0.78 mL, 5.5 mmol) were
added to the solution under ice cooling. The mixture was stirred at room
temperature for 2 hours. Water was added to the reaction mixture, and
15 the mixture was extracted twice with ethyl acetate. The organic layer was
dried over anhydrous sodium sulfate and concentrated under reduced
pressure. The obtained residue was purified by silica gel column
chromatography (petroleum ether/ethyl acetate = 85/15 to 80/20) to give
tert-butyl 4-{{(benzyloxy)carbonyl}amino}piperidine-1-carboxylate (1.17
20 g, 70%).

ESIMS, (M+H)⁺, m/z: 335.

[1161]

(Step 2)

Benzylpiperidin-4-ylcarbamate (0.80 g, 85%) was obtained from
25 tert-butyl 4-{{(benzyloxy)carbonyl}amino}piperidine-1-carboxylate (1.17
g, 3.50 mmol) obtained in step 1 in the same manner as in step 2 of
example 1a.

ESIMS, (M+H)⁺, m/z: 235.

[1162]

30 (Step 3)

tert-Butyl (S)-2-(4-[4-(4-{{[(benzyloxy)carbonyl]amino}piperidine-1-carbonyl)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (105 mg, 72%) was obtained from benzylpiperidin-4-ylcarbamate (69 mg, 0.25 mmol) obtained in step 2 and
5 (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (104 mg, 0.21 mmol) obtained in reference example 3 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 683.

10 [1163]

(Step 4)

tert-Butyl (S)-2-(4-[4-(4-{{[(benzyloxy)carbonyl]amino}piperidine-1-carbonyl)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (105 mg, 0.15 mmol) obtained in step 3 was
15 dissolved in methanol (3.0 mL), then 20% palladium hydroxide (50 mg) was added to the solution, and the mixture was stirred at room temperature for 16 hours under a hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was slurry-refined with pentane to give
20 tert-butyl (S)-2-{4-[4-(4-aminopiperidine-1-carbonyl)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (70 mg, 83%).

ESIMS, (M+H)⁺, m/z: 549.

[1164]

25 (Step 5)

Compound 1i (80 mg, 42%) was obtained from tert-butyl (S)-2-{4-[4-(4-aminopiperidine-1-carbonyl)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (105 mg, 0.19 mmol) obtained in step 4 and (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-
30 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic

acid (89 mg, 0.19 mmol) obtained in reference example 3 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 997. ¹H NMR (DMSO-d₆, δ): 1.44 (s, 19H), 1.58 (s, 4H), 1.66 (s, 3H), 1.75 (brs, 1H), 1.91 (brs, 1H), 2.36-2.42 (m, 6H), 2.60-2.64 (m, 6H), 2.95 (brs, 1H), 3.15-3.16 (m, 1H), 3.37 (m, 4H), 3.49-3.51 (m, 1H), 4.08 (brs, 1H), 4.44 (q, J = 6.5 Hz, 3H), 7.42 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.5 Hz, 4H), 7.87 (d, J = 8.0 Hz, 2H), 8.39 (d, J = 7.5 Hz, 1H). [1165]

[Example 1j]

10 N,N'-[(1r,3r)-Cyclobutane-1,3-diyl]bis(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide) (Compound 1j)
(Step 1)

tert-Butyl [(1R,3r)-3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)cyclobutyl]carbamate (70 mg, 94%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 7 of reference example 1 and tert-butyl [(1r,3r)-3-aminocyclobutyl]carbamate (28 mg, 0.148 mmol) in the same manner as in step 3 of example 1b.

20 ESIMS, (M+H)⁺, m/z: 507.
[1166]
(Step 2)

N-[(1r,3R)-3-Aminocyclobutyl]-4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (60 mg, 98%) was obtained from tert-butyl [(1R,3r)-3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)cyclobutyl]carbamate (70 mg, 0.138 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 407.
30 [1167]

(Step 3)

Compound 1j (25 mg, 28%) was obtained from N-[(1*r*,3*R*)-3-aminocyclobutyl]-4-{[(2*S*,4*R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide hydrochloride (60 mg, 0.137 mmol) obtained in step 2 and 4-{[(2*S*,4*R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (42 mg, 0.124 mmol) obtained in step 7 of reference example 1 as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 727. ¹H NMR (CDCl₃, δ): 1.11-1.19 (m, 12H), 1.23-1.37 (m, 2H), 2.31-2.45 (m, 2H), 2.44-2.53 (m, 2H), 2.53-2.75 (m, 4H), 4.16-4.33 (m, 4H), 4.59-4.75 (m, 2H), 4.90-5.02 (m, 2H), 6.24-6.29 (m, 2H), 6.59-6.64 (m, 4H), 7.14-7.32 (m, 10H), 7.63-7.69 (m, 4H).

[1168]

[Example 1k]

1,1'-{(2*S*,2'*S*,4*R*,4'*R*)-{[(2,5-Diazabicyclo[2.2.1]heptane-2,5-dicarbonyl)bis(4,1-phenylene)]bis(azanediyl)}bis[2-methyl-3,4-dihydroquinoline-4,1(2H)-diyl]}bis(propan-1-one) (Compound 1k)

(Step 1)

tert-Butyl 5-(4-{[(2*S*,4*R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (38 mg, 49%) was obtained from 4-{[(2*S*,4*R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 7 of reference example 1 and tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (35.2 mg, 0.177 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 519.

[1169]

(Step 2)

tert-Butyl 5-(4-{[(2*S*,4*R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (38 mg, 0.073 mmol) obtained in step 1 was dissolved in

dichloromethane (1 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude product of 1-[(2S,4R)-4-{[4-(2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate (38 mg).

ESIMS, (M+H)⁺, m/z: 419.

[1170]

(Step 3)

Compound 1k (17 mg, 32%) was obtained from the crude product (38 mg) of 1-[(2S,4R)-4-{[4-(2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 739. ¹H-NMR (CDCl₃, δ): 1.12-1.19 (m, 12H), 1.26-1.36 (m, 4H), 2.31-2.43 (m, 2H), 2.53-2.72 (m, 4H), 3.67-3.83 (m, 4H), 4.11-4.18 (m, 2H), 4.18-4.27 (m, 2H), 4.90-5.00 (m, 2H), 6.54- 6.66 (m, 4H), 7.14-7.33 (m, 9H), 7.39-7.49 (m, 3H).

[1171]

[Example 1l]

N,N'-(2-Oxopropane-1,3-diyl)bis(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide) (Compound 1l)

(Step 1)

N,N'-(2-Hydroxypropane-1,3-diyl)bis(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide) (200 mg, 19%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (500 mg, 1.47 mmol) obtained in step 7 of reference example 1 and 1,3-diaminopropan-2-ol (66 mg, 0.73

thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoic acid (150 mg, 0.420 mmol) obtained in reference example 4 and tert-butyl (piperidin-4-yl)carbamate (93 mg, 0.460 mmol) in the same manner as in step 1 of example 1d.

5 ESIMS, (M+H)⁺, m/z: 535.

[1174]

(Step 2)

A crude product (65 mg) of (4-aminopiperidin-1-yl)[4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl]methanone hydrochloride was obtained from tert-butyl {1-[4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)benzoyl]piperidin-4-yl}carbamate (110 mg, 0.200 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 435.

15 [1175]

(Step 3)

Compound 1m (25 mg, total yield of 2 steps 9%) was obtained from the crude product (196 mg) of (4-aminopiperidin-1-yl)[4-(2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)phenyl]methanone hydrochloride obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (120 mg, 0.350 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 755. ¹H-NMR (DMSO-d₆, δ): 0.99-1.05 (m, 6H), 1.17-1.24 (m, 1H), 1.40-1.51 (m, 2H), 1.64 (s, 3H), 1.71 (s, 1H), 1.86 (s, 1H), 2.25 (dd, J = 15.72, 7.48 Hz, 1H), 2.41 (s, 3H), 2.51-2.64 (m, 5H), 2.95 (s, 1H), 3.14-3.17 (m, 1H), 3.49-3.50 (m, 1H), 4.03 (d, J = 7.63 Hz, 1H), 4.18 (d, J = 12.82 Hz, 1H), 4.24-4.29 (m, 1H), 4.42 (s, 1H), 4.74 (d, J = 6.10 Hz, 1H), 5.27 (d, J = 12.51 Hz, 1H), 6.57 (d, J = 7.93 Hz, 1H), 6.64 (d, J = 8.54 Hz, 2H), 7.08 (d, J = 7.63 Hz, 1H), 7.16 (t, J = 7.32 Hz, 1H),

7.20-7.32 (m, 2H), 7.40 (d, J = 8.24 Hz, 2H), 7.54 (d, J = 7.93 Hz, 2H), 7.63 (d, J = 8.85 Hz, 2H), 7.85 (d, J = 7.63 Hz, 1H).

[1176]

[Example 1n]

5 tert-Butyl 2-[(S)-2,3,9-trimethyl-4-(4-{[1-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)azetidin-3-yl]carbamoyl}phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (Compound 1n)

(Step 1)

10 tert-Butyl [1-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)azetidin-3-yl]carbamate (170 mg, 81%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (150 mg, 0.440 mmol) obtained in step 7 of reference example 1 and tert-butyl (azetidin-3-yl)carbamate (76 mg, 0.440 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 493.

[1177]

(Step 2)

20 tert-Butyl [1-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)azetidin-3-yl]carbamate (170 mg, 0.340 mmol) obtained in step 1 was dissolved in dichloromethane (6 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to give 1-[(2S,4R)-4-{[4-(3-aminoazetidine-1-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate (150 mg, 89%).

ESIMS, (M+H)⁺, m/z: 393.

[1178]

30 (Step 3)

Compound 1n (69 mg, 39%) was obtained from 1-[(2S,4R)-4-{[4-(3-aminoazetidine-1-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate (100 mg, 0.190 mmol) obtained in step 2 and (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (92 mg, 0.190 mmol) obtained in reference example 3 in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 841. ¹H-NMR (DMSO-d₆, δ): 0.99-1.05 (m, 6H), 1.20-1.25 (m, 1H), 1.44 (s, 9H), 1.59 (s, 3H), 2.19-2.27 (m, 1H), 2.41 (s, 3H), 2.57-2.64 (m, 5H), 3.34-3.36 (m, 2H), 4.15 (s, 1H), 4.23-4.28 (m, 3H), 4.43 (t, J = 1.5 Hz, 1H), 4.53-4.75 (m, 3H), 6.65 (d, J = 2.5 Hz, 3H), 7.10 (d, J = 7.32 Hz, 1H), 7.16-7.19 (m, 1H), 7.25-7.32 (m, 2H), 7.47-7.51 (m, 4H), 7.91 (d, J = 8.85 Hz, 2H), 9.12 (d, J = 7.02 Hz, 1H).

[1179]

[Example 1o]

tert-Butyl 2-[(S)-2,3,9-trimethyl-4-(4-{[2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)ethyl]carbamoyl}phenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (Compound 1o)

(Step 1)

tert-Butyl (S)-2-(4-{4-[(2-{[(benzyloxy)carbonyl]amino}ethyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (290 mg, 70%) was obtained from (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (300 mg, 0.64 mmol) obtained in reference example 3 and benzyl (2-aminoethyl)carbamate (249 mg, 1.29 mmol) in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 643.

[1180]

(Step 2)

tert-Butyl (S)-2-(4-{4-[(2-aminoethyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (200 mg, 87%) was obtained from tert-butyl (S)-2-(4-{4-[(2-
5 {[(benzyloxy)carbonyl]amino}ethyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (290 mg, 0.45 mmol) obtained in step 1 in the same manner as in step 4 of example 1i.

ESIMS, (M+H)⁺, m/z: 509.

10 [1181]

(Step 3)

Compound 1o (220 mg, 67%) was obtained from tert-butyl (S)-2-(4-{4-[(2-aminoethyl)carbamoyl]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (200 mg, 0.39 mmol)
15 obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (133 mg, 0.39 mmol) obtained in step 7 of reference example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 829. ¹H-NMR (DMSO-d₆, δ): 0.99-1.06 (m, 6H), 1.17-
20 1.26 (m, 1H), 1.43 (s, 9H), 1.59 (s, 3H), 2.22-2.28 (m, 1H), 2.41 (s, 3H), 2.57-2.64 (m, 5H), 3.24-3.28 (m, 2H), 3.40 (s, 4H), 4.27 (m, 1H), 4.44 (t, J = 7.2 Hz, 1H), 4.73-4.74 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.25-7.32 (m, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.88 (d, J =
25 8.0 Hz, 2H), 8.21 (brs, 1H), 8.68 (brs, 1H).

[1182]

[Example 2a]

4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{2-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
30 tetrahydroquinolin-4-yl]amino}phenyl)amino]-2-oxoethyl}benzamide

(Compound 2a)

(Step 1)

A crude product (263 mg) of (9H-fluoren-9-yl)methyl{2-[(4-
5 {[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}phenyl)amino]-2-oxoethyl}carbamate was obtained from 1-
{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-
1(2H)-yl}propan-1-one (100 mg, 0.323 mmol obtained in step 2 of
reference example 7 and {[(9H-fluoren-9-yl)methoxy]carbonyl}glycine
(144 mg, 0.485 mmol) in the same manner as in step 1 of example 1a.
10 ESIMS, (M+H)⁺, m/z: 589.
[1183]

(Step 2)

The crude product (263 mg) of (9H-fluoren-9-yl)methyl {2-[(4-
5 {[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}phenyl)amino]-2-oxoethyl}carbamate obtained in step 1 was
dissolved in DMF (1.6 mL), then piperidine (0.160 mL, 1.62 mmol) was
added to the solution, and the mixture was stirred at room temperature
overnight. Water was added to the reaction mixture, then the reaction
mixture was filtered, and the filtrate was extracted twice with ethyl acetate.
20 The organic layer was washed with saturated aqueous sodium chloride
solution, dried over anhydrous sodium sulfate, and concentrated under
reduced pressure. The obtained residue was purified by silica gel
chromatography (chloroform/methanol = 10/0 to 9/1) to give 2-amino-N-
(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
25 yl]amino}phenyl)acetamide (50.7 mg, total yield of 2 steps 43%).
ESIMS, (M+H)⁺, m/z: 367.
[1184]

(Step 3)

Compound 2a (3.2 mg, 9%) was obtained from 2-amino-N-(4-
30 {[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

- yl]amino}phenyl)acetamide (19.5 mg, 0.053 mmol) obtained in step 2 and 4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (21.4 mg, 0.063 mmol) obtained in step 6 of reference example 1 in the same manner as in step 1 of example 1a.
- 5 ESIMS, (M+H)⁺, m/z: 687 ¹H-NMR (CDCl₃, δ): 1.10-1.20 (m, 12H), 1.24-1.33 (m, 2H), 2.31-2.44 (m, 2H), 2.51-2.73 (m, 4H), 4.10-4.19 (m, 2H), 4.21-4.30 (m, 4H), 4.88-5.00 (m, 2H), 5.32-5.37 (m, 1H), 6.59 (d, J = 9.0 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 7.13-7.30 (m, 8H), 7.33 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H).
- 10 [1185]
[Example 2b]
tert-Butyl 2-[(S)-4-{4-[2-(4-{(S)-6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzamide)acetamide]phenyl}-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (Compound 2b)
- 15 (Step 1)
(S)-4-{6-[2-(tert-Butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (200 mg, 0.430 mmol) obtained in reference example 3 was dissolved in toluene
- 20 (10 mL), then DPPA (124 mg, 0.450 mmol) and triethylamine (104 mg, 1.03 mmol) were added to the solution, and the mixture was stirred at room temperature for 3 hours. Water (3 mL) was added to the reaction mixture, and the mixture was stirred at 70°C for 2 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, dried over
- 25 anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (acetonitrile/10 mmol/L aqueous ammonium bicarbonate solution = 42/58) to give tert-butyl (S)-2-{4-(4-aminophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (45 mg, 22%).
- 30 ESIMS, (M+H)⁺, m/z: 438.

[1186]

(Step 2)

tert-Butyl (S)-2-{4-[4-(2-
{[(benzyloxy)carbonyl]amino}acetamide)phenyl]-2,3,9-trimethyl-6H-
5 thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (70 mg,
74%) was obtained from tert-butyl (S)-2-{4-(4-aminophenyl)-2,3,9-
trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate
(60 mg, 0.140 mmol) obtained in step 1, and 2-
{[(benzyloxy)carbonyl]amino}acetic acid (34.4 mg, 0.160 mmol) in the
10 same manner as in step 1 of example 1a.
ESIMS, (M+H)⁺, m/z: 629.

[1187]

(Step 3)

tert-Butyl (S)-2-{4-[4-(2-
15 {[(benzyloxy)carbonyl]amino}acetamide)phenyl]-2,3,9-trimethyl-6H-
thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (70 mg,
0.110 mmol) obtained in step 2 was dissolved in methanol (20 mL), then
palladium on carbon (70 mg, 10 wt%) was added to the solution, and the
mixture was stirred overnight at room temperature under a hydrogen
20 atmosphere. The reaction mixture was filtered, and the filtrate was
concentrated under reduced pressure to give tert-butyl (S)-2-{4-[4-(2-
aminoacetamide)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (50 mg, 84%).
ESIMS, (M+H)⁺, m/z: 495.

25 [1188]

(Step 4)

Compound 2b (17 mg, 17%) was obtained from tert-butyl (S)-2-{4-
[4-(2-aminoacetamide)phenyl]-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (53 mg, 0.110 mmol)
30 obtained in step 3 and (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-

trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (50 mg, 0.110 mmol) obtained in reference example 3 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 943. ¹H-NMR (CD₃OD, δ): 1.53 (s, 18H), 1.73 (d, J = 8.8 Hz, 6H), 2.48 (s, 6H), 2.80-2.70 (m, 6H), 3.52-3.40 (m, 4H), 4.22 (s, 2H), 4.64-4.51 (m, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H).

[1189]

[Example 2c]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{(R)-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxopropan-2-yl}benzamide (Compound 2c)

(Step 1)

tert-Butyl {(R)-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxopropan-2-yl}carbamate (160 mg, 68%) was obtained from 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (150 mg, 0.480 mmol) obtained in step 2 of reference example 7, and (tert-butoxycarbonyl)-D-alanine (92 mg, 0.480 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 481.

[1190]

(Step 2)

(R)-2-Amino-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)propanamide hydrochloride (160 mg, 92%) was obtained from tert-butyl {(R)-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxopropan-2-yl}carbamate (200 mg, 0.410 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 381.

[1191]

(Step 3)

Compound 2c (86 mg, 32%) was obtained from (R)-2-amino-N-(4-
5 {[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}phenyl)propanamide hydrochloride (160 mg, 0.380 mmol)
obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}benzoic acid (130 mg, 0.380 mmol)
obtained in step 7 of reference example 1 in the same manner as in step 1
10 of example 1d.

ESIMS, (M+H)⁺, m/z: 701. ¹H-NMR (DMSO-d₆, δ): 0.98-1.06 (m, 12H),
1.11-1.23 (m, 2H), 1.37 (d, J = 7.2 Hz, 3H), 2.20-2.33 (m, 2H), 2.55-2.67
(m, 4H), 4.12 (brs, 1H), 4.26-4.28 (m, 1H), 4.53 (t, J = 7.2 Hz, 1H), 4.71-
4.73 (m, 2H), 5.86 (d, J = 8.0 Hz, 1H), 6.57-6.67 (m, 5H), 7.09-7.18 (m,
15 4H), 7.23-7.32 (m, 6H), 7.70 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 7.6 Hz, 1H),
9.59 (s, 1H)

[1192]

[Example 2d]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
20 yl]amino}-N-{(S)-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxopropan-2-
yl}benzamide (Compound 2d)

(Step 1)

tert-Butyl {(S)-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
25 tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxopropan-2-
yl}carbamate (155 mg, 67%) was obtained from 1-{(2S*,4R*)-4-[(4-
aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-
one (150 mg, 0.480 mmol) obtained in step 2 of reference example 7, and
(tert-butoxycarbonyl)-L-alanine (92 mg, 0.480 mmol) in the same manner
30 as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 481.

[1193]

(Step 2)

(S)-2-Amino-N-(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl}propanamide hydrochloride (120 mg, 90%) was obtained from tert-butyl {(S)-1-[(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl]amino]-1-oxopropan-2-yl}carbamate (155 mg, 0.320 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 381.

[1194]

(Step 3)

Compound 2d (55 mg, 27%) was obtained from (S)-2-amino-N-(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl}propanamide hydrochloride (120 mg, 0.310 mmol) obtained in step 2 and 4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (106 mg, 0.310 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 701. ¹H-NMR (DMSO-d₆, δ): 0.98-1.06 (m, 12H), 1.14-1.24 (m, 2H), 1.35 (d, J = 7.6 Hz, 3H), 2.20-2.28 (m, 2H), 2.55-2.64 (m, 4H), 4.08-4.12 (m, 1H), 4.26-4.31 (m, 1H), 4.54 (t, J = 7.0 Hz, 1H), 4.71-4.75 (m, 2H), 5.85 (d, J = 8.0 Hz, 1H), 6.56-6.60 (m, 3H), 6.66 (d, J = 8.8 Hz, 2H), 7.09-7.18 (m, 4H), 7.24-7.32 (m, 6H), 7.71 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 7.2 Hz, 1H), 9.58 (s, 1H)

[1195]

[Example 2e]

N-{{(S)-3-Methyl-1-[(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl]amino)-1-oxobutan-2-yl}}-4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

yl]amino}benzamide (Compound 2e)

(Step 1)

tert-Butyl {(S)-3-methyl-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxobutan-2-yl}carbamate (160 mg, 67%) was obtained from 1-{[(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (150 mg, 0.480 mmol) obtained in step 2 of reference example 7 and (tert-butoxycarbonyl)-L-valine (105 mg, 0.480 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 509.

[1196]

(Step 2)

(S)-2-Amino-3-methyl-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)butanamide hydrochloride (125 mg, 92%) was obtained from tert-butyl {(S)-3-methyl-1-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-1-oxobutan-2-yl}carbamate (160 mg, 0.314 mmol) obtained in step 1 in the same manner as in step 2 of example 1a. ESIMS, (M+H)⁺, m/z: 409.

[1197]

(Step 3)

Compound 2e (55 mg, 27%) was obtained from (S)-2-amino-3-methyl-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)butanamide hydrochloride (125 mg, 0.280 mmol) obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (95 mg, 0.280 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESIMS, (M-H)⁻, m/z: 727. ¹H-NMR (DMSO-d₆, δ): 0.93-1.06 (m, 18H),

1.11-1.26 (m, 2H), 2.13-2.28 (m, 3H), 2.56-2.63 (m, 4H), 4.11-4.23 (m,

1H), 4.27-4.36 (m, 2H), 4.71-4.75 (m, 2H), 5.86 (d, J = 8.0 Hz, 1H), 6.58-6.67 (m, 4H), 7.08-7.18 (m, 4H), 7.25-7.33 (m, 5H), 7.70 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.8 Hz, 1H), 9.70 (s, 1H).

[1198]

5 [Example 2f]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{3-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-3-oxopropyl}benzamide
(Compound 2f)

10 (Step 1)

Ethyl 3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propanoate (150 mg, 77%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (150 mg, 0.44 mmol) obtained in step 7 of reference example 1 and ethyl 3-aminopropanoate hydrochloride (0.102 g, 0.66 mmol) in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 438.

[1199]

20 (Step 2)

Ethyl 3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)propanoate (150 mg, 0.34 mmol) obtained in step 1 was dissolved in a mixed solvent (5.0 mL) of THF and water (4:1), then lithium hydroxide monohydrate (0.029 g, 0.69 mmol) was added to the solution, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, then the obtained residue was diluted with ice water, and an aqueous citric acid solution was added at 0°C until the diluted residue became acidic. The precipitated solid was collected by filtration and dried under reduced pressure to give a crude product of 3-(4-{[(2S,4R)-2-

methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]benzamide}propanoic acid (100 mg).

ESIMS, (M+H)⁺, m/z: 410.

[1200]

5 (Step 3)

Compound 2f (65 mg, total yield of 2 steps 27%) was obtained from the crude product (100 mg, 0.24 mmol) of 3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]benzamide}propanoic acid obtained in step 2 and 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (75.0 mg, 0.24 mmol) obtained in step 2 of reference example 7 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 701. ¹H-NMR (DMSO-d₆, δ): 1.01-1.05 (m, 12H), 1.13-1.24 (m, 2H), 2.21-2.23 (m, 2H), 2.56-2.62 (m, 6H), 3.48 (q, J = 6.5 Hz, 2H), 4.09-4.12 (m, 1H), 4.25-4.26 (m, 1H), 4.72-4.74 (m, 2H), 5.87 (d, J = 8.0 Hz, 1H), 6.56-6.65 (m, 5H), 7.09 (d, J = 7.5 Hz, 1H), 7.15-7.18 (m, 3H), 7.23-7.31 (m, 6H), 7.63 (d, J = 8.5 Hz, 2H), 8.14 (t, J = 5.3 Hz, 1H), 9.59 (s, 1H).

[1201]

20 [Example 2g]

1-(4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]benzoyl)-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]phenyl)piperidine-4-carboxamide (Compound 2g)

25 (Step 1)

A crude product (0.12 g) of tert-butyl 4-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino]phenyl}carbamoyl]piperidine-1-carboxylate was obtained from 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.1 g, 0.32 mmol) obtained in step 2 of reference

example 7 and 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (0.074 g, 0.32 mmol) in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 521.

[1202]

5 (Step 2)

A crude product (0.15 g) of N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)piperidine-4-carboxamide hydrochloride was obtained from the crude product (0.17 g, 0.32 mmol) of tert-butyl 4-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)carbamoyl]piperidine-1-carboxylate
10 obtained in step 1 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 421.

[1203]

(Step 3)

15 Compound 2g (0.032 g, total yield of 3 steps 9%) was obtained from the crude product (0.15 g, 0.32 mmol) of N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)piperidine-4-carboxamide hydrochloride obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (0.11 g, 0.32 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 741.61. ¹H-NMR (DMSO-d₆, δ): 0.99-1.05 (m, 12H), 1.13-1.24 (m, 2H), 1.55-1.57 (m, 2H), 1.77 (d, J = 11.60 Hz, 2H), 2.21-2.25 (m, 2H), 2.53-2.62 (m, 5H), 2.92 (s, 2H), 4.09-4.22 (m, 4H), 4.73 (t, J = 7.25 Hz, 2H), 5.87 (d, J = 7.93 Hz, 1H), 6.49 (d, J = 7.63 Hz, 1H), 6.58 (d, J = 8.54 Hz, 2H), 6.66 (d, J = 8.24 Hz, 2H), 7.14-7.31 (m, 12H), 9.54 (s, 1H).

[1204]

[Example 2h]

30 1-(4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

ESIMS, (M+H)⁺, m/z: 713.53. ¹H-NMR (DMSO-d₆, δ): 1.00-1.05 (m, 12H), 1.14-1.22 (m, 2H), 2.21-2.24 (m, 2H), 2.59 (d, J = 8.5 Hz, 4H), 3.50 (s, 1H), 4.06-4.12 (m, 3H), 4.26-4.45 (m, 3H), 4.73 (s, 2H), 5.91 (d, J = 7.63 Hz, 1H), 6.59-6.67 (m, 5H), 7.01-7.19 (m, 4H), 7.26-7.32 (m, 6H), 7.45
5 (d, J = 8.54 Hz, 2H), 9.70 (s, 1H).

[1207]

[Example 2i]

(R)-1-(4-{{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl})-N-(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
10 tetrahydroquinolin-4-yl]amino}phenyl})pyrrolidine-3-carboxamide
(Compound 2i)

(Step 1)

tert-Butyl (R)-3-[(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}phenyl})carbamoyl]pyrrolidine-1-
15 carboxylate (55 mg, 84%) was obtained from 1-{{[(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]}propan-1-one (40 mg, 0.129 mmol) obtained in step 2 of reference example 7 and (R)-1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (28 mg, 0.129 mmol) in the same manner as in step 3 of example 1b.

20 ESIMS, (M+H)⁺, m/z: 507.

[1208]

(Step 2)

(R)-N-(4-{{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}phenyl})pyrrolidine-3-carboxamide
25 hydrochloride (57 mg, 100%) was obtained from tert-butyl (R)-3-[(4-{{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl})carbamoyl]pyrrolidine-1-carboxylate (65 mg, 0.128 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.
ESIMS, (M+H)⁺, m/z: 407.

30 [1209]

(Step 3)

Compound 2i (25 mg, 28%) was obtained from (R)-N-(4-
{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}phenyl)pyrrolidine-3-carboxamide hydrochloride (55 mg, 0.124
5 mmol) obtained in step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}benzoic acid (42 mg, 0.124 mmol) obtained
in step 7 of reference example 1 in the same manner as in step 3 of example
1b.

ESIMS, (M+H)⁺, m/z: 727. ¹H-NMR (CDCl₃, δ): 1.07-1.20 (m, 12H), 1.20-
10 1.33 (m, 2H), 2.32-2.44 (m, 3H), 2.50-2.68 (m, 4H), 2.86-3.14 (m, 1H),
3.36-3.66 (m, 4H), 3.72-3.92 (m, 2H), 4.07-4.25 (m, 2H), 4.82-5.02 (m,
2H), 6.52-6.66 (m, 4H), 7.11-7.49 (m, 13H), 7.99-8.19 (m, 1H).

[1210]

[Example 2j]

15 3-(4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}benzamide)-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}phenyl)benzamide (Compound 2j)

(Step 1)

A crude product (0.12 g) of methyl 3-(4-{[(2S,4R)-2-methyl-1-
20 propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)benzoate was
obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl]amino}benzoic acid (0.1 g, 0.29 mmol) obtained in
step 7 of reference example 1 and methyl 3-aminobenzoate (0.045 g, 0.29
mmol) in the same manner as in step 1 of example 1a.

25 ESIMS, (M+H)⁺, m/z: 472.

[1211]

(Step 2)

3-(4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}benzamide)benzoic acid (0.1 g, 87%) was obtained from the
30 crude product (0.12 g, 0.25 mmol) of methyl 3-(4-{[(2S,4R)-2-methyl-1-

propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)benzoate
obtained in step 1 in the same manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 458.

[1212]

5 (Step 3)

Compound 2j (0.037 g, 19%) was obtained from 3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzamide)benzoic acid (0.1 g, 0.21 mmol) obtained in step 2 and
10 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.068 g, 0.218 mmol) obtained in step 2 of reference example 7 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 749. ¹H-NMR (DMSO-d₆, δ): 0.99-1.07 (m, 12H), 1.56-1.25 (m, 2H), 2.22-2.29 (m, 2H), 2.55-2.66 (m, 4H), 4.10-4.19 (m,
15 1H), 4.27-4.36 (m, 1H), 4.75 (t, J = 6.6 Hz, 2H), 5.95 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.0 Hz, 3H), 7.12 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 5.2 Hz, 3H), 7.24-7.33 (m, 4H), 7.41-7.47 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.8 Hz, 1H), 8.23 (s, 1H), 9.91 (s, 1H), 9.98 (s, 1H).

20 [1213]

[Example 3a]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{[1-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-1H-1,2,3-triazol-4-yl]methyl}benzamide (Compound 3a)
25 (Step 1)

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-(prop-2-yn-1-yl)benzamide (52 mg, 96%) was obtained from
4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 7 of reference
30

example 1 and propargylamine (0.014 mL, 0.222 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 376.

[1214]

5 (Step 2)

1-{{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (6 mg, 0.019 mmol) obtained in step 3 of reference example 7 was dissolved in acetonitrile, then ADMP (6.6 mg, 0.023 mmol) and DMAP (2.8 mg, 0.023 mmol) were added to the
10 solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude product (15 mg) of 1-{{(2S,4R)-4-[(4-azidophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one.

ESIMS, (M+H)⁺, m/z: 336.

15 [1215]

(Step 3)

A crude product (15 mg) of 1-{{(2S,4R)-4-[(4-azidophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one obtained in step 2 and
4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-(prop-2-yn-1-yl)benzamide (6.7 mg, 0.018 mmol) obtained in
20 step 1 were dissolved in a mixed solvent (0.6 mL) of ethanol and water (1:1), then sodium L-ascorbate (1.8 mg, 0.0089 mmol) and copper sulfate pentahydrate (4.5 mg, 0.018 mmol) were added to the solution, and the mixture was stirred at 60°C overnight. The reaction mixture was diluted
25 with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (acetonitrile/0.1% TFA aqueous solution = 45/55 to 50/50) to give compound 3a (4 mg, total yield of 2 steps 9%).

ESIMS, (M+H)⁺, m/z: 711. ¹H-NMR (CDCl₃, δ): 1.12-1.21 (m, 12H), 1.23-
30 1.37 (m, 2H), 2.35-2.45 (m, 2H), 2.54-2.74 (m, 4H), 4.01 (brs, 2H), 4.20-

4.28 (m, 2H), 4.76 (d, J = 5.9 Hz, 2H), 4.95-4.97 (m, 2H), 6.61 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 7.14-7.37 (m, 8H), 7.50 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 8.05 (s, 1H).

[1216]

5 [Example 3b]

tert-Butyl 2-[(S)-4-(4-{4-[(4-{(S)-6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzamide)methyl]-1H-1,2,3-triazol-1-yl}phenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (Compound

10 3b)

(Step 1)

tert-Butyl (S)-2-[4-(4-bromophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (5.0 g, 10.0 mmol) synthesized according to the method described in WO2017/030814 was dissolved in a mixed solvent (2.0 mL) of ethanol and water (3:1), then sodium azide (26 mg, 0.399 mmol), (1R,2R)-N,N'-dimethylcyclohexane-1,2-diamine (0.00473 mL, 0.030 mmol), sodium (R)-ascorbate (2.4 mg, 0.012 mmol) and copper iodide (3.8 mg, 0.02 mmol) were added to the solution, and the mixture was refluxed for 3 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 100/0 to 60/40) to give tert-butyl (S)-2-[4-(4-azidophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (60 mg, 65%).

ESIMS, (M+H)⁺, m/z: 464.

[1217]

(Step 2)

30 tert-Butyl (S)-2-{2,3,9-trimethyl-4-[4-(prop-2-yn-1-

ylcarbamoyl)phenyl]-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (90 mg, 93%) was obtained from (S)-4-{6-[2-(tert-butoxy)-2-oxoethyl]-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl}benzoic acid (90 mg, 0.193 mmol) obtained in reference example 3 and prop-2-yn-1-amine (0.0183 mL, 0.289 mmol) in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 504.

[1218]

(Step 3)

tert-Butyl (S)-2-[4-(4-azidophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetate (21 mg, 0.045 mmol) obtained in step 1 and tert-butyl (S)-2-{2,3,9-trimethyl-4-[4-(prop-2-yn-1-ylcarbamoyl)phenyl]-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate (27 mg, 0.054 mmol) obtained in step 2 were dissolved in a mixed solvent (1.5 mL) of s-butanol and water (3: 2), then sodium (R)-ascorbate (2.4 mg, 0.012 mmol) and copper(II) sulfate pentahydrate (5.7 mg, 0.023 mmol) were added to the solution, and the mixture was stirred at 50°C for 6 hours. Water was added to the reaction mixture, and the mixture was extracted twice with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (aqueous ammonium bicarbonate solution/acetonitrile = 50/50-40/60) to give compound 3b (14 mg, 32%).

ESIMS, (M+H)⁺, m/z: 967. ¹H-NMR (CDCl₃, δ): 1.24-1.27 (m, 3H), 1.48-1.53 (m, 18H), 1.61-1.63 (m, 3H), 2.36-2.48 (m, 6H), 2.63-2.78 (m, 6H), 3.49-3.60 (m, 4H), 4.54-4.64 (m, 2H), 4.75-4.85 (m, 2H), 7.05-7.14 (m, 1H), 7.47-7.56 (m, 2H), 7.59-7.67 (m, 2H), 7.69-7.84 (m, 4H), 8.13 (s, 1H).

[1219]

[Example 3c]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{[5-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-1,3,4-oxadiazol-2-yl]methyl}benzamide (Compound 3c)

5 (Step 1)

tert-Butyl {2-[2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)hydrazinyl]-2-oxoethyl}carbamate (30 mg, 25%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (80 mg, 0.236 mmol) obtained in step 7 of reference example 1 and tert-butyl (2-hydrazinyl-2-oxoethyl)carbamate (67.1 mg, 0.355 mmol) in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 510.

[1220]

15 (Step 2)

tert-Butyl {2-[2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)hydrazinyl]-2-oxoethyl}carbamate (15 mg, 29 μmol) obtained in step 1 was dissolved in acetonitrile (0.3 mL), then triphenylphosphine (15 mg, 0.059 mmol), carbon tetrachloride (0.011 mL, 0.118 mmol) and triethylamine (0.0082 mL, 0.059 mmol) were added to the solution, and the mixture was stirred at 80°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by reverse phase HPLC (acetonitrile/0.1% TFA aqueous solution = 40/60 to 50/50) to give tert-butyl {[5-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-1,3,4-oxadiazol-2-yl]methyl}carbamate (10 mg, yield 69%).

ESI-MS, (M+H)⁺, m/z: 492.

[1221]

(Step 3)

30 tert-Butyl {[5-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-

tetrahydroquinolin-4-yl]amino}phenyl)-1,3,4-oxadiazol-2-yl]methyl}carbamate (10 mg, 0.020 mmol) obtained in step 2 was dissolved in dichloromethane (1 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude product (8 mg) of 1-[(2S,4R)-4-({4-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate.

ESI-MS, (M+H)⁺, m/z: 392.

10 [1222]

(Step 4)

Compound 3c (2.3 mg, total yield of 2 steps 16%) was obtained from the crude product (8 mg) of 1-[(2S,4R)-4-({4-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-

15 yl]propan-1-one trifluoroacetate obtained in step 3 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (10.3 mg, 0.031 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESI-MS, (M+H)⁺, m/z: 712. ¹H-NMR (CDCl₃, δ): 1.13-1.19 (m, 12H), 1.25-1.35 (m, 2H), 2.23 (t, J = 7.7 Hz, 1H), 2.33-2.43 (m, 2H), 2.54-2.65 (m, 2H), 2.64-2.74 (m, 2H), 4.23-4.30 (m, 2H), 4.91 (d, J = 5.4 Hz, 2H), 4.93-5.01 (m, 2H), 5.32-5.37 (m, 1H), 6.63 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 7.15-7.34 (m, 8H), 7.71 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.6 Hz, 2H).

25 [1223]

[Example 3d]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{[5-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-1,2,4-oxadiazol-3-

30 yl]methyl}benzamide (Compound 3d)

(Step 1)

Methyl 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (1.9 g, 5.39 mmol) obtained in step 5 of reference example 1 was dissolved in THF (20 mL), then di-tert-butyl dicarbonate (3.53 g, 16.2 mmol) and dimethylaminopyridine (66 mg, 0.539 mmol) were added to the solution, and the mixture was stirred overnight under reflux. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/2 to 6/4) to give methyl 4-{(tert-butoxycarbonyl)[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (2.09 g, 86%).
ESIMS, (M+H)⁺, m/z: 453.

[1224]

15 (Step 2)

Methyl 4-{(tert-butoxycarbonyl)[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoate (259 mg, 0.572 mmol) obtained in step 1 was dissolved in methanol (3 mL), then aqueous sodium hydroxide solution (4 mol/L, 3 mL) was added to the solution, and the mixture was stirred for 3 hours under reflux. The reaction mixture was neutralized with hydrochloric acid (5 mol/L), and extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude product (270 mg) of 4-{(tert-butoxycarbonyl)[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid.
ESIMS, (M-H)⁻, m/z: 437.

[1225]

(Step 3)

The crude product (270 mg) of 4-{(tert-butoxycarbonyl)[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid

obtained in step 2 was dissolved in DMF (3 mL), then tert-butyl [2-amino-2-(hydroxyimino)ethyl]carbamate (175 mg, 0.924 mmol), COMU (396 mg, 0.924 mmol) and N,N-diisopropylethylamine (0.209 mL, 1.23 mmol) were added to the solution, and the mixture was stirred at 60°C overnight, and
5 then at 100°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/2 to 6/4) to give tert-butyl [4-(3-{{[(tert-butoxycarbonyl)amino]methyl}-1,2,4-oxadiazol-5-yl)phenyl][(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate (57 mg, total yield of 2 steps 15%).

ESIMS, (M+H)⁺, m/z: 592.

[1226]

(Step 4)

tert-Butyl [4-(3-{{[(tert-butoxycarbonyl)amino]methyl}-1,2,4-oxadiazol-5-yl)phenyl][(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate (57 mg, 0.096 mmol) obtained in step
15 3 was dissolved in dichloromethane (1 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude product (37 mg) of 1-[(2S,4R)-4-({4-[3-(aminomethyl)-1,2,4-oxadiazol-5-yl]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate.

ESIMS, (M+H)⁺, m/z: 392.

[1227]

25 (Step 5)

Compound 3d (1.6 mg, total yield of 2 steps 2%) was obtained from the crude product (37 mg, 0.095 mmol) of 1-[(2S,4R)-4-({4-[3-(aminomethyl)-1,2,4-oxadiazol-5-yl]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one trifluoroacetate obtained in step 4
30 and 4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

yl]amino}benzoic acid (32 mg, 0.095 mmol) obtained in step 7 of reference example 1 in the same manner as in step 1 of example 1d.

ESIMS, (M+H)⁺, m/z: 712. ¹H-NMR (CDCl₃, δ): 1.11-1.20 (m, 12H), 1.27-1.37 (m, 2H), 2.33-2.44 (m, 2H), 2.54-2.74 (m, 4H), 4.22-4.33 (m, 2H), 4.81 (d, J = 5.0 Hz, 2H), 4.96 (s, 2H), 6.63 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.2 Hz, 2H), 7.14-7.34 (m, 8H), 7.72 (d, J = 8.6 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H).

[1228]

[Example 3e]

1-[(2S,4R)-2-Methyl-4-({4-[3-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl]phenyl}amino)-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (Compound 3e)
(Step 1)

tert-Butyl 3-bromo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (80 mg, 0.265 mmol) purchased from J&W PharmLab was dissolved in THF (1.5 ml), then isopropylmagnesium chloride-lithium chloride (1.3 mol/L THF solution, 0.346 ml, 0.450 mmol) was added to the solution at -10°C, and the mixture was stirred at -10°C for 1 hour. Tributyltin chloride (0.122 ml, 0.450 mmol) was added to the reaction mixture, and the mixture was stirred at 0°C for 1 hour and then at room temperature for 1 hour. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude product (312 mg) of tert-butyl 3-(tributylstannyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate.

ESIMS, (M+H)⁺, m/z: 514.

[1229]

(Step 2)

1-{(2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-

5 dihydroquinolin-1(2H)-yl}propan-1-one (39.6 mg, 0.106 mmol) obtained in reference example 2 was dissolved in toluene (2 mL), then the crude product (312 mg) of tert-butyl 3-(tributylstannyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate obtained in step 1 and Pd(PPh₃)₄ (12.3 mg, 0.011 mmol) were added to the solution, and the mixture was stirred under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol = 99/1 to 97/3) and reverse phase HPLC (0.05% TFA/acetonitrile = 53/35 to 43/45) to give tert-butyl 3-(4-
10 {[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (28.2 mg, 52%).

ESIMS, (M+H)⁺, m/z: 516.

[1230]

15 (Step 3)

1-((2S,4R)-2-Methyl-4-{[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (23.0 mg, 93%) was obtained from tert-butyl 3-(4-
20 {[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (28.2 mg, 0.055 mmol) obtained in step 2 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 416.

[1231]

25 (Step 4)

Compound 3e (15.7 mg, 42%) was obtained from 1-((2S,4R)-2-methyl-4-{[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (23.0 mg, 0.051 mmol) obtained in step 3 and 4-{[(2S,4R)-
30 2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid

(17.2 mg, 0.051 mmol) obtained in step 7 of reference example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 736.6. ¹H-NMR (DMSO-d₆, δ): 0.98-1.06 (m, 12H), 1.17-1.28 (m, 2H), 2.19-2.30 (m, 2H), 2.54-2.69 (m, 4H), 3.85-3.89 (m, 2H), 4.01-4.08 (m, 2H), 4.15-4.30 (m, 2H), 4.70-4.79 (m, 4H), 6.29 (d, J = 7.7 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 6.70 (dd, J = 8.6, 4.5 Hz, 4H), 6.88 (s, 1H), 7.12-7.37 (m, 12H).

[1232]

[Example 3f]

1-[(2S,4R)-2-Methyl-4-({4-[2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl]phenyl}amino)-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (Compound 3f)
(Step 1)

1-{{(2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (200 mg, 0.536 mmol) obtained in reference example 2 was dissolved in 1,4-dioxane (1 mL), then potassium acetate (105 mg, 1.07 mmol), bis(pinacolato)diboron (163 mg, 0.643 mmol) and PdCl₂(dppf)-CH₂Cl₂ (43.8 mg, 0.054 mmol) were added to the solution, and the mixture was stirred for 2 hours under reflux. Water and ethyl acetate were added to the reaction mixture, the mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 90/10 to 60/40) to give 1-((2S,4R)-2-methyl-4-{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (101 mg, 45%).

ESIMS, (M+H)⁺, m/z: 421.

[1233]

(Step 2)

1-((2S,4R)-2-Methyl-4-{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (50.0 mg, 0.119 mmol) obtained in step 1 was dissolved in a mixed solvent (3.3 mL) of 1,4-dioxane and water(3:1), then tert-butyl 2-bromo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (53.9 mg, 0.178 mmol) purchased from J&W PharmLab, cesium carbonate (78.0 mg, 0.238 mmol) and Pd(PPh₃)₄ (20.6 mg, 0.018 mmol) were added to the solution, and the mixture was stirred for 14 hours under reflux. Water and ethyl acetate were added to the reaction mixture, the mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 50/50 to 0/100) to give a crude product (87.4 mg) of tert-butyl 2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate.

ESIMS, (M+H)⁺, m/z: 516.

[1234]

(Step 3)

1-((2S,4R)-2-Methyl-4-{[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (49.4 mg, 92%) was obtained from the crude product (87.4 mg) of tert-butyl 2-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate obtained in step 2 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 416.

[1235]

(Step 4)

Compound 3f (11.4 mg, 15%) was obtained from 1-((2S,4R)-2-methyl-4-{[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-

yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (42.1 mg, 0.101 mmol) obtained in step 3 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (37.7 mg, 0.111 mmol) obtained in step 7 of reference example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 736. ¹H-NMR (DMSO-d₆, δ): 0.99-1.06 (m, 12H), 1.14-1.28 (m, 2H), 2.19-2.30 (m, 2H), 2.57-2.67 (m, 4H), 3.92 (t, J = 5.0 Hz, 2H), 4.05 (t, J = 5.0 Hz, 2H), 4.14-4.31 (m, 2H), 4.69-4.79 (m, 4H), 6.02 (d, J = 7.7 Hz, 1H), 6.60-6.65 (m, 3H), 6.70 (d, J = 8.6 Hz, 2H), 7.13-7.23 (m, 4H), 7.24-7.34 (m, 7H), 7.44 (d, J = 8.6 Hz, 2H).

[1236]

[Example 4a]

N¹,N⁵-bis(4-{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)glutaramide (Compound 4a)
(Step 1)

A crude product (0.15 g) of methyl 5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoate was obtained from 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.1 g, 0.32 mmol) obtained in step 2 of reference example 7 and 5-methoxy-5-oxopentanoic acid (0.047 g, 0.32 mmol) in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 438.

[1237]

(Step 2)

A crude product (0.1 g) of 5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoic acid was obtained from the crude product (0.15 g, 0.34 mmol) of methyl 5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoate obtained in step 1 in the same

manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 424.

[1238]

(Step 3)

5 Compound 4a (0.09 g, total yield of 3 steps 39%) was obtained from the crude product (0.1 g, 0.23 mmol) of 5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoic acid obtained in step 2 and 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-
10 one (0.073 g, 0.23 mmol) obtained in step 2 of reference example 7 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 715.54. ¹H-NMR (DMSO-d₆, δ): 0.98-1.04 (m, 12H), 1.11-1.18 (m, 2H), 1.84-1.88 (m, 2H), 2.21-2.29 (m, 6H), 2.59 (t, J = 15.25 Hz, 4H), 4.11 (s, 2H), 4.72 (d, J = 6.5 Hz, 2H), 5.86 (d, J = 7.93 Hz,
15 2H), 6.58 (d, J = 8.5 Hz, 4H), 7.16 (d, J = 4.27 Hz, 4H), 7.25-7.31 (m, 8H), 9.52 (s, 2H).

[1239]

[Example 4b]

3-Methyl-N¹,N⁵-bis(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)pentanediamide (Compound 4b)
20 (Step 1)

A crude product (0.1 g, 68%) of methyl 3-methyl-5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoate was obtained from 1-
25 {(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.1 g, 0.32 mmol) obtained in step 2 of reference example 7 and 5-methoxy-3-methyl-5-oxopentanoic acid (0.052 g, 0.324 mmol) in the same manner as in step 3 of example 1b .

ESIMS, (M+H)⁺, m/z: 452.

30 [1240]

(Step 2)

A crude product (0.09 g, 94%) of 3-methyl-5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoic acid was obtained from the crude product (0.1 g, 0.22 mmol) of methyl 3-methyl-5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoate obtained in step 1 in the same manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 438.

10 [1241]

(Step 3)

Compound 4b (0.04 g, 27%) was obtained from the crude product of 3-methyl-5-[(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)amino]-5-oxopentanoic acid (0.09 g, 0.20 mmol) obtained in step 2 and 1-{(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.064 g, 0.23 mmol) obtained in step 2 of reference example 7 in the same manner as in step 1 of example 1a.

ESIMS, (M+H)⁺, m/z: 729. ¹H-NMR (DMSO-d₆, δ): 0.94 (d, J = 6.41 Hz, 3H), 0.98-1.04 (m, 12H), 1.11- 1.15 (m, 2H), 2.12 (dd, J = 13.73, 8.54 Hz, 2H), 2.21-2.31 (m, 4H), 2.36-2.45 (m, 1H), 2.51-2.61 (m, 4H), 4.08-4.12 (m, 2H), 4.72 (d, J = 6.41 Hz, 2H), 5.86 (d, J = 7.93 Hz, 2H), 6.58 (d, J = 9.16 Hz, 4H), 7.16 (d, J = 4.27 Hz, 4H), 7.23-7.30 (m, 8H), 9.53 (s, 2H).

25 [1242]

[Example 4c]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{3-[N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)sulfamoyl]phenyl}benzamide

30 (Compound 4c)

(Step 1)

1-{(2S*,4R*)-4-[(4-Aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (200 mg, 0.536 mmol) obtained in step 2 of reference example 7 was dissolved in dichloromethane (1 mL),
5 then pyridine (0.026 mL, 0.323 mmol) and 3-nitrobenzenesulfonyl chloride (43.0 mg, 0.194 mmol) were added to the solution, and the mixture was stirred at room temperature for 2 hours. Hydrochloric acid (1 mol/L) and ethyl acetate were added to the reaction mixture, the mixture was filtered through diatomaceous earth, and the filtrate was concentrated under
10 reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 80/20 to 40/60) to give N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-3-nitrobenzenesulfonamide (74.4 mg, 93%).
ESIMS, (M-H)⁺, m/z: 493.

15 [1243]

(Step 2)

3-Amino-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)benzenesulfonamide (74.2 mg, quantitative) was obtained from N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-
20 1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-3-nitrobenzenesulfonamide (74.4 mg, 0.150 mmol) obtained in step 1 in the same manner as in step 2 of reference example 7.
ESIMS, (M-H)⁺, m/z: 463.

[1244]

25 (Step 3)

Compound 4c (15.9 mg, 47%) was obtained from 3-amino-N-(4-{[(2S*,4R*)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)benzenesulfonamide (20.0 mg, 0.043 mmol) obtained in
step 2 and 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-
30 4-yl]amino}benzoic acid (14.6 mg, 0.043 mmol) obtained in step 7 of

reference example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 785. ¹H-NMR (DMSO-d₆, δ): 0.95-1.07 (m, 12H), 1.22-1.28 (m, 2H), 2.14-2.30 (m, 2H), 2.57-2.69 (m, 4H), 4.00-4.08 (m, 1H), 4.29-4.36 (m, 1H), 4.62-4.78 (m, 2H), 5.97 (d, J = 8.6 Hz, 1H), 6.48-6.52 (m, 2H), 6.72 (d, J = 8.6 Hz, 2H), 6.76-6.80 (m, 3H), 7.07-7.13 (m, 2H), 7.15-7.22 (m, 2H), 7.25-7.32 (m, 4H), 7.45 (t, J = 7.9 Hz, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 9.1 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.22 (s, 1H), 9.56 (s, 1H), 10.06 (s, 1H).

[1245]

10 [Example 4d]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{2-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)sulfonamide]ethyl}benzamide
(Compound 4d)

15 (Step 1)

1-{(2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (200 mg, 0.536 mmol) obtained in reference example 2 was dissolved in 1,4-dioxane (4 mL), then (4-methoxyphenyl)methanethiol (0.112 ml, 0.804 mmol), Pd₂(dba)₃ (49.1 mg, 0.054 mmol), xantphos (62.0 mg, 0.107 mmol) and N,N-diisopropylethylamine (0.187 ml, 1.072 mmol) were added to the solution, and the mixture was stirred for 15 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 80/20 to 40/60) to give 1-[(2S,4R)-4-({4-[(4-methoxybenzyl)thio]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (244 mg, quantitative).

ESIMS, (M-H)⁺, m/z: 445.

[1246]

30 (Step 2)

1-[(2S,4R)-4-({4-[(4-Methoxybenzyl)thio]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (127 mg, 0.284 mmol) obtained in step 1 was dissolved in a mixed solvent (0.9 mL) of acetonitrile and water (8:1), then trichloroisocyanuric acid (79.0 mg, 0.341 mmol) was added to the solution at -15°C, and the mixture was stirred for 30 minutes. The reaction mixture was heated to -5°C, then N-(tert-butoxycarbonyl)-1,2-diaminoethane (0.135 ml, 0.853 mmol) was added to the reaction mixture, and the mixture was stirred for 30 minutes. The reaction mixture was heated to 5°C, then N-(tert-butoxycarbonyl)-1,2-diaminoethane (0.090 ml, 0.569 mmol) was added to the reaction mixture, and the mixture was stirred for 30 minutes. Water and saturated aqueous ammonium chloride solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 70/30 to 20/80) to give tert-butyl {2-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)sulfonamide]ethyl}carbamate (14.4 mg, 10%).

ESIMS, (M-H)⁺, m/z: 515.

[1247]

(Step 3)

A crude product (24.7 mg) of N-(2-aminoethyl)-4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzenesulfonamide hydrochloride was obtained from tert-butyl {2-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)sulfonamide]ethyl}carbamate (23.4 mg, 0.045 mmol) obtained in step 2 in the same manner as in step 2 of example 1a .

ESIMS, (M+H)⁺, m/z: 417.

[1248]

(Step 4)

Compound 4d (23.9 mg, total yield of 2 steps 72%) was obtained from the crude product (24.7 mg) of N-(2-aminoethyl)-4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

5 yl]amino}benzenesulfonamide hydrochloride obtained in step 3 and 4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (15.2 mg, 0.045 mmol) obtained in step 7 of reference example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 737.51. ¹H-NMR (DMSO-d₆, δ): 1.00 (t, J = 7.5 Hz, 6H), 1.05 (d, J = 6.3 Hz, 6H), 1.18-1.25 (m, 2H), 2.19-2.30 (m, 2H), 2.59 (q, J = 7.5 Hz, 4H), 2.80 (t, J = 6.3 Hz, 2H), 3.24 (dt, J = 6.3, 5.9 Hz, 2H), 4.24-4.32 (m, 2H), 4.69-4.78 (m, 2H), 6.57 (d, J = 7.2 Hz, 1H), 6.64 (d, J = 9.1 Hz, 2H), 6.73 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.16 (q, J = 6.3 Hz, 2H), 7.24-7.33 (m, 5H), 7.49 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 8.03 (t, J = 5.9 Hz, 1H).

[1249]

[Example 4e]

N-(4-{{[(2S*,4R*)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)-3-[(4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanamide (Compound 4e)

(Step 1)

Methyl 3-[(4-{{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanoate (0.12 g, 72%) was obtained from 1-{{(2S,4R)-4-[(4-bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.150 g, 0.403 mmol) obtained in reference example 2 and methyl 3-mercaptopropionate (0.13 mL, 1.21 mmol) in the same manner as in step 1 of example 4d.

ESIMS, (M+H)⁺, m/z: 413.

[1250]

30 (Step 2)

A crude product (0.075 g, 86%) of 3-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanoic acid was obtained from methyl 3-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanoate (0.09 g, 5 0.22 mmol) obtained in step 1 in the same manner as in step 2 of example 2f.

ESIMS, (M+H)⁺, m/z: 399.

[1251]

(Step 3)

10 Compound 4e (0.04 g, 30%) was obtained from the crude product (0.075 g, 0.19 mmol) of 3-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanoic acid obtained in step 2 and 1-[(2S*,4R*)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.058 g, 0.19 mmol) obtained in 15 step 2 of reference example 7 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 690.69. ¹H-NMR (DMSO-d₆, δ): 0.98-1.05 (m, 12H), 1.14-1.19 (m, 2H), 2.20-2.26 (m, 2H), 2.45-2.47 (m, 2H), 2.55-2.61 (m, 4H), 2.97 (t, J = 7.2 Hz, 2H), 4.11-4.15 (m, 2H), 4.72 (brs, 2H), 5.84 (d, 20 J = 8.0 Hz, 1H), 6.24 (d, J = 7.6 Hz, 1H), 6.56-6.65 (m, 4H), 7.13-7.30 (m, 12H), 9.54 (s, 1H).

[1252]

[Example 4f]

4-{[(2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-N-{2-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]ethyl}benzamide (Compound 25 4f)

(Step 1)

tert-Butyl {2-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]ethyl}carbamate (0.080 g, 30

42%) was obtained from 1-[(2S,4R)-4-[(4-bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.150 g, 0.403 mmol) obtained in reference example 2 and tert-butyl (2-mercaptoethyl)carbamate (0.214 g, 1.21 mmol) in the same manner as in
5 step 1 of example 4d.

ESIMS, (M+H)⁺, m/z: 470.

[1253]

(Step 2)

1-[(2S,4R)-4-({4-[(2-Aminoethyl)thio]phenyl}amino)-2-methyl-
10 3,4-dihydroquinolin-1(2H)-yl]propan-1-one hydrochloride (0.06 g, 87%)
was obtained from tert-butyl {2-[(4-{[(2S,4R)-2-methyl-1-propionyl-
1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]ethyl}carbamate (0.08
g, 0.17 mmol) obtained in step 1 in the same manner as in step 2 of
example 1a.

15 ESIMS, (M+H)⁺, m/z: 370.

[1254]

(Step 3)

Compound 4f (0.025 g, 25%) was obtained from 1-[(2S,4R)-4-({4-
[(2-aminoethyl)thio]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-
20 yl]propan-1-one hydrochloride (0.06 g, 0.15 mmol) obtained in step 2 and
4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}benzoic acid (0.05 g, 0.15 mmol) obtained in step 7 of reference
example 1 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 690. ¹H-NMR (DMSO-d₆, δ): 1.02-1.05 (m, 12H),
25 1.14-1.24 (m, 2H), 2.21-2.26 (m, 2H), 2.54-2.63 (m, 4H), 2.85 (t, J = 7.0
Hz, 2H), 3.35 (s, 2H), 4.15 (brs, 1H), 4.24-4.27 (m, 1H), 4.73-4.74 (m,
2H), 6.25 (d, J = 7.5 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 6.62-6.65 (m, 4H),
7.09 (d, J = 8.0 Hz, 1H), 7.13-7.19 (m, 3H), 7.22-7.31 (m, 6H), 7.60 (d, J
= 8.5 Hz, 2H), 8.17 (t, J = 5.5 Hz, 1H).

30 [1255]

[Example 5a]

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)oxazole-4-carboxamide

5 (Compound 5a)

(Step 1)

1-((2S,4R)-4-[(4-Aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (200 mg, 0.646 mmol) obtained in step 3 of reference example 7 and trimethylsilyl isocyanate (0.128 mL, 0.970 mmol) were dissolved in THF (4 mL), and the mixture was stirred for 3 hours under reflux. The reaction mixture was cooled to room temperature, then water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform/methanol = 10/0 to 9/1) to give 1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)urea (185 mg, 81%).

ESI-MS, (M+H)⁺, m/z: 353.

20 [1256]

(Step 2)

1-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)urea (180 mg, 0.511 mmol) obtained in step 1 and ethyl 3-bromopyruvate (0.077 mL, 0.613 mmol) were dissolved in ethanol (5 mL), and the mixture was stirred for 4 hours under reflux. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 6/4 to 2/8) to give ethyl 2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)oxazole-4-carboxylate (150 mg, 65%).

ESI-MS, (M+H)⁺, m/z: 449.

[1257]

(Step 3)

5 Ethyl 2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)oxazole-4-carboxylate (40 mg, 0.089 mmol) obtained in step 2 and trimethyltin hydroxide (18 mg, 0.098 mmol) were dissolved in 1,2-dichloroethane (1 mL), and the mixture was stirred at 80°C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth. The filtrate was
10 concentrated under reduced pressure to give a crude product (40 mg) of 2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)oxazole-4-carboxylic acid.

ESI-MS, (M+H)⁺, m/z: 421.

[1258]

15 (Step 4)

A crude product of compound 5a was obtained from the crude product (30 mg) of 2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)oxazole-4-carboxylic acid obtained in step 3 and 1-{{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-
20 3,4-dihydroquinolin-1(2H)-yl}}propan-1-one (27 mg, 0.086 mmol) obtained in step 3 of reference example 7 in the same manner as in step 3 of example 1b. The obtained crude product was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 60/40 to 50/50) to give compound 5a (8 mg, total yield of 2 steps 16%).

25 ESI-MS, (M+H)⁺, m/z: 712. ¹H-NMR (CDCl₃, δ): 1.10-1.18 (m, 12H), 1.22-1.31 (m, 2H), 2.32-2.43 (m, 2H), 2.52-2.71 (m, 4H), 3.79-3.86 (m, 2H), 4.12-4.22 (m, 2H), 4.94 (s, 2H), 6.63 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 9.1 Hz, 2H), 6.75 (s, 1H), 7.13-7.23 (m, 4H), 7.27-7.35 (m, 5H), 7.47 (d, J = 8.6 Hz, 2H), 7.82 (s, 1H), 8.46 (s, 1H).

30 [1259]

[Example 5b]

1-((2S,4R)-2-Methyl-4-((4-((2-(4-(((2S,4R)-2-methyl-1-propionyl-
1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-5,6-dihydroimidazo[1,2-
a]pyrazin-7(8H)-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-
5 yl)propan-1-one (Compound 5b)

(Step 1)

A saturated aqueous sodium hydrogen carbonate solution was added
to 1-((2S,4R)-2-methyl-4-{[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-
2-yl)phenyl]amino}-3,4-dihydroquinolin-1(2H)-yl)propan-1-one

10 hydrochloride (0.120 g, 0.265 mmol) obtained in step 3 of example 3f, and
the organic layer was extracted with ethyl acetate. The organic layer was
dried over anhydrous sodium sulfate and concentrated under reduced
pressure to give a crude product (0.090 g) of 1-((2S,4R)-2-methyl-4-{[4-
(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl)phenyl]amino}-3,4-
15 dihydroquinolin-1(2H)-yl)propan-1-one.

ESIMS, (M+H)⁺, m/z: 430.

[1260]

(Step 2)

The crude product (0.09 g) of 1-((2S,4R)-2-methyl-4-{[4-(5,6,7,8-
20 tetrahydroimidazo[1,2-a]pyrazin-2-yl)phenyl]amino}-3,4-dihydroquinolin-
1(2H)-yl)propan-1-one obtained in step 3 of example 3f was dissolved in
methanol (2 mL, then tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-
propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.091 g, 0.22 mmol)
obtained in reference example 8 and acetic acid (0.08 mL, 1.30 mmol) were
25 added to the solution, and the mixture was stirred at room temperature for
40 minutes. Sodium cyanoborohydride (0.041 g, 0.65 mmol) was added to
the reaction mixture, and the mixture was stirred at room temperature for
6 hours. The reaction mixture was diluted with water, and the aqueous
layer was extracted with ethyl acetate. The organic layer was dried over
30 anhydrous sodium sulfate and concentrated under reduced pressure to give

a crude product (0.120 g) of tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methyl)phenyl)carbamate.

5 ESIMS, (M+H)⁺, m/z: 822.

[1261]

(Step 3)

Compound 5b (0.020 g, yield of 3 steps 10%) was obtained from the crude product (0.140 g, 0.17 mmol) of tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methyl)phenyl)carbamate obtained in step 2 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 722: ¹H-NMR (DMSO-d₆, δ) 0.96-1.08 (m, 12H),
15 1.11-1.28 (m, 2H), 2.18-2.28 (m, 2H), 2.55-2.64 (m, 4H), 2.81 (t, J = 5.36 Hz, 2H), 3.52 (d, J = 16.93 Hz, 4H), 3.93 (t, J = 5.25 Hz, 2H), 4.10- 4.20 (m, 2H), 4.68-4.80 (m, 2H), 5.99-6.05 (m, 2H), 6.62 (t, J = 8.4 Hz, 4H), 7.08 (d, J = 8.34 Hz, 2H), 7.15 -7.22 (m, 5H), 7.23-7.32 (m, 4H), 7.42 (d, J = 8.4 Hz, 2H).

20 [1262]

[Example 5c]

1,1'-(((2S,2'S,4R,4'R)-((((5,6-Dihydroimidazo[1,2-a]pyrazine-3,7(8H)-diyl)bis(methylene))bis(4,1-phenylene))bis(azanediyl))bis(2-methyl-3,4-dihydroquinoline-4,1(2H)-diyl))bis(propan-1-one) (Compound 5c)

25 (Step 1)

Commercially available tert-butyl 3-bromo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.644 g, 2.13 mmol) was dissolved in THF (5 mL), then isopropylmagnesium chloride-lithium chloride (1.3 mol/L THF solution, 2.46 mL, 3.20 mmol) was added to the solution at 0°C, and the
30 mixture was stirred at 0°C for 30 minutes. tert-Butyl (4-

formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.3 g, 0.71 mmol) obtained in reference example 8 was added to the reaction mixture at 0°C, and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted with saturated aqueous ammonium chloride solution, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/4) to give tert-butyl 3-((4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)(hydroxy)methyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.150 g, 32%).

ESIMS, (M+H)⁺, m/z: 646.

[1263]

(Step 2)

tert-Butyl 3-((4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)(hydroxy)methyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.100 g, 0.15 mmol) obtained in step 1 was dissolved in trifluoroacetic acid (1 mL), then triethylsilane was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude product (0.085 g) of 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one trifluoroacetate.

ESIMS, (M-TFA + H)⁺, m/z: 430.

[1264]

(Step 3)

A saturated aqueous sodium hydrogen carbonate solution was added to crude product (0.120 g) of 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-

tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one trifluoroacetate obtained in step 2, and the organic layer was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product (0.090 g) of 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one.

ESIMS, (M+H)⁺, m/z: 430.

[1265]

10 (Step 4)

tert-Butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((3-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methyl)phenyl)carbamate (0.120 g, total yield of 3 steps 68%) was obtained from the crude product (0.090 g) of 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one obtained in step 3 and tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.088 g, 0.21 mmol) obtained in reference example 8 in the same manner as in step 2 of example 5b.

ESIMS, (M+H)⁺, m/z: 836.

[1266]

(Step 5)

25 Compound 5c (0.027 g, 26%) was obtained from tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((3-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methyl)phenyl)carbamate (0.120 g, 0.14 mmol) obtained in step 4 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 736; ¹H-NMR (DMSO-d₆, δ) 0.97-1.05 (m, 12H), 1.12-1.22 (m, 2H), 2.18-2.32 (m, 2H), 2.57-2.61 (m, 4H), 2.68-2.78 (m, 2H), 3.45 (s, 2H), 3.50 (s, 2H), 3.61-3.70 (m, 2H), 3.73 (s, 2H), 4.05-4.15 (m, 2H), 4.71-4.73 (m, 2H), 5.93 (d, J = 7.6 Hz, 1H), 6.02 (d, J = 7.6 Hz, 1H), 6.50 (s, 1H), 6.59 (dd, J = 12.99, 8.46 Hz, 4H), 6.90 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.14-7.19 (m, 4H), 7.22-7.30 (m, 4H).

[1267]

[Example 5d]

2,2'-Azanediylbis(N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)acetamide) (Compound 5d)
(Step 1)

tert-Butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-(2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)glycinate (250 mg, 97%) was obtained from 1-{{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}}propan-1-one (0.112 g, 0.36 mmol) and N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-(2-(tert-butoxy)-2-oxoethyl)glycine (0.150 g, 0.36 mmol) obtained in reference example 7 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 703.48.

[1268]

(Step 2)

tert-Butyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-(2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)glycinate (240 mg, 0.34 mmol) obtained in step 1 was dissolved in dichloromethane (3 mL), then trifluoroacetic acid (1.5 mL) was added to the solution under ice cooling, and the mixture was stirred for 2 hours. The reaction mixture was concentrated under reduced pressure to give a crude product (0.200 g) of N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-(2-(4-(((2S,4R)-2-methyl-1-

propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)glycine.

ESIMS, (M+H)⁺, m/z: 647.02.

[1269]

5 (Step 3)

A crude product (0.200 g) of (9H-fluoren-9-yl)methyl bis(2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)carbamate was obtained from the crude product (0.200 g) of N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-(2-
10 ((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)glycine obtained in step 2 and 1-
{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.095 g, 0.31 mmol) obtained in reference example 7 in the same manner as in step 3 of example 1b.

15 ESIMS, (M+H)⁺, m/z: 938.60.

[1270]

(Step 4)

Compound 5d (0.037 g, total yield of 3 steps 19%) was obtained from the crude product (0.250 g) of (9H-fluoren-9-yl)methyl bis(2-((4-
20 (((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)carbamate obtained in step 3 and in the same manner as in step 2 of example 2a.

ESIMS, (M+H)⁺, m/z: 716.21. ¹H-NMR (DMSO-d₆, δ): 0.98-1.04 (m, 12H), 1.13-1.17 (m, 2H), 2.20-2.26 (m, 2H), 2.53-2.61 (m, 4H), 3.29 (s, 4H),
25 4.10-4.14 (m, 2H), 4.72-4.74 (m, 2H), 5.87 (d, J = 7.6 Hz, 2H), 6.60 (d, J = 9.2 Hz, 4H), 7.16 (d, J = 3.2 Hz, 4H), 7.23-7.35 (m, 8H), 9.63 (s, 2H).

[1271]

[Example 5e]

1-((2S,4R)-2-Methyl-4-((4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-
30 1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoyl)azetidin-3-

yl)amino)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 5e)

(Step 1)

tert-Butyl [1-(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoyl)azetidin-3-yl]carbamate (0.160 g, 0.32 mmol) obtained in step 1 of example 1n was dissolved in dichloromethane (2 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, then the obtained residue was neutralized with a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 1-[(2S,4R)-4-{[4-(3-aminoazetidine-1-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.115 g, 90%).

ESIMS, (M+H)⁺, m/z: 393.66.

[1272]

(Step 2)

tert-Butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoyl)azetidin-3-yl)amino)methyl)phenyl)carbamate (0.180 g, 76%) was obtained from 1-[(2S,4R)-4-{[4-(3-aminoazetidine-1-carbonyl)phenyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (0.115 g, 0.29 mmol) obtained in step 1 and tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.123 g, 0.29 mmol) obtained in reference example 8 in the same manner as in step 2 of example 5b.

ESIMS, (M+H)⁺, m/z: 799.79.

[1273]

(Step 3)

Compound 5e (0.063 g, 41%) was obtained from tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoyl)azetidin-3-yl)amino)methyl)phenyl)carbamate (0.180 g, 5 0.22 mmol) obtained in step 2 in the same manner as in step 1. ESI-MS m/z: 699.5 (M+H)⁺: ¹H-NMR (DMSO-d₆, δ): 0.98-1.05 (m, 12H), 1.09-1.25 (m, 2H), 2.18-2.28 (m, 2H), 2.53-2.67 (m, 4H), 3.48-3.57 (m, 3H), 3.65-4.33 (m, 6H), 4.61-4.82 (m, 2H), 5.92 (d, J = 7.67 Hz, 1H), 6.57-6.65 (m, 5H), 7.03 (d, J = 8.55 Hz, 2H), 7.09-7.19 (m, 4H), 7.22-10 7.31 (m, 4H), 7.41 (d, J = 8.8 Hz, 2H).

[1274]

[Example 5f]

1-((2S,4R)-2-Methyl-4-((4-(((2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1H-pyrazol-1-yl)ethyl)amino)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 5f)

tert-Butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (30 mg, 0.071 mmol) obtained in reference example 8 was dissolved in dichloromethane (1.5 mL), then 1-20 ((2S,4R)-4-((4-(1-(2-aminoethyl)-1H-pyrazol-4-yl)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (28.7 mg, 0.071 mmol) obtained in step 2 of example 6q was added to the solution, and the mixture was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (75 mg, 0.355 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with 1 mol/L aqueous sodium hydroxide solution, and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was dissolved in dichloromethane 25 (5 mL), then trifluoroacetic acid (1 mL) was added to the solution, and the 30

mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate solution, and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under
5 reduced pressure. The obtained residue was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 50/50-40/60) to give compound 5f (46.3 mg, 92%).

ESIMS, (M+H)⁺, m/z: 710: ¹H-NMR (CDCl₃, δ) 1.06-1.41 (m, 16H), 2.30-2.41 (m, 2H), 2.50-2.71 (m, 4H), 3.09 (t, J = 5.2 Hz, 2H), 3.70 (s, 2H),
10 3.79 (d, J = 7.6 Hz, 1H), 3.90 (d, J = 7.6 Hz, 1H), 4.09-4.31 (m, 4H), 4.85-5.08 (m, 1H), 6.58 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 7.06-7.36 (m, 12H), 7.54 (s, 1H), 7.69 (s, 1H).

[1275]

[Example 5g]

15 1-((2S,4R)-2-Methyl-4-((4-(((5-(4-((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1,3,4-oxadiazol-2-yl)methyl)amino)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 5g)

(Step 1)

20 A crude product (468 mg) of tert-butyl (4-(2-((tert-butoxycarbonyl)glycyl)hydrazine-1-carbonyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate was obtained from 4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid (300 mg, 0.684 mmol)
25 obtained in step 2 of reference example 8 and tert-butyl (2-hydrazinyl-2-oxoethyl)carbamate (259 mg, 1.37 mmol) in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 610.

(Step 2)

30 A crude product (374 mg) of tert-butyl (4-(5-(((tert-

butoxycarbonyl)amino)methyl)-1,3,4-oxadiazol-2-yl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate was obtained from the crude product (450 mg) of tert-butyl (4-(2-((tert-butoxycarbonyl)glycyl)hydrazine-1-carbonyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate obtained in step 1 in the same manner as in step 2 of example 3c.

ESIMS, (M+H)⁺, m/z: 592.

(Step 3)

The crude product (370 mg) of tert-Butyl (4-(5-(((tert-butoxycarbonyl)amino)methyl)-1,3,4-oxadiazol-2-yl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate obtained in step 2 was dissolved in dichloromethane (10 mL), then trifluoroacetic acid (2 mL) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (chloroform/methanol = 100/0 to 80/20) to give 1-((2S,4R)-4-((4-(5-(aminomethyl)-1,3,4-oxadiazol-2-yl)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (250 mg, total yield of 3 steps 97%).

ESIMS, (M+H)⁺, m/z: 392.

(Step 4)

Compound 5g (42.9 mg, total yield of 2 steps 87%) was obtained from tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (30 mg, 0.071 mmol) obtained in reference example 8 and 1-[(2S,4R)-4-({4-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]phenyl}amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl]propan-1-one (27.8 mg, 0.071 mmol) obtained in step 3 in the same manner as in example 5f.

ESIMS, (M-H)⁻, m/z: 696: ¹H-NMR (CDCl₃, δ) 1.06-1.41 (m, 16H), 2.31-2.46 (m, 2H), 2.52-2.65 (m, 3H), 2.67-2.78 (m, 1H), 3.79 (s, 2H), 4.06 (s, 2H), 4.06-4.17 (m, 1H), 4.21-4.40 (m, 2H), 4.81-5.08 (m, 2H), 6.58 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 7.09-7.38 (m, 10H), 7.85 (d, J = 8.8 Hz, 2H).

[1276]

[Example 5h]

1-((2S,4R)-2-Methyl-4-((4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 5h)

(Step 1)

tert-Butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((prop-2-yn-1-ylamino)methyl)phenyl)carbamate (0.140 g, 85%) was obtained from tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.150 g, 0.35 mmol) obtained in reference example 8 and prop-2-yn-1-amine (0.023 g, 0.42 mmol) in the same manner as in step 2 of example 5b.

ESIMS, (M+H)⁺, m/z: 462.39.

[1277]

(Step 2)

tert-Butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)methyl)phenyl)carbamate (0.130 g, 53%) was obtained from tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((prop-2-yn-1-ylamino)methyl)phenyl)carbamate (0.140 g, 0.30 mmol) obtained in step 1 and the crude product (0.102 g) of 1-{(2S,4R)-4-[(4-azidophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-

1-one obtained in step 2 of example 3a in the same manner as in step 3 of example 5j.

ESIMS, (M+H)⁺, m/z: 797.67.

[1278]

5 (Step 3)

Compound 5h (0.040 g, 35%) was obtained from tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1H-1,2,3-triazol-4-

10 yl)methyl)amino)methyl)phenyl)carbamate (0.130 g, 0.16 mmol) obtained in step 2 in the same manner as in step 2 of example 1a.

ESI-MS m/z: 697.69 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.98-1.07 (m, 12H), 1.13-1.26 (m, 2H), 2.21-2.28 (m, 2H), 2.55-2.66 (m, 4H), 3.76 (s, 2H), 3.94 (s, 2H), 4.10-4.19 (m, 1H), 4.21-4.31 (m, 1H), 4.65-4.84 (m, 2H),
15 6.05 (d, J = 7.34 Hz, 1H), 6.50 (d, J = 7.82 Hz, 1H), 6.63 (d, J = 8.31 Hz, 2H), 6.80 (d, J = 8.56 Hz, 2H), 7.13-7.20 (m, 6H), 7.24-7.33 (m, 4H), 7.54 (d, J = 8.56 Hz, 2H), 8.44 (s, 1H).

[1279]

[Example 5i]

20 2-((4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzyl)amino)-N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)acetamide hydrochloride
(Compound 5i)

(Step 1)

25 A crude product (0.170 g) of tert-butyl (2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)carbamate was obtained from 1-{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.150 g, 0.48 mmol) obtained in reference example 7 and (tert-
30 butoxycarbonyl)glycine (0.084 g, 0.48 mmol) in the same manner as in

step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 467.28.

[1280]

(Step 2)

5 A crude product (0.130 g) of 2-amino-N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)acetamide hydrochloride was obtained from the crude product (0.170 g) of tert-butyl (2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)carbamate obtained in step 1 in the
10 same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 367.25.

[1281]

(Step 3)

 A crude product (0.120 g) of tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxoethyl)amino)methyl)phenyl)carbamate was obtained from the crude
15 product (0.130 g) of 2-amino-N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)acetamide hydrochloride obtained in step 2 and tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.136 g, 0.32 mmol)
20 obtained in reference example 8 in the same manner as in step 2 of example 5b.

ESIMS, (M+H)⁺, m/z: 773.70.

25 [1282]

(Step 4)

 Compound 5i (0.030 g, total yield of 3 steps 28%) was obtained from the crude product (0.120 g) of tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-(((2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-
30 1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-

oxoethyl)amino)methyl)phenyl)carbamate obtained in step 3 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 673.61. ¹H-NMR (DMSO-d₆, δ): 0.99-1.05 (m, 12H), 1.12-1.20 (m, 1H), 2.20-2.27 (m, 2H), 2.56-2.63 (m, 4H), 3.67-3.78 (m, 2H), 4.03-4.21 (m, 4H), 4.73-4.75 (m, 2H), 5.99-6.05 (m, 1H), 6.29-6.32 (m, 1H), 6.62-6.69 (m, 4H), 7.08-7.18 (m, 4H), 7.22-7.32 (m, 8H), 9.15 (brs, 2H), 10.18 (s, 1H).

[1283]

[Example 5j]

1-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzyl)-N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide (Compound 5j)

(Step 1)

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)propiolamide (0.140 g, 80%) was obtained from 1-(((2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl})propan-1-one (0.150 g, 0.48 mmol) obtained in reference example 7 and propiolic acid (0.036 g, 0.51 mmol) in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 362.25.

[1284]

(Step 2)

tert-Butyl (4-(hydroxymethyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.150 g, 0.35 mmol) obtained in step 3 of reference example 8 was dissolved in toluene (3 mL), then DPPA (0.11 mL, 0.53 mmol) and DBU (0.1 mL, 0.70 mmol) were added to the solution, and the mixture was stirred at room temperature for 16 hours. Water (3 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over

anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product (0.180 g) of tert-butyl (4-(azidomethyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate.

5 ESIMS, (M+H)⁺, m/z: 450.29.

[1285]

(Step 3)

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)propiolamide (0.085 g, 0.23 mmol) obtained in step 1 and
10 the crude product (0.180 g) of tert-butyl (4-(azidomethyl)phenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate obtained in step 2 were dissolved in t-butanol (2 mL), then sodium L-ascorbate (9 mg, 0.05 mmol), copper sulfate pentahydrate (6 mg, 0.023 mmol) and water (1 mL) were added to the solution, and the mixture was stirred at
15 room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase column chromatography (acetonitrile/0.1% formic acid aqueous solution = 45/55) to give tert-butyl
20 ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)phenyl)carbamate (0.100 g, 52%).

ESIMS, (M+H)⁺, m/z: 811.58.

25 [1286]

(Step 4)

Compound 5j (0.020 g, 23%) was obtained from tert-butyl ((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)(4-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)carbamoyl)-1H-1,2,3-triazol-1-
30 yl)methyl)phenyl)carbamate (0.100 g, 52%).

yl)methyl)phenyl)carbamate (0.1 g, 0.12 mmol) obtained in step 3 in the same manner as in step 2 of example 1a.

ESIMS, (M+H)⁺, m/z: 711.50. ¹H NMR (DMSO-d₆, δ): 0.98-1.12 (m, 12H), 1.15-1.17 (m, 2H), 2.20-2.27 (m, 2H), 2.51-2.62 (m, 4H), 4.11-4.17 (m, 2H), 4.71-4.74 (m, 2H), 5.47 (s, 2H), 5.96 (d, J = 7.87 Hz, 1H), 6.22 (d, J = 7.63 Hz, 1H), 6.60-6.65 (m, 4H), 7.10-7.18 (m, 6H), 7.23-7.30 (m, 4H), 7.48 (d, J = 8.82 Hz, 2H), 8.61 (s, 1H), 10.03 (s, 1H).

[1287]

[Example 5k]

10 N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridin-1(2H)-yl)acetamide (Compound 5k)

(Step 1)

15 1-(((2S,4R)-4-((4-Bromophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (300 mg, 0.804 mmol) obtained in reference example 2 and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (373 mg, 1.21 mmol) were dissolved in a mixed solvent of 1,4-dioxane (2.5 mL) and water (1.0 mL), then Pd(dppf)Cl₂ dichloromethane complex (65.6 mg, 0.080 mmol) and potassium phosphate (512 mg, 2.41 mmol) were added to the solution, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the
25 obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 8/2 to 5/5) to give tert-butyl 4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (348 mg, 91%).

ESI-MS, (M+H)⁺, m/z: 476.

30 [1288]

(Step 2)

A crude product (275 mg) of 1-((2S,4R)-2-methyl-4-((4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one trifluoroacetate was obtained from tert-butyl 4-(4-
5 (((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (348 mg, 0.732 mmol) obtained in step 1 in the same manner as in step 2 of example 1k. ESI-MS, (M+H)⁺, m/z: 376.

[1289]

10 (Step 3)

The crude product (275 mg) of 1-((2S,4R)-2-methyl-4-((4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one trifluoroacetate obtained in step 2 was dissolved in DMF (5 mL), then tert-butyl bromoacetate (0.161 mL, 1.10 mmol) and cesium
15 carbonate (716 mg, 2.2 mmol) were added to the solution, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with water and once with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to
20 give a crude product (421 mg) of tert-butyl 2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridin-1(2H)-yl)acetate.

ESI-MS, (M+H)⁺, m/z: 490.

[1290]

25 (Step 4)

A crude product (100 mg) of 2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridin-1(2H)-yl)acetic acid trifluoroacetate was obtained from the
crude product (421 mg) of tert-butyl 2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-
30

dihydropyridin-1(2H)-yl)acetate obtained in step 3 in the same manner as in step 2 of example 1k.

ESI-MS, (M+H)⁺, m/z: 434.

[1291]

5 (Step 5)

A crude product of compound 5k was obtained from the crude product (40 mg) of 2-(4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3,6-dihydropyridin-1(2H)-yl)acetic acid trifluoroacetate obtained in step 4 and 1-{{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (35 mg, 0.112 mmol) obtained in step 3 of reference example 7 in the same manner as in step 3 of example 1b. The crude product obtained was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 45/55 to 35/65) to give compound 5k
15 (4 mg, total yield of 4 steps 6%).

ESI-MS, (M+H)⁺, m/z: 725. ¹H-NMR (CDCl₃) δ: 1.11-1.19 (m, 12H), 2.20-2.25 (m, 1H), 2.32-2.42 (m, 2H), 2.51-2.71 (m, 6H), 2.85 (t, J = 5.7 Hz, 2H), 3.24 (s, 2H), 3.31 (d, J = 2.7 Hz, 2H), 3.78 (d, J = 8.2 Hz, 1H), 3.90 (d, J = 7.2 Hz, 1H), 4.13-4.24 (m, 2H), 4.89-4.99 (m, 2H), 5.32-5.37 (m, 1H), 5.98 (s, 1H), 6.59-6.64 (m, 4H), 7.13-7.22 (m, 4H), 7.25-7.32 (m, 20 6H), 7.39 (d, J = 9.1 Hz, 2H), 9.03 (s, 1H).

[1292]

[Example 5I]

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)sulfonyl)propanamide (Compound 5I)
25

(Step 1)

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-
30

tetrahydroquinolin-4-yl)amino)phenyl)thio)propanamide (0.4 g, 62%) was obtained from 3-[(4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)thio]propanoic acid (0.370 g, 0.93 mmol) obtained in step 2 of example 4e and 1-{(2S,4R)-4-[(4-aminophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl}propan-1-one (0.287 g, 0.93 mmol) obtained in step 3 of reference example 7 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 690.

[1293]

10 (Step 2)

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)thio)propanamide (0.2 g, 0.29 mmol) obtained in step 1 was dissolved in dichloromethane (4 mL), then meta-chloroperbenzoic acid (60% w/w (water content), 0.167 g, 0.58 mmol) was added to the solution at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and the aqueous layer was extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 40/60 to 10/90) to give compound 5l (0.027 g, 13%).

ESIMS, (M+H)⁺, m/z: 722: ¹H-NMR (DMSO-d₆, δ) 0.97-1.05 (m, 12H), 1.13-1.21 (m, 2H), 2.19-2.26 (m, 2H), 2.54-2.62 (m, 6H), 3.40 (t, J = 7.56 Hz, 2H), 4.08-4.13 (m, 1H), 4.25-4.34 (m, 1H), 4.71-4.74 (m, 2H), 5.86 (d, J = 7.89 Hz, 1H), 6.57 (d, J = 8.99 Hz, 2H), 6.78 (d, J = 8.77 Hz, 2H), 7.07 (t, J = 8.0 Hz, 2H), 7.14 -7.33 (m, 9H), 7.56 (d, J = 8.99 Hz, 2H), 9.69 (s, 1H).

30 [1294]

[Example 5m]

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)sulfinyl)propanamide (Compound 5m)

N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)thio)propanamide (0.150 g, 0.22 mmol) obtained in step 1 of example 5l was dissolved in dichloromethane (2 mL), then meta-chloroperbenzoic acid (60% w/w (containing water), 0.037 g, 0.13 mmol) was added to the solution at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and the aqueous layer was extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 55/45 to 19/81) to give compound 5m (0.042 g, 27%).

ESIMS, (M+H)⁺, m/z: 706: ¹H-NMR (DMSO-d₆, δ) 0.98-1.05 (m, 12H), 1.10-1.25 (m, 2H), 2.20-2.27 (m, 2H), 2.38-2.45 (m, 1H), 2.53-2.64 (m, 5H), 2.94-3.01 (m, 1H), 3.06-3.13 (m, 1H), 4.07-5.13 (m, 1H), 4.22- 4.28 (m, 1H), 4.71-4.76 (m, 2H), 5.85 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.77 Hz, 2H), 6.65 (dd, J = 7.2, 2.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 7.11-7.19 (m, 4H), 7.24-7.32 (m, 6H), 7.38-7.40 (m, 2H), 9.64 (s, 1H).

[1295]

[Example 5n]

4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-N-(2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenoxy)ethyl)benzamide (Compound 5n)

(Step 1)

1-((2S,4R)-4-((4-Bromophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (500 mg, 1.34 mmol) obtained in reference example 2 was dissolved in 1,4-dioxane (10 mL), then
5 bis(pinacolato)diboron (395 mg, 1.61 mmol) and potassium acetate (276 mg, 2.82 mmol) were added to the solution, and the mixture was stirred at room temperature for 5 minutes under an argon atmosphere. PdCl₂(dppf) dichloromethane complex (49 mg, 0.067 mmol) was added to the mixture, and the mixture was stirred at 100°C for 16 hr under an argon atmosphere.
10 The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 100/0 to 70/30) to give 1-((2S,4R)-2-methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-
15 one (380 mg, 67%).

ESI-MS m/z: 421 (M+H)⁺

[1296]

(Step 2)

1-((2S,4R)-2-Methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-
20 one (380 mg, 0.900 mmol) obtained in step 1 was dissolved in THF (5 mL), then 30% aqueous hydrogen peroxide solution (0.51 mL, 4.52 mmol) was added to the solution under ice cooling, and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture, and
25 the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 70/30) to give 1-((2S,4R)-4-((4-hydroxyphenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-
30 one (190 mg, 68%).

ESI-MS m/z: 311 (M+H)⁺

[1297]

(Step 3)

1-((2S,4R)-4-((4-hydroxyphenyl)amino)-2-methyl-3,4-
5 dihydroquinolin-1(2H)-yl)propan-1-one (300 mg, 0.97 mmol) obtained in
step 2 was dissolved in acetonitrile (5 mL), then potassium carbonate (400
mg, 2.90 mmol) and tert-butyl (2-bromoethyl)carbamate (431 mg, 1.93
mmol) were added to the solution, and the mixture was stirred at 80°C for
16 hours. The reaction mixture was filtered through Celite, and the filtrate
10 was concentrated under reduced pressure. The obtained residue was
purified by reverse phase silica gel column chromatography
(acetonitrile/0.1% formic acid = 50/50) to give a crude product (300 mg)
of tert-butyl (2-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl)amino)phenoxy)ethyl)carbamate. 1-((2S,4R)-4-
15 ((4-(2-aminoethoxy)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-
yl)propan-1-one hydrochloride (200 mg, 77%) was obtained from the crude
product obtained (0.03 g, 0.07 mmol) in the same manner as in step 2 of
example 1a.

ESI-MS m/z: 354 (M+H)⁺

20 [1298]

(Step 4)

Compound 5n (13 mg, 37%) was obtained from 1-((2S,4R)-4-((4-
(2-aminoethoxy)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-
yl)propan-1-one hydrochloride (20 mg, 0.05 mmol) obtained in step 3 and
25 4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl)amino)benzoic acid (14 mg, 0.04 mmol) obtained in reference example
1 in the same manner as in step 3 of example 1b.

ESI-MS m/z: 674 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.98-1.06 (m, 12H),
1.11-1.13 (m, 2H), 2.22-2.25 (m, 2H), 2.52-2.64 (m, 4H), 3.52 (q, J =
30 5.90 Hz, 2H), 3.94 (t, J = 6.10 Hz, 2H), 4.05 (m, 1H), 4.27 (m, 1H), 4.66-

4.80 (m, 2H), 5.64 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.85 Hz, 3H), 6.65 (d, J = 8.85 Hz, 2H), 6.75 (d, J = 9.16 Hz, 2H), 7.09 (d, J = 7.63 Hz, 1H), 7.14-7.17 (m, 3H), 7.23-7.31 (m, 4H), 7.65 (d, J = 8.85 Hz, 2H), 8.22 (t, J = 5.5 Hz, 1H).

5 [1299]

[Example 5o]

2,2'-Oxybis(N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)acetamide) (Compound 5o)
(Step 1)

10 A crude product (0.15 g) of methyl 2-(2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxyethoxy)acetate was obtained from 1-((2S,4R)-4-((4-aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (270 mg, 0.63 mmol) obtained in reference example 7 in the same
15 manner as in step 3 of example 1b. From the crude product obtained, a crude product (0.13 g) of 2-(2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxyethoxy)acetic acid was obtained in the same manner as in step 2 of example 2f.

ESI-MS m/z: 426 (M+H)⁺

20 [1300]

(Step 2)

Compound 5o (6 mg, total yield of 2 steps 13%) was obtained from the crude product (0.13 g) of 2-(2-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)amino)-2-oxyethoxy)acetic
25 acid obtained in step 1 and 1-((2S,4R)-4-((4-aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (270 mg, 0.63 mmol) obtained in reference example 7 in the same manner as in step 3 of example 1b.

ESI-MS m/z: 717 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 1.01-1.04 (m, 12H),

30 1.14-1.17 (m, 2H), 2.21-2.25 (m, 2H), 2.56-2.61 (m, 4H), 4.20-4.31 (m,

6H), 4.72-4.74 (m, 2H), 5.96 (d, J = 8.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 4H), 7.15-7.18 (m, 4H), 7.24-7.30 (m, 4H), 7.34 (d, J = 8.85 Hz, 4H), 9.76 (s, 2H).

[1301]

5 [Example 5p]

4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-N-(3-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenoxy)propyl)benzamide (Compound 5p)

(Step 1)

10 1-((2S,4R)-4-((4-Hydroxyphenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (190 mg, 68%) obtained in step 2 of example 5n was dissolved in acetonitrile (5 mL), then potassium carbonate (0.334 g, 2.41 mmol) and tert-butyl (3-bromopropyl)carbamate (0.288 g, 1.21 mmol) were added to the solution, and the mixture was
15 stirred at 80°C for 16 hours. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by reverse phase column chromatography (acetonitrile/0.1% formic acid = 60/40) to give tert-butyl (3-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenoxy)propyl)carbamate (0.05 g, 13%).
20

ESI-MS m/z: 468 (M+H)⁺

[1302]

(Step 2)

25 1-((2S,4R)-4-((4-(3-Aminopropoxy)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (0.04 g, 93%) was obtained from tert-butyl (3-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenoxy)propyl)carbamate (0.05 g, 0.11 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESI-MS m/z: 368 (M+H)⁺

30 [1303]

(Step 3)

Compound 5p (0.024 g, 35%) was obtained from 1-((2S,4R)-4-((4-(3-aminopropoxy)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (0.04 g, 0.1 mmol) obtained in step 2 and 4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoic acid (30 mg, 0.09 mmol) obtained in reference example 1 in the same manner as in step 3 of example 1b.

ESI-MS m/z : 688 ($M+H$)⁺: ¹H-NMR (DMSO- d_6 , δ): 0.97-1.08 (m, 12H), 1.10-1.25 (m, 2H), 1.89 (quin, $J = 6.47$ Hz, 2H), 2.20-2.28 (m, 2H), 2.54-2.63 (m, 4H), 3.34-3.37 (m, 2H), 3.88 (t, $J = 6.25$ Hz, 2H), 4.02-4.06 (m, 1H), 4.26-4.28 (m, 1H), 4.71-4.79 (m, 2H), 5.60 (d, $J = 7.67$ Hz, 1H), 6.53 (d, $J = 7.67$ Hz, 1H), 6.58 (d, $J = 8.99$ Hz, 2H), 6.64 (d, $J = 8.77$ Hz, 2H), 6.73 (d, $J = 8.99$ Hz, 2H), 7.09 (d, $J = 7.2$ Hz, 1H), 7.14-7.19 (m, 3H), 7.24-7.31 (m, 4H), 7.63 (d, $J = 8.77$ Hz, 2H), 8.07 (d, $J = 5.4$ Hz, 1H).

[1304]

[Example 5q]

1-((2S,4R)-2-Methyl-4-((4-((7-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 5q)

(Step 1)

tert-Butyl 3-((4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)(hydroxy)methyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.20 g, 0.31 mmol) obtained in step 1 of example 6a was dissolved in trifluoroacetic acid (2.0 mL), then triethylsilane (0.1 mL, 0.62 mmol) was added to the solution, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to give 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-

dihydroquinolin-1(2H)-yl)propan-1-one trifluoroacetate (0.2 g, 98%).

ESI-MS m/z : 430 (M+H)⁺

[1305]

(Step 2)

5 Compound 5q (0.1 g, 45%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (0.1 g, 0.29 mmol) obtained in reference example 1 and 1-((2S,4R)-2-methyl-4-((4-((5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-3,4-dihydroquinolin-1(2H)-yl)propan-1-one
10 trifluoroacetate (0.19 g, 0.29 mmol) obtained in step 1 in the same manner as in step 3 of example 1b.

ESI-MS m/z : 750 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.97-1.06 (m, 12H), 1.11-1.26 (m, 2H), 2.19-2.26 (m, 2H), 2.54-2.64 (m, 4H), 3.73-3.87 (m, 6H), 4.07-4.13 (m, 1H), 4.22-4.27 (m, 1H), 4.65-4.73 (m, 4H), 5.92 (d, J
15 = 7.67 Hz, 1H), 6.55-6.60 (m, 4H), 6.68 (d, J = 8.55 Hz, 2H), 6.91-6.93 (m, 2H), 7.13-7.21 (m, 4H), 7.22-7.32 (m, 6H).

[1306]

[Example 5r]

N,4-Bis(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)butanamide (Compound 5r)
20 (Step 1)

1-((2S,4R)-4-[(4-Bromophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (55.3 mg, 0.148 mmol) obtained in reference example 2 was dissolved in THF (1.0 mL), then SPhos (24.33
25 mg, 0.059 mmol), palladium acetate (6.65 mg, 0.030 mmol) and 4-ethoxy-4-oxobutylzinc bromide (0.5 mol/L THF solution, 0.44 mL, 0.22 mmol) were added to the solution, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous ammonium chloride solution and ethyl acetate were added to the reaction mixture, the mixture was filtered
30 through diatomaceous earth, and the filtrate was concentrated under

reduced pressure. The obtained residue was purified by silica gel column chromatography (heptane/ethyl acetate = 90/10 to 70/30) to give ethyl 4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)butanoate (57.5 mg, 95%).

5 ESIMS, (M+H)⁺, m/z: 409.

[1307]

(Step 2)

Ethyl 4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)butanoate (53.8 mg, 0.132 mmol)
10 obtained in step 1 was dissolved in ethanol (0.88 mL), then aqueous sodium hydroxide solution (4 mol/L, 0.17 mL, 0.66 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, then water was added to the obtained residue, and the mixture was washed with ethyl
15 acetate. Hydrochloric acid (1 mol/L) was added to the aqueous layer, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)butyric acid (42.0 mg, 84%).

20 ESIMS, (M-H)⁻, m/z: 379.

[1308]

(Step 3)

Compound 5r (30.1 mg, 81%) was obtained from 4-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)butyric acid (21.0 mg, 0.055 mmol) obtained in step 2,
25 and 1-((2S,4R)-4-((4-aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (13.76 g, 68.81 mmol) obtained in reference example 7 in the same manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 672. ¹H-NMR (DMSO-d₆, δ): 0.98-1.04 (m, 12H),
30 1.10-1.21 (m, 2H), 1.75-1.83 (m, 2H), 2.19-2.28 (m, 4H), 2.45 (t, J = 7.2

Hz, 2H), 2.53-2.62 (m, 4H), 4.06-4.15 (m, 2H), 4.68-4.77 (m, 2H), 5.84 (d, J = 6.8 Hz, 2H), 6.57 (d, J = 8.2 Hz, 4H), 6.93 (d, J = 8.2 Hz, 2H), 7.14-7.18 (m, 4H), 7.23-7.30 (m, 6H), 9.47 (s, 1H).

[1309]

5 [Example 6a]

1-((2S,4R)-4-((4-(3-(Hydroxy(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (Compound 6a)

10 (Step 1)

Commercially available tert-butyl 3-bromo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.4 g, 1.32 mmol) was dissolved in THF (4 mL), then isopropylmagnesium chloride-lithium chloride (1.3 mol/L THF solution, 1.52 mL, 1.99 mmol) was added to the solution under ice-cooling, and the mixture was stirred for 30 minutes at room temperature. The THF solution (1 mL) of tert-butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (0.558 g, 1.32 mmol) obtained in reference example 8 was added dropwise to the reaction mixture under ice cooling, and the mixture was further stirred at room temperature for 2 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase column chromatography (acetonitrile/0.1% formic acid = 40/60) to give tert-butyl 3-((4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)(hydroxy)methyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (0.4 g, 46%).

ESI-MS m/z: 646 (M+H)⁺

[1310]

30 (Step 2)

1-((2S,4R)-4-((4-(Hydroxy(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (0.110 g, 98%) was obtained from tert-butyl 3-((4-((tert-butoxycarbonyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)(hydroxy)methyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (150 mg, 0.23 mmol) obtained in step 1 in the same manner as in step 2 of example 1a.

ESI-MS m/z: 446 (M+H)⁺

[1311]

10 (Step 3)

Compound 6a (0.045 g, 28%) was obtained from 4-{[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}benzoic acid (0.070 g, 0.21 mmol) obtained in reference example 1 and 1-((2S,4R)-4-((4-(hydroxy(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)methyl)phenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one hydrochloride (0.107 g, 0.21 mmol) obtained in step 2 in the same manner as in step 3 of example 1b.

ESI-MS m/z: 766 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.98-1.06 (m, 12H), 1.13-1.26 (m, 2H), 2.19-2.28 (m, 2H), 2.55-2.67 (m, 4H), 3.86-3.94 (m, 4H), 4.15-4.28 (m, 2H), 4.61-4.75 (m, 4H), 5.59 (brs, 2H), 6.02 (d, J = 6.58 Hz, 1H), 6.36 (d, J = 3.29 Hz, 1H), 6.59-6.63 (m, 3H), 6.69 (d, J = 8.77 Hz, 2H), 7.09-7.23 (m, 6H), 7.26-7.32 (m, 6H).

[1312]

[Example 6b]

25 N-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)-3-(N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)sulfamoyl)propanamide (Compound 6b)

(Step 1)

30 Methyl 3-(N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-

tetrahydroquinolin-4-yl)amino)phenyl)sulfamoyl)propanoate (0.12 g, 81%) was obtained from 1-((2S,4R)-4-((4-aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (100 mg, 0.32 mmol) obtained in reference example 7 and methyl 3-(chlorosulfonyl)propanoate (0.046 mg, 0.35 mmol) in the same manner as in step 1 of example 6g.

ESI-MS m/z: 460 (M+H)⁺

[1313]

(Step 2)

1-((2S,4R)-4-((4-Aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (0.067 g, 0.21 mmol) obtained in reference example 7 was dissolved in toluene (2 mL), then trimethylaluminum (2 mol/L toluene solution, 0.326 mL, 0.65 mmol) was added to the solution under ice cooling, and the mixture was stirred for 30 minutes at room temperature. Methyl 3-(N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)sulfamoyl)propanoate (100 mg, 0.21 mmol) obtained in step 1 was added to the reaction mixture, and the mixture was stirred at 80°C for 16 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by reverse phase HPLC (10 mmol/L aqueous ammonium bicarbonate solution/acetonitrile = 65/35 to 10/90) to give compound 6b (0.048 g, 30%).

ESI-MS m/z: 737 (M+H)⁺; ¹H-NMR (DMSO-d₆, δ): 0.97-1.04 (m, 12H), 1.10-1.20 (m, 2H), 2.20-2.26 (m, 2H), 2.54-2.61 (m, 4H), 2.66-2.70 (m, 2H), 3.22 (t, J = 7.8 Hz, 2H), 4.09-4.14 (m, 2H), 4.70-4.75 (m, 2H), 5.87 (d, J = 8.0 Hz, 1H), 6.05 (d, J = 7.6 Hz, 1H), 6.60 (dd, J = 16.4, 8.8 Hz, 4H), 6.99 (d, J = 8.8 Hz, 2H), 7.15-7.17 (m, 4H), 7.23-7.29 (m, 6H), 9.15 (s, 1H), 9.70 (s, 1H).

[1314]

[Example 6c]

4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)-
N-(2-(1-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl)amino)phenyl)-1H-1,2,3-triazol-4-yl)ethyl)benzamide (Compound 6c)

5 (Step 1)

N-(But-3-yn-1-yl)-4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl)amino)benzamide (38 mg, 66%) was obtained
from 4-[[[(2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-
yl]amino}benzoic acid (50 mg, 0.148 mmol) obtained in step 7 of reference
10 example 1 and 3-butyn-1-amine (0.018 μ L, 0.222 mmol) in the same
manner as in step 3 of example 1b.

ESIMS, (M+H)⁺, m/z: 390.

[1315]

(Step 2)

15 A crude product of compound 6c was obtained from the crude
product (30 mg) of 1-{{(2S,4R)-4-[(4-azidophenyl)amino]-2-methyl-3,4-
dihydroquinolin-1(2H)-yl}propan-1-one obtained in step 2 of example 3a
and N-(but-3-yn-1-yl)-4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-
tetrahydroquinolin-4-yl)amino)benzamide (20 mg, 0.051 mmol) obtained
20 in step 1 of example 6c in the same manner as in step 3 of example 3a.
The crude product obtained was purified by reverse phase HPLC (0.05%
TFA aqueous solution/acetonitrile = 55/45 to 50/50) to give compound 6c
(11 mg, total yield of 2 steps 29%).

ESIMS, (M+H)⁺, m/z: 725. ¹H-NMR (CDCl₃) δ : 1.13-1.20 (m, 12H), 1.24-
25 1.35 (m, 2H), 2.33-2.44 (m, 2H), 2.54-2.74 (m, 4H), 3.07 (t, J = 6.1 Hz,
2H), 3.84 (q, J = 6.0 Hz, 2H), 4.10-4.27 (m, 4H), 4.96 (s, 2H), 6.61 (d, J
= 8.6 Hz, 2H), 6.70 (d, J = 9.1 Hz, 2H), 7.02 (t, J = 5.0 Hz, 1H), 7.15-7.22
(m, 5H), 7.25-7.33 (m, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 7.2 Hz,
3H).

30 [1316]

[Example 6d]

1-(4-(((2S,4R)-2-Methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)benzyl)-N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)azetidine-3-carboxamide

5 (Compound 6d)

(Step 1)

tert-Butyl 3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)carbamoyl)azetidine-1-carboxylate (55 mg, 49%) was obtained from 1-((2S,4R)-4-((4-aminophenyl)amino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)propan-1-one (70 mg, 0.23 mmol) obtained in step 3 of reference example 7 in the same manner as in step 3 of example 1b.

ESI-MS m/z: 493 (M+H)⁺

[1317]

15 (Step 2)

tert-Butyl 3-((4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)carbamoyl)azetidine-1-carboxylate (0.08 g, 0.162 mmol) obtained in step 1 was dissolved in ethyl acetate (0.8 mL), then 4 mol/L hydrochloric acid (0.61 mL, 2.4 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to give N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)amino)phenyl)azetidine-3-carboxamide hydrochloride (43 mg, 67%).

ESI-MS m/z: 393 (M+H)⁺

25 [1318]

(Step 3)

tert-Butyl (4-formylphenyl)((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (51 mg, 0.12 mmol) obtained in reference example 8 was dissolved in dichloromethane (1.5 mL), then N-(4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

30 (4-(((2S,4R)-2-methyl-1-propionyl-1,2,3,4-tetrahydroquinolin-4-

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 477

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 477

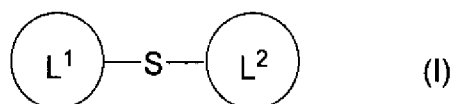
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

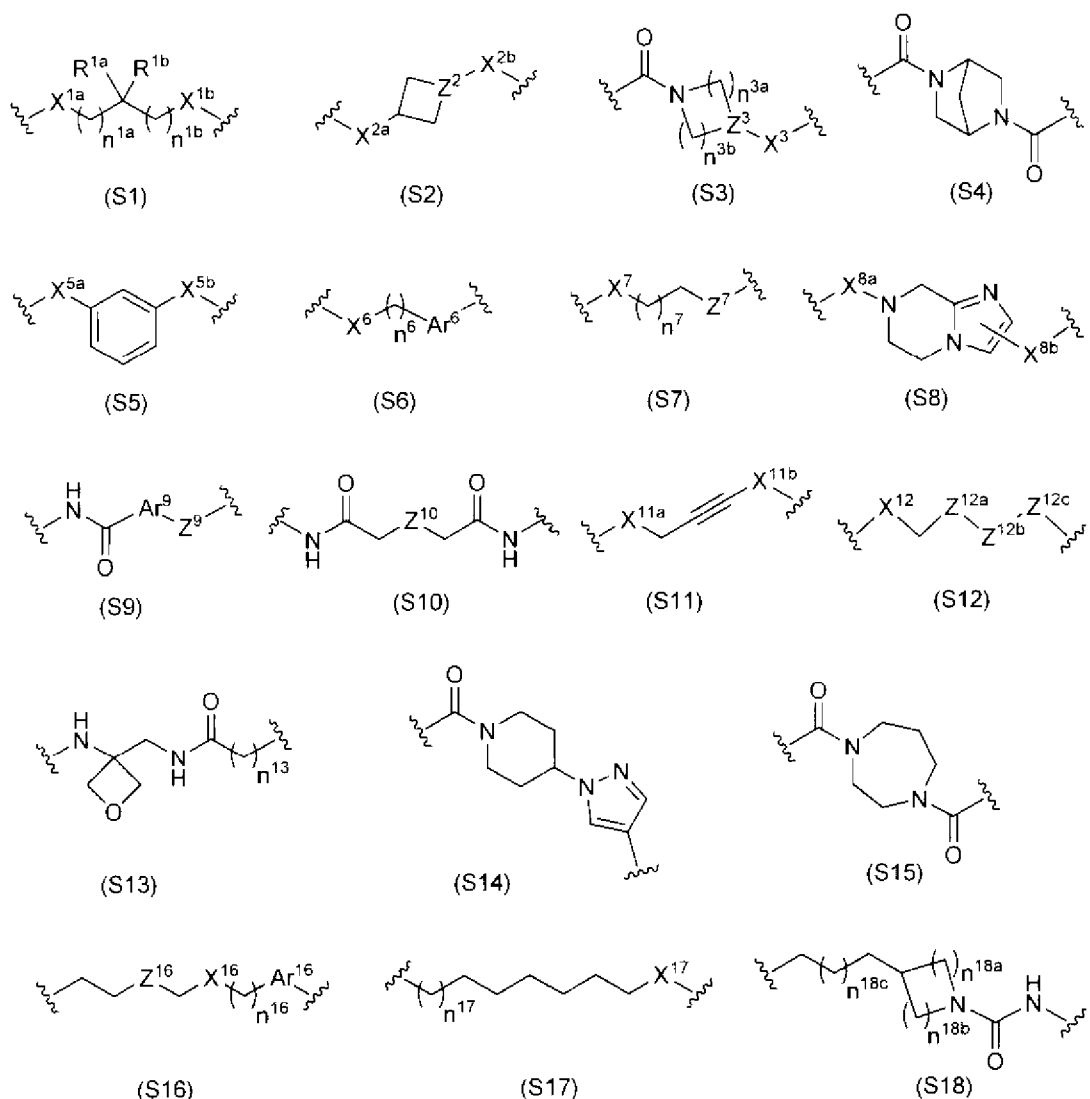
NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. A BET degrader, comprising as an active ingredient a compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



wherein L^1 and L^2 are the same or different and each represents a small molecular ligand for BET protein, and S represents a group represented by a formula selected from the group consisting of the following formulas (S1) to (S18):



wherein

the wavy lines each represents the bonding site to L^1 or L^2 ,

n^{1a} and n^{1b} are the same or different and each represents 0 or 1,

X^{1a} and X^{1b} are the same or different and each represents $-\text{C}(=\text{O})\text{---NH-}$, $-\text{NH-C}(=\text{O})\text{---}$, $-\text{SO}_2\text{---NH-}$, $-\text{NH-SO}_2\text{---}$, $-\text{O-C}(=\text{S})\text{---NH-}$, $-\text{O-C}(=\text{O})\text{---NH-}$, $-\text{NH-C}(=\text{O})\text{---O-}$, or $-\text{NH-C}(=\text{O})\text{---NH-}$,

R^{1a} represents a hydrogen atom and R^{1b} represents a hydrogen atom or lower alkyl, or R^{1a} and R^{1b} together represent carbonyl,

X^{2a} represents $-\text{C}(=\text{O})\text{---NH-}$, $-\text{NH-C}(=\text{O})\text{---}$, $-\text{SO}_2\text{---NH-}$, or $-\text{NH-SO}_2\text{---}$,

X^{2b} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -CH₂-,

Z² represents CH or N,

n^{3a} and n^{3b} are the same or different and each represents 1 or 2,

X³ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -NH-C(=O)-NH-, or -NH-CH₂-,

Z³ represents CH or N,

X^{5a} and X^{5b} are the same or different and each represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-SO₂-,

n⁶ represents 1 or 2,

Ar⁶ represents triazolediyl, oxadiazolediyl, pyrazolediyl, thiophenediyl, or tetrahydropyridinediyl,

X⁶ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, -CH₂-NH-, -NH-CH₂-, or -NH-C(=O)-NH-,

X⁷ represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, or -NH-C(=O)-NH-,

n⁷ represents 1, 2, or 3,

Z⁷ represents S, SO, or SO₂,

X^{8a} represents -C(=O)-, -CH₂-, or -NH-C(=O)-,

X^{8b} represents a bond, -C(=O)-, -CH₂-, or -CH(OH)-,

Ar⁹ represents triazolediyl or oxazolediyl,

Z⁹ represents CH₂ or NH,

Z¹⁰ represents O or NH,

X^{11a} represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,

X^{11b} represents -C(=O)-NH-, -NH-C(=O)-, or -C(=O)-,

X¹² represents -C(=O)-NH-, -NH-C(=O)-, -SO₂-NH-, -NH-SO₂-, or -NH-C(=O)-NH-,

Z^{12a} represents CH₂ or NH,

Z^{12b} represents CH₂ or O,

Z^{12c} represents a bond, CH_2 , or O,
 n^{13} represents 0, 1, or 2,
 n^{16} represents 1 or 2,
 Z^{16} represents a bond, CH_2 , or O,
 X^{16} represents $-CH_2-O-$, $-C(=O)-NH-$, $-NH-C(=O)-$, or $-NH-C(=O)-NH-$,
 Ar^{16} represents triazolediyl, oxadiazolediyl, or pyrazolediyl,
 n^{17} represents 1 or 2,
 X^{17} represents $-C(=O)-NH-$, $-NH-C(=O)-$, $-NH-SO_2-$, or $-NH-C(=O)-NH-$, and
 n^{18a} , n^{18b} , and n^{18c} are the same or different and each represents 1 or 2.

FIG. 1



FIG. 2

