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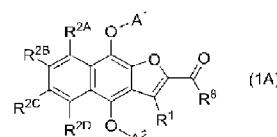
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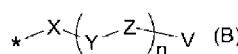
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(54) Title: WATER-SOLUBLE PRODRUGS

[Chem. 1]



[Chem. 2]



wherein * denotes a bonding position.

(57) Abstract: The present invention provides compounds represented by formula (1A), or pharmaceutically acceptable salts. Compounds represented by formula (1A), or pharmaceutically acceptable salts thereof, wherein A¹ and A² are identical or different, and each independently -C (=O) B, -C (=O) CR^{3A}R^{3B}, -C0₂B, -C(=S)0B, -C0NR^{3C}B, -C(=S)NR^{3C}B, a hydrogen atom, or the like, wherein A¹ and A² are not both hydrogen atoms, wherein B is an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted 3- to 12-membered cyclic amino group, or a group represented by the following formula (B), wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring; R¹ is a hydrogen atom or the like; R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently a hydrogen atom or the like; and R⁸ is alkyl.

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WATER-SOLUBLE PRODRUGS

[Technical Field]

5 [0001]

The present invention relates to novel water-soluble prodrugs of 2-acetylnaphtho[2,3-b]furan-4,9-dione, pharmaceutically acceptable salts thereof, or hydrates or solvates thereof useful as a medicament. The invention also 10 relates to pharmaceutical compositions comprising a novel water-soluble prodrug of 2-acetylnaphtho[2,3-b]furan-4,9-dione, a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof. Further, the invention relates to therapeutic agents or 15 prophylactic agents, wherein the therapeutic agents or prophylactic agents comprise a novel water-soluble prodrug of 2-acetylnaphtho[2,3-b]furan-4,9-dione, a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof, or treating methods for treating cancer 20 using the same.

[Background Art]

[0002]

Cancer develops when abnormality in gene occurs by an action of radiation, ultra violet rays, carcinogen, virus, 25 and the like. The number of deaths by cancer increases year by year, and cancer is currently the top cause of death in Japan. As means for such cancer therapy, antitumor agents, surgical operation, radiotherapy, immunotherapy, and the like are performed. However, among these, the therapeutic 30 use of an antitumor agent is the most important as an internally therapeutic means. Major antitumor agents act on any of metabolism of a nucleic acid precursor, DNA synthesis, RNA synthesis, or protein synthesis. However,

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such metabolic processes occur in not only cancer cells, but also normal cells. Therefore, many antitumor agents act on not only on cancer cells, but also on normal cells, and consequently a variety of side effects develop.

5 [0003]

In recent years, a new type of antitumor agent, called molecular targeting agent, has been introduced. This molecular targeting agent is a pharmaceutical agent designed to target a molecule specifically expressed in each 10 cancer. Therefore, it is believed that a molecular targeting agent has higher specificity to cancer cells than conventional antitumor agents, and has fewer side effects. However, with regard to molecular targeting agents, although previous side effects are reduced, there are 15 problems that new side effects are exhibited and alternatives of pharmaceutical agents are limited. Although the aforementioned antitumor agents were clinically used for the purpose of cancer therapy and prolonging the life of a cancer patient, there are still 20 a number of unsolved problems including problems of side effects and the like as described above. Accordingly, it is recognized that the development of a novel antitumor agent is an important object in the future.

[0004]

25 In recent studies, the existence of cancer stem cells (CSC) having self-replication competence has been revealed, the CSC is closely related to the malignant transformation of cancer. In nearly all of major types of cancer in human, such as breast cancer, colon cancer, lung cancer, 30 hematological malignancy, and the like, CSCs are identified. A CSC and a conventional cancer cell differentiated from the CSC are significantly different in biological characteristics. A CSC is shown to be important in

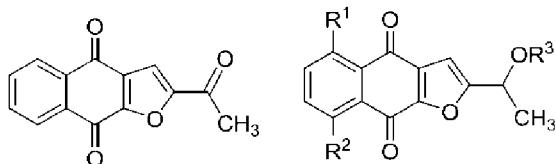
continuous proliferation of malignant tumor, metastasis and recurrence of cancer, and its resistance to an antitumor agent. Although Conventional therapy that targets conventional cancer cells accounting for most part of tumor lumps can reduce the size of a tumor, as long as a CSC is also targeted at the same time, a meaningful survival effect cannot be expected. Therefore, targeting a CSC is very promising as a new method to treat a cancer (Non Patent Literature 1). One of the characteristics of CSCs is to have replication competence. Reliable methods established as a method of measuring replication competence of a cell include measurement of cancer cell sphere-forming ability in non-adhesion state in the absence of serum (Non Patent Literature 2). A compound that inhibits not only the proliferation of a non-CSC cancer cell, but also cancer cell sphere-forming ability is possibly very useful as a novel antitumor agent.

[0005]

(1) Non Patent Literature 3 discloses that the following quinone derivatives isolated from the extract of a plant of the *Tabebuia* genus in the *Bignoniaceae* family have antitumor activity:

[0006]

[Chem. 1]



25

[wherein R¹, R², and R³ are hydrogen atoms; R¹ and R³ are hydrogen atoms, and R² is a hydroxyl group; R¹ is a hydroxyl group, and R² and R³ are hydrogen atoms; R¹ and R² are hydrogen atoms, and R³ is COCH₃; or R¹ and R² are hydrogen atoms, and

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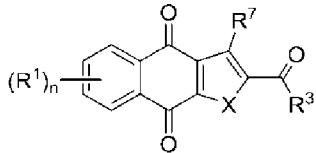
R³ is COC (CF₃) (OCH₃) C₆H₅].

[0007]

(2) Patent Literature 1 describes the following compound having antitumor activity and suppressing cancer cell sphere-forming ability:

[0008]

[Chem. 2]



[0009]

[wherein X is O or S, R¹ is a hydrogen atom, a halogen atom, a cyano group, a nitro group, a trifluoromethyl group, a trifluoromethoxy group, an optionally substituted alkyl group, or the like, R³ is a hydrogen atom, a cyano group, an optionally substituted alkyl group, or the like, R⁷ is a hydrogen atom, a halogen atom, a cyano group, a nitro group, an optionally substituted alkyl group, or the like, n is 1 to 4, with the proviso that when R³ is not an amino group, R⁷ is not a hydrogen atom and at least one of R¹ and R⁷ is a halogen atom, an aryl group, or an optionally substituted aryl group].

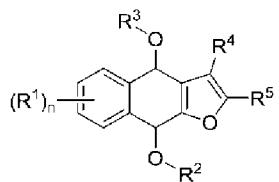
[0010]

(3) Patent Literature 2 describes the following compound as a hydrophobic prodrug for oral administration that is administered as a non-crystalline compound:

[0011]

[Chem. 3]

- 5 -



[0012]

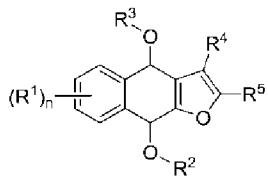
[wherein n is 0 to 4, each R¹ is independently halogen, -NO₂, -CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, 5 each of R² and R³ is independently a hydrogen atom, -S(=O)₂OR^a, -P(=O)OR^aOR^b, or -C(=O)R^c, each of R^a and R^b is independently a hydrogen atom, sodium, potassium, an amine cation, a C₁₋₁₂aliphatic, or the like, R^c is a hydrogen atom, -N(R)₂, -OR, -SR, a C₁₋₁₂aliphatic, or the like, R⁴ is independently 10 a hydrogen atom, halogen, -NO₂, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, R⁵ is independently halogen, -NO₂, -CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, and each R is independently a hydrogen atom, or an optionally 15 substituted group selected from a C₁₋₁₂aliphatic, a 3- to 14-membered carbocycle, or a 3- to 14-membered heterocycle, a 6- to 14-membered aryl ring, or a 5- to 14-membered heteroaryl ring, with the proviso that (a) when each of R² and R³ is acetyl, R¹ is not acetoxy, (b) when each of R² and R³ is acetyl and R⁴ is ethoxycarbonyl, R⁵ is not 2-oxo-propyl, 20 (c) when each of R², R³, and R⁵ is acetyl, either of R¹ or R⁴ is not hydrogen].

[0013]

(4) Patent Literature 3 describes the following compound exhibiting antitumor activity against various 25 drug-resistant cancer cells:

[0014]

[Chem. 4]



[0015]

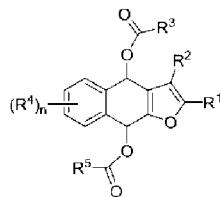
[wherein n is 0 to 4, each R¹ is independently halogen, -NO₂, -CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, 5 each of R² and R³ is independently a hydrogen atom, -S(=O)₂OR^a, -P(=O)OR^aOR^b, -C(=O)R^c, each of R^a and R^b is independently a hydrogen atom, sodium, potassium, an amine cation, a C₁₋₁₂aliphatic, or the like, R^c is a hydrogen atom, -N(R)₂, -OR, -SR, a C₁₋₁₂aliphatic, or the like, R⁴ is independently 10 a hydrogen atom, halogen, -NO₂, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, R⁵ is independently halogen, -NO₂, -CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, and each R is independently a hydrogen atom, or an optionally 15 substituted group selected from a C₁₋₁₂aliphatic, a 3- to 14-membered carbocycle, or a 3- to 14-membered heterocycle, a 6- to 14-membered aryl ring, or a 5- to 14-membered heteroaryl ring].

[0016]

(5) Patent Literature 4 describes the following compound 20 as a hydrophobic prodrug for parenteral administration that is administered as aqueous nanoparticle suspension:

[0017]

[Chem. 5]



25 [0018]

[wherein n is 0 to 4, each R¹ is independently halogen, -NO₂,

-CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, R² is independently a hydrogen atom, halogen, -NO₂, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, each of R³ and R⁵ is independently optionally substituted a C₁₋₂₁aliphatic, 5 R⁴ is independently halogen, -NO₂, -CN, -OR, -SR, -N⁺(R)₃, -N(R)₂, -C(O)R, CO₂R, or the like, and each R is independently a hydrogen atom, or an optionally substituted group selected from a C₁₋₁₂aliphatic, a 3- to 14-membered carbocycle, or a 3- to 14-membered heterocycle, a 6- to 10 14-membered aryl ring, or a 5- to 14-membered heteroaryl ring].

[0019]

Generally, for most hydrophobic prodrugs to be enzymatically converted to an activated form, since 15 interspecies difference and individual difference in conversion to an activated form are observed, a problem of drug concentration estimation in clinical practice occurs (Non Patent Literature 4). A prodrug for oral administration described in Patent Literature 2, after 20 administration, is affected by a first-pass effect in a small intestine and a liver, which causes interspecies difference. Even in the case of an intravenously-administrable prodrug for parenteral administration described in Patent Literature 4, although it is not affected by a first-pass 25 effect in a small intestine and a liver, it is converted to an activated form by an *in vivo* enzyme, esterase, and accordingly interspecies difference and individual difference may be observed in conversion to an activated form.

30 [Citation List]

[Patent Literature]

[0020]

[PTL 1]

- 8 -

International Publication No. 2009/036059 pamphlet
[PTL 2]

International Publication No. 2012/119265 pamphlet
[PTL 3]

5 International Publication No. 2013/166618 pamphlet
[PTL 4]

International Publication No. 2013/120229 pamphlet
[0021]

[Non Patent Literature]

10 [NPL 1]

Ponti *et al.* Cancer Res 65(13): 5506-11. (2005)

[NPL 2]

Lodo *et al.* Annu Rev Cell Dev Biol 23: 675-99. (2007)

[NPL 3]

15 Rao *et al.* J Nat Prod 45(5): 600-4. (1982)

[NPL 4]

Kumpulainen *et al.* Nature Reviews Drug Discovery 7(3):
255-270. (2008)

[Summary Of Invention]

20 [Solution to Problem]

[0022]

25 Since 2-acetylnaphtho[2,3-b]furan-4,9-dione targets a cancer stem cell in addition to a conventional cancer cell, it is expected as a novel anticancer agent. The present invention solves problems associated with its absorption in oral administration due to its high crystallizability as well as its use in parenteral administration has been limited.

30 The present invention provides improvements for known hydrophobic prodrugs for oral administration that is administered as a non-crystalline compound, and hydrophobic prodrugs for parenteral administration that is administered as aqueous nanoparticle suspension.

Specifically, known prodrugs for oral administration are affected by a first-pass effect in an intestine and a liver after administration, which causes interspecies difference. In addition, since known prodrugs for parenteral administration are intravenously administrable, they are not affected by a first-pass effect in an intestine and a liver. However, since they are metabolized by an esterase *in vivo* and converted to an activated form, problems of interspecies difference and individual difference are concerned. Therefore, the present invention provides improvements for developing a prodrug compound that is hard to be affected by enzymatic conversion and exhibit slight interspecies difference and individual difference.

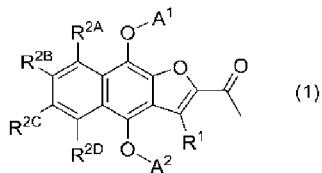
The present invention provides an orally and intravenously administrable, water-soluble prodrug of 2-acetylnaphtho[2,3-b]furan-4,9-dione that is converted to an activated form *in vivo* via a route other than an enzymatic conversion, and provides a compound very useful as a novel anticancer agent.

The present invention relates to a prodrug that has high water-solubility and is converted to an activated form without the need of an enzyme. When a prodrug of the present invention is orally administrated, since the prodrug is dissolved in the stomach and subsequently converted to an activated form depending on pH in the following digestive tract, it is not affected by an *in vivo* enzyme, which causes interspecies difference and individual difference. On the other hand, when it is intravenously administered, it is not affected by a first-pass effect in an small intestine and a liver, which causes interspecies difference and individual difference, and that is converted to an activated form depending from pH in the plasma and without depending on an enzyme.

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Therefore, none of Non Patent Literatures 1, 2, and 3 and Patent Literatures 1-4 discloses or suggests any compound represented by the following formula (1).

[Chem. 6]



5

[0023]

The present inventors intensively studied to provides improvements, and consequently found that a compound having a soluble side chain of a certain structure exhibits high 10 water-solubility suitable for oral administration and intravenous administration, and additionally is converted to an active form by chemical conversion. The present inventors finally reached the completion of the present invention.

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[0024]

The present invention is as described below.

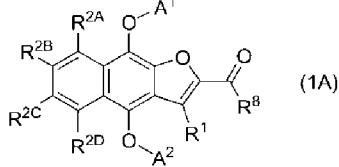
[0025]

[Item 1] A compound represented by formula (1A) or a pharmaceutically acceptable salt thereof:

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[0026]

[Chem. 7]



wherein

A¹ and A² are identical or different, and each 25 independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -C(=S)OB, -CONR^{3C}B, -C(=S)NR^{3C}B, -SO₂B, -SO₂CR^{3A}R^{3B}B, -SO₂(OB), -SO₂NR^{3C}B, -P(=O)(B)₂, -P(=O)(CR^{3A}R^{3B}B)₂, -P(=O)(OB)₂, -P(=O)(NR^{3C}B)₂,

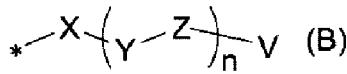
or a hydrogen atom, wherein A¹ and A² are not both hydrogen atoms,

wherein

B is an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted 3- to 12-membered cyclic amino group, or a group represented by the following formula (B):

[0027]

[Chem. 8]



wherein

* denotes a bonding position,

X is a single bond, an optionally substituted C₁₋₁₀alkylene, an optionally substituted C₃₋₁₀cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C₂₋₁₀alkenylene, an optionally substituted C₂₋₁₀alkynylene, an optionally substituted C₆₋₁₀arylene, or an optionally substituted C₅₋₁₀heteroarylene,

Y is a single bond, an oxygen atom, -OCO-, -OCO₂-, -OCONR^{4A}-, -OSO₂-, -OSO₂NR^{4A}-, -CO-, -CO₂-, -CONR^{4A}-, -NR^{4A}-, -NR^{4A}CO-, -NR^{4A}CO₂-, -NR^{4A}CONR^{4B}-, -NR^{4A}SO₂-, -NR^{4A}SO₂O-, -NR^{4A}SO₂NR^{4B}-, a sulfur atom, -SO-, -SO₂-, -SO₂O-, -SO₂NR^{4A}-, or an optionally substituted 3- to 12-membered cyclic aminyl linker group,

30 R^{4A} and R^{4B} are identical or different, and each independently a hydrogen atom, an optionally substituted C₁₋₁₀alkyl group, an optionally substituted C₃₋₁₀cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C₂₋₁₀alkenyl group, an optionally substituted

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C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group,

Z is a single bond, an optionally substituted C_{1-10} alkylene, an optionally substituted C_{3-10} cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C_{2-10} alkenylene, an optionally substituted C_{2-10} alkynylene, an optionally substituted C_{6-10} arylene, or an optionally substituted C_{5-10} heteroarylene,

n is 0, 1, or 2,

V is $-NHR^5$, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, or an optionally substituted 3- to 12-membered cyclic amino group, wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

R^5 is a hydrogen atom, an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group, and

wherein

the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl

group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group;

R^1 is a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-10} aryl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{1-6} alkylcarbonyl group, an optionally substituted C_{3-10} cycloalkylcarbonyl group, an optionally substituted C_{6-10} arylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, a carboxyl group, an optionally substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted C_{6-10} aryloxycarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{3-10} cycloalkylthio group, an optionally substituted C_{6-10} arylthio group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclthio group, a sulfinate group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted

C_{3-10} cycloalkylsulfinyl group, an optionally substituted C_{6-10} arylsulfinyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, an optionally substituted aminosulfinyl group, an 5 optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{3-10} cycloalkylsulfonyl group, an optionally substituted C_{6-10} arylsulfonyl group, an optionally 10 substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 12-membered cyclic aminosulfonyl group;

15 R^{2A} , R^{2B} , R^{2C} , and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{6-10} aryl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{3-10} cycloalkoxy group, an optionally substituted C_{6-10} aryloxy group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclyloxy group, a carboxyl group, an optionally substituted C_{1-6} alkylcarbonyl group, an optionally substituted C_{3-10} cycloalkylcarbonyl group, an optionally substituted C_{6-10} arylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylcarbonyl group, an optionally substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted C_{6-10} aryloxycarbonyl group, an

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optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycloloxy carbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted C₁₋₆alkylthio group, an optionally substituted C₃₋₁₀cycloalkylthio group, an optionally substituted C₆₋₁₀arylthio group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylthio group, a sulfinate group, an optionally substituted C₁₋₆alkylsulfinyl group, an optionally substituted C₃₋₁₀cycloalkylsulfinyl group, an optionally substituted C₆₋₁₀arylsulfinyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, an optionally substituted aminosulfinyl group, an optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C₁₋₆alkylsulfonyl group, an optionally substituted C₃₋₁₀cycloalkylsulfonyl group, an optionally substituted C₆₋₁₀arylsulfonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 12-membered cyclic aminosulfonyl group; and

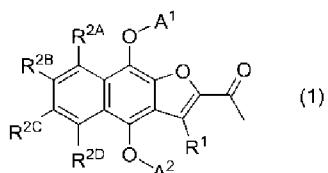
R⁸ is an optionally substituted C₁₋₁₀alkyl group.

25 [0028]

[Item 2] A compound represented by formula (1) or a pharmaceutically acceptable salt thereof:

[0029]

[Chem. 9]



30

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wherein

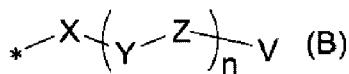
A^1 and A^2 are identical or different, and each independently $-C(=O)B$, $-C(=O)CR^{3A}R^{3B}B$, $-CO_2B$, $-C(=S)OB$, $-CONR^{3C}B$, $-C(=S)NR^{3C}B$, $-SO_2B$, $-SO_2CR^{3A}R^{3B}B$, $-SO_2(OB)$, $-SO_2NR^{3C}B$, 5 $-P(=O)(B)_2$, $-P(=O)(CR^{3A}R^{3B}B)_2$, $-P(=O)(OB)_2$, $-P(=O)(NR^{3C}B)_2$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms,

wherein

B is an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted 3- to 12-membered cyclic amino group, or a group represented by the following formula (B):

[0030]

[Chem. 10]



wherein

* denotes a bonding position,

X is a single bond, an optionally substituted C_{1-10} alkylene, an optionally substituted C_{3-10} cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C_{2-10} alkenylene, an optionally substituted C_{2-10} alkynylene, an optionally substituted C_{6-10} arylene, or 20 an optionally substituted C_{5-10} heteroarylene,

Y is a single bond, an oxygen atom, $-OCO-$, $-OCO_2-$, $-OCO NR^{4A}-$, $-OSO_2-$, $-OSO_2 NR^{4A}-$, $-CO-$, $-CO_2-$, $-CONR^{4A}-$, $-NR^{4A}-$, $-NR^{4A}CO-$, $-NR^{4A}CO_2-$, $-NR^{4A}CONR^{4B}-$, $-NR^{4A}SO_2-$, $-NR^{4A}SO_2O-$, $-NR^{4A}SO_2NR^{4B}-$, a sulfur atom, $-SO-$, $-SO_2-$, $-SO_2O-$, $-SO_2NR^{4A}-$, 25 or an optionally substituted 3- to 12-membered cyclic aminyl linker group,

R^{4A} and R^{4B} are identical or different, and each

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5 independently a hydrogen atom, an optionally substituted C₁₋₁₀alkyl group, an optionally substituted C₃₋₁₀cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C₂₋₁₀alkenyl group, an optionally substituted C₂₋₁₀alkynyl group, an optionally substituted C₆₋₁₀aryl group, or an optionally substituted C₅₋₁₀heteroaryl group,

10 Z is a single bond, an optionally substituted C₁₋₁₀alkylene, an optionally substituted C₃₋₁₀cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C₂₋₁₀alkenylene, an optionally substituted C₂₋₁₀alkynylene, an optionally substituted C₆₋₁₀arylene, or 15 an optionally substituted C₅₋₁₀heteroarylene,

n is 0, 1, or 2,

20 V is -NHR⁵, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, or an optionally substituted 3- to 12-membered cyclic amino group, wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

25 R⁵ is a hydrogen atom, an optionally substituted C₁₋₁₀alkyl group, an optionally substituted C₃₋₁₀cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C₂₋₁₀alkenyl group, an optionally substituted C₂₋₁₀alkynyl group, an optionally substituted C₆₋₁₀aryl group, or an optionally substituted C₅₋₁₀heteroaryl group, and 30

wherein

the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino

group have at least one or more secondary nitrogen atoms in the ring, and

5 R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group;

10 R^1 is a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C_{1-6} alkyl group, an 15 optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-10} aryl group, an optionally substituted 3- to 20 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{1-6} alkylcarbonyl group, an optionally substituted C_{3-10} cycloalkylcarbonyl group, an optionally substituted C_{6-10} arylcarbonyl group, an optionally substituted 3- to 25 12-membered monocyclic or polycyclic heterocyclcarbonyl group, a carboxyl group, an optionally substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted C_{6-10} aryloxycarbonyl group, an optionally substituted 3- to 30 12-membered monocyclic or polycyclic heterocyclloxycarbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted

C₃₋₁₀cycloalkylthio group, an optionally substituted C₆₋₁₀arylthio group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylthio group, a sulfinato group, an optionally substituted 5 C₁₋₆alkylsulfinyl group, an optionally substituted C₃₋₁₀cycloalkylsulfinyl group, an optionally substituted C₆₋₁₀arylsulfinyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, an optionally substituted aminosulfinyl group, an 10 optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C₁₋₆alkylsulfonyl group, an optionally substituted C₃₋₁₀cycloalkylsulfonyl group, an optionally substituted C₆₋₁₀arylsulfonyl group, an optionally 15 substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 12-membered cyclic aminosulfonyl group; and

20 R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C₁₋₆alkyl group, an 25 optionally substituted C₃₋₁₀cycloalkyl group, an optionally substituted C₆₋₁₀aryl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C₁₋₆alkoxy group, an optionally substituted C₃₋₁₀cycloalkoxy group, an optionally substituted C₆₋₁₀aryloxy group, an optionally substituted 30 3- to 12-membered monocyclic or polycyclic heterocyclxy group, a carboxyl group, an optionally substituted C₁₋₆alkylcarbonyl group, an optionally substituted C₃₋₁₀cycloalkylcarbonyl group, an optionally substituted

C₆-₁₀arylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, an optionally substituted C₁-₆alkoxycarbonyl group, an optionally substituted C₃-₁₀cycloalkoxycarbonyl group, an
5 optionally substituted C₆-₁₀aryloxycarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclloxycarbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted
10 C₁-₆alkylthio group, an optionally substituted C₃-₁₀cycloalkylthio group, an optionally substituted C₆-₁₀arylthio group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclthio group, a sulfinate group, an optionally substituted
15 C₁-₆alkylsulfinyl group, an optionally substituted C₃-₁₀cycloalkylsulfinyl group, an optionally substituted C₆-₁₀arylsulfinyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group, an optionally substituted aminosulfinyl group, an
20 optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C₁-₆alkylsulfonyl group, an optionally substituted C₃-₁₀cycloalkylsulfonyl group, an optionally substituted C₆-₁₀arylsulfonyl group, an optionally substituted
25 3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 12-membered cyclic aminosulfonyl group.

[0031]

30 [Item 3] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof,
wherein
a substituent of the optionally substituted 3- to

12-membered monocyclic or polycyclic heterocyclic group, the optionally substituted 3- to 12-membered cyclic amino group, the optionally substituted amino group, the optionally substituted C_{1-10} alkyl group, the optionally substituted 5 C_{1-6} alkyl group, the optionally substituted C_{3-10} cycloalkyl group, the optionally substituted C_{2-10} alkenyl group, the optionally substituted C_{2-6} alkenyl group, the optionally substituted C_{2-10} alkynyl group, the optionally substituted C_{2-6} alkynyl group, the optionally substituted 10 C_{1-6} alkoxy group, the optionally substituted C_{3-10} cycloalkoxy group, the optionally substituted C_{6-10} aryloxy group, the optionally substituted 15 3- to 12-membered monocyclic or polycyclic heterocyclyloxy group, the optionally substituted C_{6-10} aryl group, the optionally substituted C_{1-6} alkylcarbonyl group, the optionally substituted C_{3-10} cycloalkylcarbonyl group, the optionally substituted C_{6-10} arylcarbonyl group, the optionally substituted 20 substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, the optionally substituted C_{1-6} alkoxycarbonyl group, the optionally substituted C_{3-10} cycloalkoxycarbonyl group, the optionally substituted C_{6-10} aryloxycarbonyl group, the optionally substituted 25 3- to 12-membered monocyclic or polycyclic heterocyclloxycarbonyl group, the optionally substituted aminocarbonyl group, the optionally substituted 3- to 12-membered cyclic aminocarbonyl group, the optionally substituted C_{1-6} alkylthio group, the optionally substituted C_{3-10} cycloalkylthio group, the optionally substituted 30 C_{6-10} arylthio group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclthio group, the optionally substituted C_{1-6} alkylsulfinyl group, the optionally substituted C_{3-10} cycloalkylsulfinyl group, the optionally substituted C_{6-10} arylsulfinyl group, the

optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group, the optionally substituted aminosulfinyl group, the optionally substituted 3- to 12-membered cyclic aminosulfinyl group,
5 the optionally substituted C_{1-6} alkylsulfonyl group, the optionally substituted C_{3-10} cycloalkylsulfonyl group, the optionally substituted C_{6-10} arylsulfonyl group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group, the optionally substituted aminosulfonyl group, the optionally substituted 3- to 12-membered cyclic aminosulfonyl group,
10 the optionally substituted C_{5-10} heteroaryl group, the optionally substituted C_{1-10} alkylene, the optionally substituted C_{3-10} cycloalkylene, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C_{2-10} alkynylene, the optionally substituted C_{2-10} alkynylene, the optionally substituted C_{6-10} arylene, and optionally substituted
15 C_{5-10} heteroarylene in B, R^1 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{4A} , R^{4B} , R^5 , R^8 , X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of
20 (1) a halogen atom,
(2) a hydroxyl group,
(3) a carboxyl group,
(4) a sulfinate group,
(5) a sulfonate group,
25 (6) a phosphate group,
(7) an optionally substituted C_{1-6} alkyl group,
(8) an optionally substituted C_{3-10} cycloalkyl group,
(9) an optionally substituted C_{6-10} aryl group,
30

(10) an optionally substituted C₅₋₁₀heteroaryl group,

(11) an optionally substituted C₁₋₆alkoxy group,

(12) an optionally substituted C₃₋₁₀cycloalkoxy group,

(13) an optionally substituted C₁₋₆alkoxycarbonyl group,

5 (14) an optionally substituted C₁₋₆alkylcarbonyl group,

(15) an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group,

(16) an optionally substituted 3- to 12-membered cyclic amino group,

10 (17) -NR⁶R⁷,

(18) -CO₂R⁶,

(19) a guanidine group,

(20) -CONR⁶R⁷,

(21) -SO₂R⁶,

15 (22) -SO₂NR⁶R⁷,

(23) a cyano group,

(24) -OCO₂R⁶,

(25) -OCONR⁶R⁷, and

(26) -NR⁶CO₂R⁷

20 wherein a substituent in the (7), (8), (9), (10), (11), (12), (13), (14), (15), and (16) is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

25 (a) a halogen atom,

(b) a hydroxyl group,

(c) a C₁₋₆alkyl group,

(d) a C₁₋₆alkoxy group,

(e) a cyano group,

30 (f) a carboxyl group,

(g) a sulfinate group,

(h) a sulfonate group,

(i) a phosphate group,

(j) a C₁₋₆alkoxycarbonyl group,

(k) a C₁₋₆alkylcarbonyl group,

(l) -NR⁶R⁷,

(m) -CO₂R⁶,

5 (n) a guanidine group,

(o) -CONR⁶R⁷,

(p) -SO₂R⁶,

(q) -SO₂NR⁶R⁷,

(r) a C₆₋₁₀aryl group,

10 (s) a C₅₋₁₀heteroaryl group,

(t) a 3- to 12-membered cyclic amino group optionally substituted with one to three C₁₋₆alkyl groups, and

15 (u) a 3- to 12-membered monocyclic or polycyclic heterocyclic group optionally substituted with one to three C₁₋₆alkyl groups; and

R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₁₀alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

25 [0032]

[Item 4] The compound according to any one of items 1 to 3, or a pharmaceutically acceptable salt thereof, wherein

30 a substituent of the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, the optionally substituted 3- to 12-membered cyclic amino group, the optionally substituted amino group, the optionally substituted C₁₋₁₀alkyl group, the optionally

substituted C_{1-6} alkyl group, the optionally substituted C_{3-10} cycloalkyl group, the optionally substituted C_{2-10} alkenyl group, the optionally substituted C_{2-6} alkenyl group, the optionally substituted C_{2-10} alkynyl group, the 5 optionally substituted C_{2-6} alkynyl group, the optionally substituted C_{1-6} alkoxy group, the optionally substituted C_{3-10} cycloalkoxy group, the optionally substituted C_{6-10} aryloxy group, the optionally substituted 3- to 10 12-membered monocyclic or polycyclic heterocyclyloxy group, the optionally substituted C_{6-10} aryl group, the optionally substituted C_{1-6} alkylcarbonyl group, the optionally substituted C_{3-10} cycloalkylcarbonyl group, the optionally substituted C_{6-10} arylcarbonyl group, the optionally substituted 15 3- to 12-membered monocyclic or polycyclic heterocyclylcarbonyl group, the optionally substituted C_{1-6} alkoxycarbonyl group, the optionally substituted C_{3-10} cycloalkoxycarbonyl group, the optionally substituted C_{6-10} aryloxycarbonyl group, the optionally substituted 3- to 20 12-membered monocyclic or polycyclic heterocyclyloxycarbonyl group, the optionally substituted aminocarbonyl group, the optionally substituted 3- to 12-membered cyclic aminocarbonyl group, the optionally substituted C_{1-6} alkylthio group, the optionally substituted C_{3-10} cycloalkylthio group, the optionally substituted 25 C_{6-10} arylthio group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylthio group, the optionally substituted C_{1-6} alkylsulfinyl group, the optionally substituted C_{3-10} cycloalkylsulfinyl group, the optionally substituted C_{6-10} arylsulfinyl group, the optionally substituted 30 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, the optionally substituted aminosulfinyl group, the optionally substituted 3- to 12-membered cyclic aminosulfinyl group,

the optionally substituted C_{1-6} alkylsulfonyl group, the optionally substituted C_{3-10} cycloalkylsulfonyl group, the optionally substituted C_{6-10} arylsulfonyl group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, the optionally substituted aminosulfonyl group, the optionally substituted 3- to 12-membered cyclic aminosulfonyl group, the optionally substituted C_{5-10} heteroaryl group, the optionally substituted C_{1-10} alkylene, the optionally substituted C_{3-10} cycloalkylene, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C_{2-10} alkenylene, the optionally substituted C_{2-10} alkynylene, the optionally substituted C_{6-10} arylene, and optionally substituted C_{5-10} heteroarylene in B, R^1 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{4A} , R^{4B} , R^5 , X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

(1) a halogen atom,

(2) a hydroxyl group,

(3) a carboxyl group,

(4) a sulfinate group,

(5) a sulfonate group,

(6) a phosphate group,

(7) an optionally substituted C_{1-6} alkyl group,

(8) an optionally substituted C_{3-10} cycloalkyl group,

(9) an optionally substituted C_{6-10} aryl group,

(10) an optionally substituted C_{5-10} heteroaryl group,

(11) an optionally substituted C_{1-6} alkoxy group,

(12) an optionally substituted C_{3-10} cycloalkoxy group,

(13) an optionally substituted C_{1-6} alkoxycarbonyl group,

(14) an optionally substituted C_{1-6} alkylcarbonyl group,

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(15) an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group,

(16) an optionally substituted 3- to 12-membered cyclic amino group,

5 (17) $-\text{NR}^6\text{R}^7$,

(18) $-\text{CO}_2\text{R}^6$,

(19) a guanidine group,

(20) $-\text{CONR}^6\text{R}^7$,

(21) $-\text{SO}_2\text{R}^6$,

10 (22) $-\text{SO}_2\text{NR}^6\text{R}^7$, and

(23) a cyano group,

wherein a substituent in the (7), (8), (9), (10),

(11), (12), (13), (14), (15), and (16) is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

(a) a halogen atom,

(b) a hydroxyl group,

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

20 (d) a C_{1-6} alkoxy group,

(e) a cyano group,

(f) a carboxyl group,

(g) a sulfinate group,

(h) a sulfonate group,

25 (i) a phosphate group,

(j) a C_{1-6} alkoxycarbonyl group,

(k) a C_{1-6} alkylcarbonyl group,

(l) $-\text{NR}^6\text{R}^7$,

(m) $-\text{CO}_2\text{R}^6$,

30 (n) a guanidine group,

(o) $-\text{CONR}^6\text{R}^7$,

(p) $-\text{SO}_2\text{R}^6$,

(q) $-\text{SO}_2\text{NR}^6\text{R}^7$,

5 (r) a C₆₋₁₀aryl group,
(s) a C₅₋₁₀heteroaryl group,
(t) a 3- to 12-membered cyclic amino group
optionally substituted with one to three C₁₋₆alkyl groups,
and

10 (u) a 3- to 12-membered monocyclic or polycyclic
heterocyclic group optionally substituted with one to three
C₁₋₆alkyl groups; and

15 R⁶ and R⁷ are identical or different, and each
independently a hydrogen atom, or a C₁₋₁₀alkyl group
optionally substituted with one to two groups selected from
the group consisting of a halogen atom and a carboxyl group,
wherein R⁶ and R⁷, when both are optionally substituted
C₁₋₁₀alkyl groups, may be taken together with the nitrogen
15 atom to which they are attached to form a 3- to 12-membered
cyclic amino group.

[0033]

20 [Item 5] The compound according to any one of items 1 to
4, or a pharmaceutically acceptable salt thereof,
wherein

25 a substituent of the optionally substituted C₁₋₁₀alkyl
group, the optionally substituted C₁₋₆alkyl group, the
optionally substituted C₃₋₁₀cycloalkyl group, the optionally
substituted 3- to 10-membered monocyclic or polycyclic
heterocyclic group, the optionally substituted C₂₋₁₀alkenyl
group, the optionally substituted C₂₋₆alkenyl group, the
optionally substituted C₂₋₁₀alkynyl group, the optionally
substituted C₂₋₆alkynyl group, the optionally substituted
C₆₋₁₀aryl group, the optionally substituted C₅₋₁₀heteroaryl
30 group, the optionally substituted 3- to 10-membered cyclic
amino group, the optionally substituted C₁₋₁₀alkylene, the
optionally substituted C₃₋₁₀cycloalkylene, the optionally
substituted 3- to 12-membered monocyclic or polycyclic

heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C_{2-10} alkenylene, the optionally substituted C_{2-10} alkynylene, the optionally substituted C_{6-10} arylene, and the optionally substituted C_{5-10} heteroarylene in B, R^{3A} , R^{3B} , R^{3C} , R^{4A} , R^{4B} , 5 R^5 , X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

- (1) a halogen atom,
- 10 (2) a hydroxyl group,
- (3) a carboxyl group,
- (4) a sulfinate group,
- (5) a sulfonate group,
- (6) a phosphate group,
- 15 (7) a C_{1-6} alkyl group,
- (8) a C_{3-10} cycloalkyl group,
- (9) an optionally substituted C_{6-10} aryl group,
- (10) an optionally substituted C_{5-10} heteroaryl group,
- (11) a C_{1-6} alkoxy group,
- 20 (12) a C_{3-8} cycloalkoxy group,
- (13) a C_{1-6} alkoxycarbonyl group,
- (14) a C_{1-6} alkylcarbonyl group,
- (15) a 3- to 12-membered monocyclic or polycyclic heterocyclic group,

25 (16) a 3- to 12-membered cyclic amino group

(17) $-NR^6R^7$,

(18) $-CO_2R^6$,

(19) a guanidine group,

(20) $-CONR^6R^7$,

30 (21) $-SO_2R^6$, and

(22) $-SO_2NR^6R^7$,

wherein

a substituent in the (9) and (10) is a group

optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

- (a) a halogen atom,
- 5 (b) a hydroxyl group,
- (c) a C₁₋₆alkyl group,
- (d) a C₁₋₆alkoxy group,
- (e) a cyano group,
- (f) a carboxyl group,
- 10 (g) a sulfinate group,
- (h) a sulfonate group,
- (i) a phosphate group,
- (j) a C₁₋₆alkoxycarbonyl group,
- (k) a C₁₋₆alkylcarbonyl group,
- 15 (l) -NR⁶R⁷,
- (m) -CO₂R⁶,
- (n) a guanidine group,
- (o) -CONR⁶R⁷,
- (p) -SO₂R⁶, and
- 20 (q) -SO₂NR⁶R⁷; and

R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₁₀alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

[0034]

30 [Item 6] The compound according to any one of items 1 to 5, or a pharmaceutically acceptable salt thereof, wherein a substituent of the optionally substituted C₁₋₁₀alkyl

group, the optionally substituted C_{1-6} alkyl group, the optionally substituted C_{3-10} cycloalkyl group, the optionally substituted 3- to 10-membered monocyclic or polycyclic heterocyclic group, the optionally substituted C_{2-10} alkenyl group, the optionally substituted C_{2-6} alkenyl group, the optionally substituted C_{2-10} alkynyl group, the optionally substituted C_{2-6} alkynyl group, the optionally substituted C_{6-10} aryl group, the optionally substituted C_{5-10} heteroaryl group, the optionally substituted 3- to 12-membered cyclic amino group, the optionally substituted C_{1-10} alkylene, the optionally substituted C_{3-10} cycloalkylene, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C_{2-10} alkenylene, the optionally substituted C_{2-10} alkynylene, the optionally substituted C_{6-10} arylene, and the optionally substituted C_{5-10} heteroarylene in B, R^{3A} , R^{3B} , R^{3C} , R^{4A} , R^{4B} , R^5 , X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

- (1) a halogen atom,
- (2) a hydroxyl group,
- (3) a carboxyl group,
- (4) a sulfinate group,
- (5) a sulfonate group,
- (6) a phosphate group,
- (7) a C_{1-6} alkoxy group,
- (8) $-NR^6R^7$,
- (9) $-CO_2R^6$,
- (10) a guanidine group,
- (11) $-CONR^6R^7$, and
- (12) $-SO_2NR^6R^7$; and

R^6 and R^7 are identical or different, and each

5 independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₁₀alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

[0035]

10 [Item 7] The compound according to any one of items 1 to 6, or a pharmaceutically acceptable salt thereof, wherein

15 a substituent of the optionally substituted C₁₋₁₀alkyl group, the optionally substituted C₁₋₆alkyl group, the optionally substituted C₃₋₁₀cycloalkyl group, the optionally substituted 3- to 10-membered monocyclic or polycyclic heterocyclic group, the optionally substituted C₂₋₁₀alkenyl group, the optionally substituted C₂₋₆alkenyl group, the optionally substituted C₂₋₁₀alkynyl group, the optionally substituted C₂₋₆alkynyl group, the optionally substituted C₆₋₁₀aryl group, the optionally substituted C₅₋₁₀heteroaryl group, the optionally substituted 3- to 12-membered cyclic amino group, the optionally substituted C₁₋₁₀alkylene, the optionally substituted C₃₋₁₀cycloalkylene, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C₂₋₁₀alkenylene, the optionally substituted C₂₋₁₀alkynylene, the optionally substituted C₆₋₁₀arylene, and the optionally substituted C₅₋₁₀heteroarylene in B, R^{3A}, R^{3B}, R^{3C}, R^{4A}, R^{4B}, R⁵, R⁸, X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group consisting of

20 (1) a halogen atom,

25

30

(2) a carboxyl group,

(3) a C₆₋₁₀aryl group,

(4) -NR⁶R⁷,

(5) -CO₂R⁶,

5 (6) -CONR⁶R⁷,

(7) -SO₂R⁶,

(8) -SO₂NR⁶R⁷,

(9) -OCO₂R⁶,

(10) -OCONR⁶R⁷, and

10 (11) -NR⁶CO₂R⁷; and

R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered cyclic amino group.

[0036]

20 [Item 8] The compound according to any one of items 1 to 7, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -CONR^{3C}B, -SO₂B, -SO₂CR^{3A}R^{3B}B, -SO₂(OB), -SO₂NR^{3C}B, -P(=O)(B)₂, -P(=O)(CR^{3A}R^{3B}B)₂, -P(=O)(OB)₂, -P(=O)(NR^{3C}B)₂, or a hydrogen atom.

[0037]

25 [Item 9] The compound according to any one of items 1 to 7, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -CONR^{3C}B, or a hydrogen atom.

[0038]

[Item 10] The compound according to any one of items 1 to 7, or a pharmaceutically acceptable salt thereof, wherein

A¹ and A² are identical or different, and each independently -C(=O)B, -CO₂B, -CONR^{3C}B, or a hydrogen atom.

[0039]

[Item 11] The compound according to any one of items 1 to 7, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -SO₂B, -SO₂CR^{3A}R^{3B}B, -SO₂(OB), -SO₂NR^{3C}B, or a hydrogen atom.

[0040]

[Item 12] The compound according to any one of items 1 to 7, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -P(=O)(B)₂, -P(=O)(CR^{3A}R^{3B}B)₂, -P(=O)(OB)₂, -P(=O)(NR^{3C}B)₂, or a hydrogen atom.

[0041]

[Item 13] The compound according to any one of items 1 to 12, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

[0042]

[Item 14] The compound according to any one of items 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R¹ is a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C₁₋₆alkyl group, an optionally substituted C₃₋₁₀cycloalkyl group, an optionally substituted C₂₋₆alkenyl group, an optionally substituted C₂₋₆alkynyl group, an optionally substituted C₁₋₆alkoxy group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C₁₋₆alkylcarbonyl group, an optionally substituted C₃₋₁₀cycloalkylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylcarbonyl group, a carboxyl group, an optionally

substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted aminocarbonyl group, or an optionally substituted 3- to 12-membered cyclic aminocarbonyl group.

5 [0043]

[Item 15] The compound according to any one of items 1 to 13, or a pharmaceutically acceptable salt thereof, wherein

10 R^1 is

- 10 (1) a hydrogen atom;
- (2) a halogen atom;
- (3) a cyano group;
- (4) a hydroxyl group;

15 (5) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

20 (6) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered cyclic amino group);

25 (7) a C_{1-6} alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, and a C_{3-10} cycloalkyl group);

30 (8) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

(9) a C_{1-6} alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group

consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered cyclic amino group);

(10) a carboxyl group;

5 (11) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

10 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group),

15 (b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

20 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group)); or

25 (12) a 3- to 12-membered cyclic aminocarbonyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups).

[0044]

25 [Item 16] The compound according to any one of items 1 to 13, or a pharmaceutically acceptable salt thereof, wherein

30 R¹ is

(1) a hydrogen atom,

(2) a hydroxyl group,

30 (3) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy

group, and a C₃₋₁₀cycloalkyl group),

(4) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a C₃₋₁₀cycloalkyl group),

(5) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered cyclic amino group), or

(6) a carboxyl group.

[0045]

[Item 17] The compound according to any one of items 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R¹ is a hydrogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₁₋₆alkylcarbonyl group, or a carboxyl group.

[0046]

[Item 18] The compound according to any one of items 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R¹ is a hydrogen atom.

[0047]

[Item 19] The compound according to any one of items 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently

- (1) a hydrogen atom;
- (2) a halogen atom;
- (3) a cyano group;
- (4) a hydroxyl group;

(5) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of

- (a) a C₁₋₆alkyl group (the alkyl group is optionally

substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(c) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

(d) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group));

(6) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three C₁₋₆alkyl groups);

(7) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

(8) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(9) a C₆₋₁₀aryl group (the aryl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

5 (10) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

10 (11) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

15 (12) a C₃₋₁₀cycloalkoxy group (the cycloalkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

20 (13) a C₆₋₁₀aryloxy group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (14) a 3- to 12-membered monocyclic or polycyclic heterocyclyloxy group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(15) a carboxyl group;

30 (16) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

(17) a C_{3-10} cycloalkylcarbonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

5 (18) a C_{6-10} arylcarbonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

10 (19) a 3- to 12-membered monocyclic or polycyclic heterocyclylcarbonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

15 (20) a C_{1-6} alkoxycarbonyl group (the alkoxy is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, $-NR^6R^7$, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

20 (21) a C_{3-10} cycloalkoxycarbonyl group (the cycloalkoxy is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

25 (22) a C_{6-10} aryloxycarbonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

30 (23) a 3- to 12-membered monocyclic or polycyclic heterocyclyloxycarbonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

(24) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group

consisting of

(a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

(c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group));

(25) a 3- to 12-membered cyclic aminocarbonyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups);

(26) a C₁₋₆alkylthio group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

(27) a C₃₋₁₀cycloalkylthio group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(28) a C₆₋₁₀arylthio group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(29) a 3- to 12-membered monocyclic or polycyclic

heterocyclylthio group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

5 (30) a sulfinate group;

(31) a C₁₋₆alkylsulfinyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 10 12-membered monocyclic or polycyclic heterocyclic group);

(32) a C₃₋₁₀cycloalkylsulfinyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

15 (33) a C₆₋₁₀arylsulfinyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

20 (34) a 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (35) an aminosulfinyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

30 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is

optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

5 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group));

10 (36) a 3- to 12-membered cyclic aminosulfinyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups);

(37) a sulfonate group;

15 (38) a C₁₋₆alkylsulfonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

20 (39) a C₃₋₁₀cycloalkylsulfonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (40) a C₆₋₁₀arylsulfonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

30 (41) a 3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(42) an aminosulfonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

5 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

10 (b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

15 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group)); or

(43) a 3- to 12-membered cyclic aminosulfonyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups).

[0048]

20 [Item 20] The compound according to any one of items 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently

25 (1) a hydrogen atom;

(2) a halogen atom;

(3) a cyano group;

(4) a hydroxyl group;

30 (5) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of

(a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a

C₁₋₆alkoxy group),

(b) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and C₁₋₆alkoxy group),

(c) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

(d) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group));

(6) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three C₁₋₆alkyl groups);

(7) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

(8) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(9) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

(10) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally

substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

5 (11) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

10 (12) a C₃₋₁₀cycloalkylcarbonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(13) a carboxyl group;

15 (14) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

20 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

25 (b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

30 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group)); or

(15) a sulfonate group.

[0049]

[Item 21] The compound according to any one of items 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each 5 independently

(1) a hydrogen atom,

(2) a halogen atom,

(3) a hydroxyl group,

10 (4) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of a C₁₋₆alkyl group and a C₁₋₆alkylcarbonyl group),

15 (5) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a C₁₋₆alkoxy group),

(6) a C₃₋₁₀cycloalkyl group,

20 (7) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a C₁₋₆alkoxy group),

(8) a carboxyl group, or

25 (9) an aminocarbonyl group (the amino is optionally substituted with a C₁₋₆alkyl group).

[0050]

30 [Item 22] The compound according to any one of items 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a C₁₋₆alkyl group, a C₃₋₁₀cycloalkyl group, a C₁₋₆alkoxy group, or a carboxyl group.

[0051]

[Item 23] The compound according to any one of items 1 to 18, or a pharmaceutically acceptable salt thereof, wherein

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms.

[0052]

[Item 24] The compound according to any one of items 1 to 23, or a pharmaceutically acceptable salt thereof, wherein 5 R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, or a C_{1-10} alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a 10 sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$.

[0053]

[Item 25] The compound according to any one of items 1 to 15 23, or a pharmaceutically acceptable salt thereof, wherein R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, or a C_{1-10} alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a 20 carboxyl group, $-NR^6R^7$, and $-CO_2R^6$.

[0054]

[Item 26] The compound according to any one of items 1 to 23, or a pharmaceutically acceptable salt thereof, wherein R^{3A} , R^{3B} , and R^{3C} are all hydrogen atoms.

25 [0055]

[Item 27] The compound according to any one of items 1 to 26, or a pharmaceutically acceptable salt thereof, wherein 30 R^8 is a C_{1-10} alkyl group optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, $-NR^6R^7$, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, a C_{6-10} aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group.

[0056]

[Item 28] The compound according to any one of items 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R⁸ is a C₁₋₁₀alkyl group optionally substituted with one to three groups selected from the group consisting of a halogen atom, -NR⁶R⁷, a C₁₋₆alkoxy group, and a C₃₋₁₀cycloalkyl group.

5

[0057]

[Item 29] The compound according to any one of items 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R⁸ is a C₁₋₆alkyl group optionally substituted with one to 10 three halogen atoms.

[0058]

[Item 30] The compound according to any one of items 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R⁸ is a methyl group.

15

[0059]

[Item 31] The compound according to any one of items 1 to 30, or a pharmaceutically acceptable salt thereof, wherein

B is

20

(1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

25

(2) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

30

(3) a group represented by the formula (B), wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

5 [0060]

[Item 32] The compound according to any one of items 1 to 30, or a pharmaceutically acceptable salt thereof, wherein B is a 3- to 6-membered monocyclic heterocyclic group optionally substituted with one to two substituents 10 selected from the group consisting of a fluorine atom, a carboxyl group, and $-\text{CO}_2\text{R}^6$, or a group represented by the formula (B), wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

15 [0061]

[Item 33] The compound according to any one of items 1 to 30, or a pharmaceutically acceptable salt thereof, wherein B is a 3- to 6-membered monocyclic heterocyclic group optionally substituted with one to two substituents 20 selected from the group consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$, or a group represented by the formula (B), wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

[0062]

25 [Item 34] The compound according to any one of items 1 to 30, or a pharmaceutically acceptable salt thereof, wherein

30 B is a 3- to 6-membered monocyclic heterocyclic group, a 3- to 6-membered cyclic amino group, or a group represented by the formula (B),

wherein the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

[0063]

[Item 35] The compound according to any one of items 1 to 34, or a pharmaceutically acceptable salt thereof, wherein

5 X is

(1) a single bond,

10 (2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$),

15 (3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$),

20 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$), or

25 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$).

[0064]

[Item 36] The compound according to any one of items 1 to 34, or a pharmaceutically acceptable salt thereof, wherein

X is

5 (1) a single bond,
(2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-NR^6R^7$, and $-CO_2R^6$),

10 (3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-NR^6R^7$, and $-CO_2R^6$),

15 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-NR^6R^7$, and $-CO_2R^6$), or

20 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-NR^6R^7$, and $-CO_2R^6$).

[0065]

[Item 37] The compound according to any one of items 1 to 34, or a pharmaceutically acceptable salt thereof, wherein

30 X is

(1) a single bond;
(2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group

consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$); or

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$).

[0066]

[Item 38] The compound according to any one of items 1 to 34, or a pharmaceutically acceptable salt thereof, wherein X is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-\text{CO}_2\text{R}^6$.

[0067]

[Item 39] The compound according to any one of items 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Y is a single bond, an oxygen atom, $-\text{OCO}_2-$, $-\text{OCONR}^{4A}-$, $-\text{CONR}^{4A}-$, $-\text{NR}^{4A}-$, $-\text{NR}^{4A}\text{CO}-$, $-\text{NR}^{4A}\text{CO}_2-$, $-\text{NR}^{4A}\text{CONR}^{4B}-$, $-\text{NR}^{4A}\text{SO}_2-$, $-\text{NR}^{4A}\text{SO}_2\text{NR}^{4B}-$, a sulfur atom, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{4A}-$, or an optionally substituted 3- to 12-membered cyclic aminyl linker group.

[0068]

[Item 40] The compound according to any one of items 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Y is a single bond, an oxygen atom, $-\text{CONR}^{4A}-$, $-\text{NR}^{4A}\text{CO}-$, or a sulfur atom.

[0069]

[Item 41] The compound according to any one of items 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Y is a single bond, an oxygen atom, or $-\text{NR}^{4A}-$.

[0070]

[Item 42] The compound according to any one of items 1 to

41, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷.

[0071]

10 [Item 43] The compound according to any one of items 1 to 41, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are hydrogen atoms.

[0072]

15 [Item 44] The compound according to any one of items 1 to 43, or a pharmaceutically acceptable salt thereof, wherein

wherein

Z is

(1) a single bond,

20 (2) C₁₋₁₀alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

25 (3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

30 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting

of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

5 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

10 (6) C₆₋₁₀arylene (the arylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

15 (7) C₅₋₁₀heteroarylene (the heteroarylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

20 [0073]

25 [Item 45] The compound according to any one of items 1 to 43, or a pharmaceutically acceptable salt thereof, wherein

Z is

(1) a single bond,

30 (2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and

$-\text{CO}_2\text{R}^6$),

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

(5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$).

[0074]

[Item 46] The compound according to any one of items 1 to 43, or a pharmaceutically acceptable salt thereof, wherein Z is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-\text{CO}_2\text{R}^6$.

[0075]

[Item 47] The compound according to any one of items 1 to 43, or a pharmaceutically acceptable salt thereof, wherein Z is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$.

[0076]

[Item 48] The compound according to any one of items 1 to 47, or a pharmaceutically acceptable salt thereof, wherein

V is

5 (1) $-\text{NHR}^5$,

10 (2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$), or

15 (3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$); and

20 wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

25 [0077]

[Item 49] The compound according to any one of items 1 to 47, or a pharmaceutically acceptable salt thereof, wherein V is $-\text{NHR}^5$, a 3- to 6-membered monocyclic heterocyclic group, or a 3- to 6-membered cyclic amino group, wherein the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

30 [0078]

[Item 50] The compound according to any one of items 1 to 3 and 7 to 49, or a pharmaceutically acceptable salt thereof, wherein

35 R^5 is

(1) a hydrogen atom;

5 (2) a C_{1-10} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{6-10} aryl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, $-OCO_2R^6$, $-OCONR^6R^7$, and $-NR^6CO_2R^7$);

10 (3) a C_{3-10} cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

15 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

20 (5) a C_{6-10} aryl group (the aryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$); or

25 (6) a C_{5-10} heteroaryl group (the heteroaryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and

$-\text{SO}_2\text{NR}^6\text{R}^7$).

[0079]

[Item 51] The compound according to any one of items 1 to 49, or a pharmaceutically acceptable salt thereof,

5 wherein

R^5 is

(1) a hydrogen atom,

10 (2) a $\text{C}_{1-10}\text{alkyl}$ group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-8}\text{cycloalkoxy}$ group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$),

15 (3) a $\text{C}_{3-10}\text{cycloalkyl}$ group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-8}\text{cycloalkoxy}$ group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$),

20 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-8}\text{cycloalkoxy}$ group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$),

25 (5) a $\text{C}_{6-10}\text{aryl}$ group (the aryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-8}\text{cycloalkoxy}$ group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$), or

5 (6) a C₅₋₁₀heteroaryl group (the heteroaryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

[0080]

10 [Item 52] The compound according to any one of items 1 to 49, or a pharmaceutically acceptable salt thereof, wherein

R⁵ is

(1) a hydrogen atom,

15 (2) C₁₋₁₀alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶),

20 (3) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶), or

25 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶).

30 [0081]

[Item 53] The compound according to any one of items 1 to 3 and 7 to 49, or a pharmaceutically acceptable salt thereof, wherein

R^5 is

(1) a hydrogen atom; or

(2) a C_{1-10} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{6-10} aryl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, $-OCO_2R^6$, $-OCONR^6R^7$, and $-NR^6CO_2R^7$).

10 [0082]

[Item 54] The compound according to any one of items 1 to 53, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R^6 and R^7 , when both are optionally substituted C_{1-6} alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

15 [0083]

[Item 55] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

20 A^1 and A^2 are identical or different, and each independently $-C(=O)B$, $-C(=O)CR^{3A}R^{3B}B$, $-CO_2B$, $-CONR^{3C}B$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms, wherein

B is

25 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a

phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$),

(2) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$), or

(3) a group represented by the formula (B),
wherein

X is

(1) a single bond,

(2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$),

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$), or

(5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

Y is a single bond, an oxygen atom, -CONR^{4A}-, -NR^{4A}CO-, or a sulfur atom,

R^{4A} is a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, and -CONR⁶R⁷,

Z is

(1) a single bond,

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a

sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

(5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

n is 0 or 1,

V is

(1) -NHR⁵,

(2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

(3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring,

R⁵ is

(1) a hydrogen atom,

(2) a C₁₋₁₀alkyl group (the alkyl group is

5 optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

10 (3) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

15 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), and

20 R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group, and

25 wherein

30 the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

5 R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$;

R^1 is a hydrogen atom; and

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms.

[0084]

10 [Item 56] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

A^1 and A^2 are identical or different, and each independently $-CO_2B$, $-CONR^{3C}B$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms,

15 wherein

 B is

20 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$), or

 (2) a group represented by the formula (B),

 wherein

 X is

25 (1) a single bond,

 (2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

30 (3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$), or

5 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

10 Y is a single bond or an oxygen atom,

Z is

(1) a single bond,

15 (2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

20 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$), or

25 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

30 n is 0 or 1,

V is

(1) $-NHR^5$,

(2) a 3- to 12-membered monocyclic or polycyclic

heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

5 (3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

10 wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring,

R^5 is

(1) a hydrogen atom,

15 (2) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

20 (3) a C_{3-10} cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

25 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), and

30 R^6 and R^7 are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two groups selected from the group consisting of a carboxyl group, wherein R^6 and R^7 , when both are optionally substituted C_{1-6} alkyl groups, may be taken together with the nitrogen atom to which they are

attached to form a 3- to 6-membered cyclic amino group, and
wherein

the 3- to 12-membered monocyclic or polycyclic
heterocyclic group and the 3- to 12-membered cyclic amino
group have at least one or more secondary nitrogen atoms
in the ring, and

R^{3C} is a hydrogen atom, or a C_{1-6} alkyl group
optionally substituted with one to two groups selected from
the group consisting of a carboxyl group and $-CO_2R^6$;

10 R^1 is a hydrogen atom; and

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms.

[0085]

[Item 57] The compound according to item 1, or a
pharmaceutically acceptable salt thereof,

15 wherein

A^1 and A^2 are identical or different, and each
independently $-C(=O)B$, $-CO_2B$, $-CONR^{3C}B$, or a hydrogen atom,
wherein A^1 and A^2 are not both hydrogen atoms,

wherein

20 B is

(1) a 3- to 6-membered monocyclic or polycyclic
heterocyclic group,

(2) a 3- to 6-membered cyclic amino group, or

(3) a group represented by the formula (B),

25 wherein

X is

(1) a single bond,

(2) C_{1-6} alkylene (the alkylene is optionally
substituted with one to three substituents selected from
30 the group consisting of a carboxyl group and $-CO_2R^6$), or

(3) C_{3-10} cycloalkylene;

Y is a single bond, an oxygen atom, or $-NR^{4A}-$;

R^{4A} is a hydrogen atom;

5 Z is

(1) a single bond, or

(2) C₁₋₆alkylene;

n is 0 or 1;

10 V is

(1) -NHR⁵,

(2) a 3- to 6-membered monocyclic or polycyclic heterocyclic group, or

(3) a 3- to 6-membered cyclic amino group,

15 wherein the 3- to 6-membered monocyclic or polycyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring;

20 R⁵ is

15 (1) a hydrogen atom, or

(2) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a 20 sulfonate group, a phosphate group, a C₆₋₁₀aryl group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, -SO₂NR⁶R⁷, -OCO₂R⁶, -OCONR⁶R⁷, and -NR⁶CO₂R⁷), and

25 R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two carboxyl groups, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered 30 cyclic amino group, and

wherein

the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at

least one or more secondary nitrogen atoms in the ring, and
R^{3C} is a hydrogen atom;

R¹ is a hydrogen atom;

R^{2A}, R^{2B}, R^{2C}, and R^{2D} are all hydrogen atoms; and

5 R⁸ is a methyl group.

[0086]

[Item 58] The compound according to any one of items 1 to 57, or a pharmaceutically acceptable salt thereof, wherein X is a single bond, or C₁₋₆alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶.

[0087]

[Item 59] The compound according to any one of items 1 to 58, or a pharmaceutically acceptable salt thereof, wherein B is a 3- to 6-membered monocyclic heterocyclic group, or a group represented by the formula (B), wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

[0088]

20 [Item 60] The compound according to any one of items 1 to 59, or a pharmaceutically acceptable salt thereof, wherein V is -NHR⁵.

[0089]

25 [Item 61] The compound according to any one of items 1 to 60, or a pharmaceutically acceptable salt thereof, wherein R⁵ is a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two groups selected from the group consisting of a fluorine atom, a carboxyl group, and -CO₂R⁶.

[0090]

30 [Item 62] The compound according to any one of items 1 to 60, or a pharmaceutically acceptable salt thereof, wherein R⁵ is a hydrogen atom, or C₁₋₆alkyl optionally substituted with one to two substituents selected from the group

consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$.

[0091]

[Item 63] The compound according to any one of items 1 to 62, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are C_{1-6} alkyl groups optionally substituted with one to two carboxyl groups.

[0092]

[Item 64] The compound according to any one of items 1 to 62, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are C_{1-6} alkyl groups.

[0093]

[Item 65] The compound according to any one of items 1 to 64, or a pharmaceutically acceptable salt thereof, wherein n is 1.

[0094]

[Item 66] The compound according to any one of items 1 to 64, or a pharmaceutically acceptable salt thereof, wherein n is 0.

[0095]

[Item 67] The compound according to any one of items 1 to 66, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^2 are identical or different, and each independently $-\text{CO}_2\text{B}$ or a hydrogen atom.

[0096]

[Item 68] The compound according to any one of items 1 to 66, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^2 are identical or different, and each independently $-\text{CONR}^{3c}\text{B}$ or a hydrogen atom.

[0097]

[Item 69] The compound according to any one of items 1 to 66, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^2 are identical or different, and each independently $-\text{CONHB}$ or a hydrogen atom.

[0098]

[Item 70] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

5 A¹ and A² are -CONHB,
 wherein

 B is a 3- to 6-membered monocyclic heterocyclic group, or a group represented by the formula (B),
 wherein

10 X is C₁₋₆alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶,

 n is 0,

15 V is -NHR⁵ or a 3- to 6-membered monocyclic heterocyclic group, wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring,

 R⁵ is a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two carboxyl groups, and

20 R⁶ is a C₁₋₆alkyl group, and
 wherein

 the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring;

25 R¹ is a hydrogen atom;

 R^{2A}, R^{2B}, R^{2C}, and R^{2D} are all hydrogen atoms.

[0099]

[Item 71] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following compounds:

2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-aminopropyl)carbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((2-aminoethyl) carbamate),
(2S,2'S)-4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)
bis(oxy))bis(carbonyl))bis(azanediyl))bis(2-(methylamin
o)butanoic acid),
5 2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)
))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis
(azanediyl) diacetic acid,
3,3'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)
))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis
10 (azanediyl) dipropionic acid,
(2S,2'S)-3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)
bis(oxy))bis(carbonyl))bis(azanediyl))bis(2-aminopropio
nic acid),
dimethyl
15 4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutano
ate),
dimethyl
3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
20 bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminopropan
oate),
2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)
))bis(carbonyl))bis(azanediyl))bis(propane-3,1-diyl))bi
s(azanediyl) diacetic acid,
25 2,2'-((2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)
bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-di
yl))bis(azanediyl))bis(acetyl))bis(azanediyl) diacetic
acid,
2-acetylnaphtho[2,3-b]furan-4,9-diyl
30 bis((2-((2-(piperidin-1-ylsulfonyl)ethyl)amino)ethyl)ca
rbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(N,N-dimethylsulfamoyl)ethyl)amino)ethyl)car

bamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(isopropylsulfonyl)ethyl)amino)ethyl)carbamate),
5 2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-((2-(N,N-dimethylsulfamoyl)ethyl)amino)propyl)carbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-((2-(methylsulfonyl)ethyl)amino)propyl)carbamate)
10),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(methylsulfonyl)ethyl)amino)ethyl)carbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(azetidin-1-yl)-2-oxoethyl)amino)ethyl)carbamate),
15 2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-((2-(azetidin-1-yl)-2-oxoethyl)amino)propyl)carbamate),
2,2'-((2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)
20 bis(oxy))bis(carbonyl))bis(azanediyl))bis(propane-3,1-diyl))bis(azanediyl))bis(acetyl))bis(azanediyl))diacetic
acid,
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(carbamoyloxy)ethyl)amino)ethyl)carbamate),
25 2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-((2-(carbamoyloxy)ethyl)amino)propyl)carbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((2-((2-(methoxycarbonyl)amino)ethyl)amino)ethyl)carbamate),
30 2-acetylnaphtho[2,3-b]furan-4,9-diyl
bis((3-((2-(methoxycarbonyl)amino)ethyl)amino)propyl)carbamate),
2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((2-((2-((methoxycarbonyl)oxy)ethyl)amino)ethyl)carbamate),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((3-((2-((methoxycarbonyl)oxy)ethyl)amino)propyl)carbamate),

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-(N,N-dimethylsulfamoyl)ethyl)amino)propyl)carbamate,

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-(methylsulfonyl)ethyl)amino)propyl)carbamate,

(3-(((2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl)oxy)carbonyl)amino)propyl)glycylglycine,

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-(azetidin-1-yl)-2-oxoethyl)amino)propyl)carbamate,

15 e,

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-(carbamoyloxy)ethyl)amino)propyl)carbamate,

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-((methoxycarbonyl)amino)ethyl)amino)propyl)carbamate, and

2-acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl

(3-((2-((methoxycarbonyl)oxy)ethyl)amino)propyl)carbamate.

[0100]

25 [Item 72] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following compounds:

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))diacetic acid,

30 3,3'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))dipropionic acid,

dimethyl

4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutano
ate),

5 2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
bis(carbonyl))bis(azanediyl))bis(propane-3,1-diyl))bi
s(azanediyl) diacetic acid,

2-acetylnaphtho[2,3-b]furan-4,9-diyl

10 bis((2-((2-(N,N-dimethylsulfamoyl)ethyl)amino)ethyl)car
bamate),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((2-((2-(isopropylsulfonyl)ethyl)amino)ethyl)carbama
te),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

15 bis((2-((2-(methylsulfonyl)ethyl)amino)ethyl)carbamate),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((2-((2-(azetidin-1-yl)-2-oxoethyl)amino)ethyl)carba
mate)),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

20 bis((2-((2-(carbamoyloxy)ethyl)amino)ethyl)carbamate),

2-acetylnaphtho[2,3-b]furan-4,9-diyl

bis((2-((2-(methoxycarbonyl)amino)ethyl)amino)ethyl)ca
bamate), and

2-acetylnaphtho[2,3-b]furan-4,9-diyl

25 bis((2-((2-(methoxycarbonyl)oxy)ethyl)amino)ethyl)car
bamate).

[0101]

[Item 73] The compound according to item 1 or 2, or a
pharmaceutically acceptable salt thereof, wherein the
30 compound is selected from the following compounds:

2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bi
s(azanediyl) diacetic acid,

3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid, and
dimethyl

5 4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate).

[0102]

10 [Item 74] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is

2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)diacetic acid.

15 [0103]

[Item 75] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is

20 3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid.

[0104]

25 [Item 76] The compound according to item 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is dimethyl

4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate).

[0105]

30 [Item 77] The compound according to item 1 or 2, which is dimethyl

4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))(2S,2'S)-bis(2-aminobutano

ate) dihydrochloride.

[0106]

[Item 78] The compound according to item 1 or 2, which is 2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) diacetic acid dihydrochloride.

[0107]

[Item 79] The compound according to item 1 or 2, which is 3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) dipropionic acid dihydrochloride.

[0108]

[Item 80] The compound according to item 1 or 2, which is 2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) diacetic acid monohydrochloride dihydrate.

[0109]

[Item 81] The compound according to item 1 or 2, which is 2,2'-[(2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxycarbonyliminoethane-2,1-diylimino)]diacetic acid dimethanesulfonate salt monohydrate.

[0110]

[Item 82] The compound according to item 1 or 2, which is dimethyl

25 4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate) dimethanesulfonate salt.

[0111]

[Item 83] The compound according to item 1 or 2, which is dimethyl

30 4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate) ditoluenesulfonate salt monohydrate.

[0112]

[Item 84] The compound according to item 1 or 2, which is dimethyl 5 $4,4'$ -(((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate) dibenzenesulfonate salt.

[0113]

10 [Item 85] The compound according to item 1 or 2, which is 3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid dimethanesulfonate salt monohydrate.

[0114]

15 [Item 86] The compound according to item 1 or 2, which is 3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid ditoluenesulfonate salt monohydrate.

[0115]

20 [Item 87] The compound according to item 1 or 2, which is 3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid dibenzenesulfonate salt.

[0116]

25 [Item 88] A pharmaceutical composition comprising a compound according to any one of items 1 to 87, or a pharmaceutically acceptable salt thereof.

[0117]

30 [Item 89] A therapeutic agent and/or prophylactic agent for cancer, wherein the agent comprises a compound according to any one of items 1 to 87, or a pharmaceutically acceptable salt thereof as an active ingredient, or the agent comprises a pharmaceutical composition according to item 88.

[0118]

[Item 90] The therapeutic agent and/or prophylactic agent according to item 89, wherein the cancer is at least one type of cancer selected from the group consisting of acute 5 leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, breast cancer, gastric cancer, gallbladder•bile duct cancer, 10 hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, 15 Ewing's sarcoma, and soft tissue sarcoma.

[0119]

[Item 91] A method for treating and/or preventing a cancer, characterized by administering to a patient in need thereof a therapeutically and/or prophylactically effective amount 20 of a compound according to any one of items 1 to 87, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition according to item 88 or a therapeutic agent and/or prophylactic agent according to item 89 or 90.

[0120]

25 [Item 92] The method for treating and/or preventing according to item 91, wherein the cancer is at least one type of cancer selected from the group consisting of acute leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, 30 breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer,

chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, 5 Ewing's sarcoma, and soft tissue sarcoma.

[0121]

[Item 93] The use of a compound according to any one of items 1 to 87, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to item 88, for the 10 manufacture of a therapeutic agent and/or prophylactic agent for cancer.

[0122]

[Item 94] The use of a compound according to item 93, or a pharmaceutically acceptable salt thereof, wherein the 15 cancer is at least one type of cancer selected from the group consisting of acute leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, 20 non-small-cell lung cancer, breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, 25 testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma.

[0123]

[Item 95] The compound according to any one of items 1 to 30 87, or a pharmaceutically acceptable salt thereof, or a phramceutical composition according to item 88, for use in treating and/or preventing cancer.

[0124]

[Item 96] The compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to item 95, wherein the cancer is at least one type of cancer selected from the group consisting of acute leukemia, 5 chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, breast cancer, 10 gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, 15 Ewing's sarcoma, and soft tissue sarcoma.

[0125]

[Item 97] A pharmaceutical composition for treating and/or preventing a cancer, wherein the pharmaceutical composition comprises:

20 (a) a composition comprising a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof; and (b) a composition comprising a second active substance selected from the group consisting of a chemotherapeutic 25 agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

[0126]

30 [Item 98] A pharmaceutical composition for treating and/or preventing a cancer, comprising (a) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is characterized in that the

first active substance is administered in combination with
(b) a second active substance selected from the group
consisting of a chemotherapeutic agent, a hormonal
therapeutic agent, an immunotherapeutic agent, a biological
agent, a cell growth factor inhibitor, and a cell growth
factor receptor inhibitor.

[0127]

[Item 99] A pharmaceutical composition for treating and/or
preventing a cancer, comprising (a) a second active
substance selected from the group consisting of a
chemotherapeutic agent, a hormonal therapeutic agent, an
immunotherapeutic agent, a biological agent, a cell growth
factor inhibitor, and a cell growth factor receptor
inhibitor, wherein the pharmaceutical composition is
characterized in that the second active substance is
administered in combination with (b) a first active
substance consisting of a compound according to any one of
items 1 to 87 or a pharmaceutically acceptable salt thereof.

[0128]

[Item 100] The pharmaceutical composition according to any
one of items 97 to 99, which is a kit.

[0129]

[Item 101] The pharmaceutical composition according to any
one of items 97 to 100, characterized by administering the
first active substance and the second active substance in
combination simultaneously, separately, or sequentially or
over time.

[0130]

[Item 102] The pharmaceutical composition according to any
one of items 97 to 100, wherein the chemotherapeutic agent
is an alkylating agent, an antimetabolite, a topoisomerase
inhibiting drug, a DNA intercalator, an antimitotic agent,
an anticancer antibiotic, a plant-derived anticancer agent,

an epigenome drug, an immunomodulator, a molecule-targeting therapeutic drug, an angiogenesis inhibitor, or an other chemotherapeutic agent.

[0131]

5 [Item 103] The pharmaceutical composition according to any one of items 97 to 102, wherein the alkylating agent is selected from the group consisting of Nitrogen mustard, Nitrogen mustard N-oxide hydrochloride, Chlorambucil, Cyclophosphamide, Ifosfamide, Thiotepa, Carboquone, 10 Imrosulfan tosylate, Busulfan, Nimustine hydrochloride, Mitobronitol, Melphalan, Dacarbazine, Ranimustine, Estramustine phosphate sodium, Triethylenemelamine, Carmustine, Lomustine, Streptozocin, Pipobroman, Etoglucide, Carboplatin, Cisplatin, Miboplatin, Nedaplatin, 15 Oxaliplatin, Altretamine, Ambamustine, Dibrospidium chloride, Fotemustine, Prednimustine, Pumitepa, Ribomustin, Temozolomide, Treosulfan, Trofosfamide, Zinostatin stimalamer, Adozelesin, Cystemustine, Bizelesin, Mechlorethamine, Uracil mustard, Streptozocin, Satraplatin, 20 Trabectedin, Bevacizumab, Chlormethine, Bendamustine, Uramustine, Semustine, Triplatin tetranitrate, Mannosulfan, Triaziquon, Procarbazine, Canfosfamide, and nitrosourea.

[0132]

25 [Item 104] The pharmaceutical composition according to any one of items 97 to 103, wherein the antimetabolite is a folic acid antagonist, a pyrimidine metabolism-inhibiting drug, a purine metabolism-inhibiting drug, a ribonucleotide reductase inhibiting drug, or a nucleotide analog.

[0133]

30 [Item 105] The pharmaceutical composition according to any one of items 97 to 103, wherein the antimetabolite is selected from the group consisting of Mercaptapurine, 6-Mercaptapurine riboside, Thioinosine, Methotrexate,

Pemetrexed, Enocitabine, Cytarabine, Cytarabin ocfosfate, Ancitabine hydrochloride, Fluorouracil, Tegafur, UFT, Doxifluridine, Carmofur, Galocitabine, Emitefur, Capecitabine, Aminopterin, Nelzarabine, Leucovorin calcium, 5 tabloid, Butocin, calcium folinate, calcium levofolinate, Cladribine, Emitefur, Fludarabine, Gemcitabine, hydroxycarbamide, Pentostatin, Piritrexim, Idoxuridine, Mitoguazone, Tiazofurin, Ambamustine, Bendamustine, Floxuridine, Nelarabine, Leucovorin, Hydroxyurea, 10 Thioguanine, Asparaginase, Bortezomib, Raltitrexed, Clofarabine, Enocitabine, Sapacitabine, Azacytidine, Sulfadiazine, Sulfamethoxazole, and Trimethoprim.

[0134]

[Item 106] The pharmaceutical composition according to any one of items 97 to 105, wherein the topoisomerase inhibiting drug is selected from the group consisting of Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Anthracenedione, Mitoxantrone, Mitomycin C, Bleomycin, Dactinomycin, Plicamycin, Irinotecan, Camptothecin, Rubitecan, Belotecan, 15 Etoposide, Teniposide, Topotecan, and Amsacrine.

[0135]

[Item 107] The pharmaceutical composition according to any one of items 97 to 106, wherein the DNA intercalator is selected from the group consisting of Proflavine, 20 Doxorubicin (Adriamycin), Daunorubicin, Dactinomycin, and Thalidomide.

[0136]

[Item 108] The pharmaceutical composition according to any one of items 97 to 107, wherein the antimitotic agent is selected from the group consisting of Paclitaxel, DHA Paclitaxel, Paclitaxel Polyglutamate, Nab-paclitaxel, Paclitaxel Micelle, 7 α -Glucosyloxyacetylpaclitaxel, BMS-275183, Docetaxel, Vinorelbine, Vincristine,

Vinblastine, Vindesine, Vinzolidine, Etoposide, Teniposide, Ixabepilone, Larotaxel, Ortataxel, Tesetaxel, Ispinesib, Colchicine, and Vinflunine.

[0137]

5 [Item 109] The pharmaceutical composition according to any one of items 97 to 108, wherein the anticancer antibiotic is selected from the group consisting of Actinomycin D, Actinomycin C, Mitomycin C, Chromomycin A3, Bleomycin hydrochloride, Bleomycin sulfate, Peplomycin sulfate, 10 Daunorubicin hydrochloride, Doxorubicin hydrochloride, Aclarubicin hydrochloride, Pirarubicin hydrochloride, Epirubicin hydrochloride, Neocarzinostatin, Mithramycin, Sarkomycin, Carzinophilin, Mitotane, Zorubicin hydrochloride, Mitoxantrone hydrochloride, Idarubicin 15 hydrochloride, and mithramycin.

[0138]

20 [Item 110] The pharmaceutical composition according to any one of items 97 to 109, wherein the plant-derived anticancer agent is selected from the group consisting of Etoposide, Etoposide phosphate, Vinblastine sulfate, Vincristine sulfate, Vindesine sulfate, Teniposide, Paclitaxel, Docetaxel, DJ-927, Vinorelbine, Irinotecan, and Topotecan.

[0139]

25 [Item 111] The pharmaceutical composition according to any one of items 97 to 110, wherein the epigenome drug is selected from the group consisting of Vorinostat, Belinostat, Entinostat, Romidepsin, Azacytidine, and Decitabine.

[0140]

30 [Item 112] The pharmaceutical composition according to any one of items 97 to 111, wherein the immunomodulator is selected from the group consisting of Thalidomide, Lenalidomide, and Pomalidomide.

[0141]

5 [Item 113] The pharmaceutical composition according to any one of items 97 to 112, wherein the molecule-targeting therapeutic drug is selected from the group consisting of a kinase inhibitor, a proteasome inhibitor, a monoclonal antibody, a mTOR inhibitor, a TNF inhibiting drug, and a T-cell inhibiting drug.

[0142]

10 [Item 114] The pharmaceutical composition according to any one of items 97 to 113, wherein the kinase inhibitor is a tyrosine kinase inhibitor, a serine/threonine kinase inhibitor, a Raf kinase inhibitor, a CDK inhibitor, or a MEK inhibitor.

[0143]

15 [Item 115] The pharmaceutical composition according to any one of items 97 to 113, wherein the kinase inhibitor is selected from the group consisting of Imatinib, Gefitinib, Erlotinib, Afatinib, Dasatinib, Bosutinib, Vandetanib, Sunitinib, Axitinib, Pazopanib, Lenvatinib, Lapatinib, Nintedanib, Nilotinib, Crizotinib, Ceritinib, Alectinib, 20 Ruxolitinib, Tofacitinib, Ibrutinib, Sorafenib, Vemurafenib, Dabrafenib, Palbociclib, Trametinib, Regorafenib, Cediranib, Lestaurtinib, Vandetinib, Vatalanib, Seliciclib, Tivantinib, Canertinib, Pelitinib, Tesevatinib, Motesanib, Midostaurin, Foretinib, 25 Cabozantinib, Selumetinib, Neratinib, Volasertib, Saracatinib, Enzastaurin, Tandutinib, Semaxanib, Alvocidib, ICR-62, AEE788, PD0325901, PD153035, TK787, and BBI503.

[0144]

30 [Item 116] The pharmaceutical composition according to any one of items 97 to 115, wherein the proteasome inhibitor is selected from the group consisting of Bortezomib and Carfilzomib.

[0145]

[Item 117] The pharmaceutical composition according to any one of items 97 to 116, wherein the monoclonal antibody is selected from the group consisting of an anti-CD22 antibody, an anti-CD20 antibody, an anti-CD25 antibody, an anti-CD30 antibody, an anti-CD33 antibody, an anti-CD5 antibody, an anti-CD52 antibody, an anti-epidermal growth factor receptor antibody, an anti-endothelial cell growth factor antibody, an anti-TNF- α antibody, an anti-IL-1 receptor antibody, an anti-IL-2 receptor antibody, an anti-IL-5 receptor antibody, an anti-IL-6 receptor antibody, an anti-HER2 antibody, an anti-IgE antibody, an anti-IgG antibody, an anti-RS virus antibody, an anti-CCR4 antibody, an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-RANKL antibody, or an anti-c-Met antibody.

15 [0146]

[Item 118] The pharmaceutical composition according to any one of items 97 to 117, wherein the monoclonal antibody is selected from the group consisting of Ibritumomab tiuxetan, Rituximab, Cetuximab, Infliximab, Basiliximab, Brentuximab vedotin, Tocilizumab, Trastuzumab, Bevacizumab, Omalizumab, Mepolizumab, Gemtuzumab ozogamicin, Palivizumab, Ranibizumab, Certolizumab, Ocrelizumab, Mogamulizumab, Eculizumab, Pertuzumab, Alemtuzumab, Inotuzumab, Panitumumab, Ofatumumab, Golimumab, Adalimumab, Ramucirumab, Nivolumab, Infliximab, Anakinra, Denosumab, Ipilimumab, Pembrolizumab, and matuzumab.

25 [0147]

[Item 119] The pharmaceutical composition according to any one of items 97 to 118, wherein the mTOR inhibitor is selected from the group consisting of Everolimus, Rapamycin, and Temsirolimus.

30 [0148]

[Item 120] The pharmaceutical composition according to any

one of items 97 to 119, wherein the TNF inhibiting drug is Etanercept.

[0149]

[Item 121] The pharmaceutical composition according to any one of items 97 to 120, wherein the T-cell inhibiting drug is Abatacept.

[0150]

[Item 122] The pharmaceutical composition according to any one of items 97 to 121, wherein the angiogenesis inhibitor is selected from the group consisting of CM101, IFN- α , IL-12, platelet factor-4, Suramin, Semaxanib, Thrombospondin, a VEGFR antagonist, an angiogenesis inhibiting steroid plus heparin, cartilage-derived angiogenesis inhibitory factor, a matrix metalloproteinase inhibitor, Batimastat, Marimastat, Angiostatin, Endostatin, 2-methoxyestradiol, Tecogalan, Thrombospondin, an α V β 3 inhibitor, Linomide, and ADH-1.

[0151]

[Item 123] The pharmaceutical composition according to any one of items 97 to 122, wherein the other chemotherapeutic agent is selected from the group consisting of Sobuzoxane, Obatoclax, Efaproxiral, Tipifarnib, and Lonafarnib.

[0152]

[Item 124] The pharmaceutical composition according to any one of items 97 to 123, wherein the "hormonal therapeutic agent" is selected from the group consisting of Fosfestrol, Diethylstilbestrol, Fluoxymesterone, Chlorotrianisene, Medroxyprogesterone acetate, Megestrol acetate, Chlormadinone acetate, Cyproterone acetate, Danazol, Dienogest, Asoprinsil, Allylestrenol, Gestrinone, Nomegestrol, Tadenan, Mepartinicin, Raloxifene, Ormeloxifene, Levormeloxifene, Tamoxifen citrate, Toremifene citrate, Idoxifene, a pill formulation,

Mepitiostane, Testololactone, Aminoglutethimide,
Goserelin acetate, Buserelin, Leuprorelin, Leuprolide,
Droloxifene, Epitiostanol, Ethynodiol sulfonate,
Fadrozole hydrochloride, Anastrozole, Tetrazole,
5 Ketoconazole, Letrozole, Exemestane, Vorozole, Formestane,
Exemestane, Flutamide, Bicalutamide, Nilutamide,
Enzalutamide, Mifepristone, Finasteride, Dexamethasone,
Prednisolone, Betamethasone, Triamcinolone, Abiraterone,
Liarozole, Bexarotene, and DN101.

10 [0153]

[Item 125] The pharmaceutical composition according to any one of items 97 to 124, wherein the immunotherapeutic agent is selected from the group consisting of Picibanil, Krestin, Schizophyllan, Lentinan, Ubenimex, an interferon, an interleukin, macrophage colony stimulating factor, granulocyte colony stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, Corynebacterium parvum, Levamisole, Polysaccharide K, Procodazole, an anti-CTLA4 antibody, a PD-1 antibody, and Toll-like Receptors agonist.

15 [0154]

[Item 126] The pharmaceutical composition according to any one of items 97 to 125, wherein the biological agent is selected from the group consisting of Interleukin-2, Interferon- α , Interferon- β , Interferon- γ , Erythropoietin, Filgrastim, granulocytes, Sargramostim, IL13-PE38QQR, Bacillus Calmette-Guerin, Levamisole, Octreotide, CPG7909, Provenge, GVAX, Myvax, Favld, Lenalidomide, Trastuzumab, Rituximab, Gemtuzumab ozogamicin, Alemtuzumab, Endostatin, Ibritumomab tiuxetan, Tositumomab, Cetuximab, Zanolimumab, 20 Ofatumumab, HGS-ETR1, Pertuzumab, M200, SGN-30, Matuzumab, Adecatumumab, Denosumab, Zalutumumab, MDX-060, Nimotuzumab, MORAb-003, Vitaxin, MDX-101, MDX-010, a DPC4 antibody, a 25 NF-1 antibody, a NF-2 antibody, a Rb antibody, a p53 antibody,

a WT1 antibody, a BRCA1 antibody, a BRCA2 antibody, Ganglioside, a prostate - specific antigen, α -Fetoprotein, a carcinoembryonic antigen, a melanoma-associated antigen, and Papilloma virus E6 and E7 fragments.

5 [0155]

[Item 127] The pharmaceutical composition according to any one of items 97 to 126, wherein the cell growth factor inhibitor is selected from the group consisting of a epidermal growth factor inhibitor, an insulin - like growth factor inhibitor, a nerve growth factor inhibitor, a brain - derived neurotrophic factor inhibitor, an endothelial cell growth factor inhibitor, a colony stimulating factor inhibitor, a platelet - derived growth factor inhibitor, an Erythropoietin inhibitor, a fibroblast growth factor inhibitor, a hepatocyte growth factor inhibitor, a heregulin inhibitor, and an Angiopoietin inhibitor.

15 [0156]

[Item 128] The pharmaceutical composition according to any one of items 97 to 127, wherein the cell growth factor receptor inhibitor is selected from the group consisting of an epidermal growth factor receptor inhibitor, an insulin-like growth factor receptor inhibitor, a nerve growth factor receptor inhibitor, a brain-derived neurotrophic factor receptor inhibitor, an endothelial cell growth factor inhibitor, a colony stimulating factor inhibitor, a platelet-derived growth factor receptor inhibitor, an Erythropoietin receptor inhibitor, a fibroblast growth factor receptor inhibitor, a hepatocyte growth factor receptor inhibitor, a heregulin receptor inhibitor, and an Angiopoietin receptor inhibitor.

20 [0157]

[Item 129] The pharmaceutical composition according to any one of items 97 to 128, wherein the second active substance

is a chemotherapeutic agent or a hormonal therapeutic agent.

[0158]

[Item 130] The pharmaceutical composition according to any one of items 97 to 101, wherein the second active substance 5 is selected from the group consisting of Cisplatin, Oxaliplatin, Temozolomide, Pemetrexed, Fluorouracil, Capecitabine, Gemcitabine, Leucovorin, Bortezomib, Irinotecan, Paclitaxel, Imatinib, Ibrutinib, Sorafenib, Regorafenib, Bortezomib, Cetuximab, Bevacizumab, 10 Panitumumab, Nivolumab, Ipilimumab, Pembrolizumab, and Dexamethasone.

[0159]

[Item 131] The pharmaceutical composition according to any one of items 97 to 130, wherein the cancer is at least one 15 type of cancer selected from the group consisting of acute leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, 20 breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin 25 cancer, malignant melanoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma.

[0160]

[Item 132] The pharmaceutical composition according to any one of items 97 to 131, wherein the first active substance 30 is administered prior to the second active substance or the second active substance is administered prior to the first active substance.

[0161]

[Item 133] The pharmaceutical composition according to any one of items 97 to 131, characterized in that the second active substance or the first active substance is administered between administrations of the first active substance or the second active substance, respectively.

5 [0162]

[Item 134] A method for treating and/or preventing a cancer in a subject in need thereof, comprising:

10 (a) a step of administering to the subject a first active substance consisting of a compound according to any one of items 1 to 87, or a pharmaceutically acceptable salt thereof; and

15 (b) a step of administering to the subject a second active substance selected from the group consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

20 [0163]

25 [Item 135] A method for treating and/or preventing a cancer in a subject in need thereof, comprising a step of administering to the subject (a) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof in combination with (b) a second active substance selected from the group consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

30 [0164]

[Item 136] The method according to item 134 or 135, characterized by administering to the subject the first active substance and the second active substance in

combination simultaneously, separately, sequentially or over time.

[0165]

5 [Item 137] The method according to any one of items 134 to 136, wherein the first active substance is administered prior to the second active substance or the second active substance is administered prior to the first active substance.

[0166]

10 [Item 138] The method according to any one of items 134 to 136, wherein the administration of the first active substance and the administration of the second active substance are carried out simultaneously.

[0167]

15 [Item 139] The method according to any one of items 134 to 138, wherein the first active substance and the second active substance are administered in therapeutically and/or prophylactically effective amounts.

[0168]

20 [Item 140] The method according to any one of items 134 to 139, wherein the amount of the first active substance administered and/or the amount of the second active substance administered are less than a therapeutically and/or prophylactically effective amount when administered alone, however, both are administered in therapeutically and/or prophylactically effective amounts when they are combined.

[0169]

25 [Item 141] The method according to any one of items 134 to 140, further having the characteristic(s) in any one or more of items 102 to 133.

[0170]

[Item 142] The compound according to any one of items 1 to

87 or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0171]

[Item 143] The compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof, for the treatment and/or prevention or prophylaxis of a cancer.

[0172]

[Item 144] The compound according to item 143 or a pharmaceutically acceptable salt thereof, wherein the cancer is at least one type of cancer selected from the group consisting of acute leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, 10 non-small-cell lung cancer, breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, 15 testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma.

[0173]

[Item 145] A combination for treating and/or preventing a 25 cancer, comprising:

(a) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof; and

(b) a second active substance selected from the group 30 consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

[0174]

[Item 146] (a) A first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof, for treating and/or preventing a cancer, characterized in that the first active substance is administered in combination with (b) a second active substance selected from the group consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

[0175]

[Item 147] (a) A second active substance selected from the group consisting of a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor, for treating and/or preventing a cancer, characterized in that the second active substance is administered in combination with (b) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof.

[0176]

[Item 148] The combination according to item 145, the first active substance according to item 146, or the second active substance according to item 147, further having the characteristic(s) according to any one or more of items 100 to 133.

[0177]

[Item 149] Use of a combination comprising (a) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof, and

(b) a second active substance selected from the group

consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor,

5 in the manufacture of a medicament for treating and/or preventing a cancer.

[0178]

[Item 150] Use of (a) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating and/or preventing a cancer, characterized in that the first active substance is administered in combination with (b) a second active substance selected from the group consisting of a chemotherapeutic agent, a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor.

[0179]

[Item 151] The use of (a) a second active substance selected from the group consisting of a hormonal therapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, and a cell growth factor receptor inhibitor, in the manufacture of a medicament for treating and/or preventing a cancer, characterized in that the second active substance is administered in combination with (b) a first active substance consisting of a compound according to any one of items 1 to 87 or a pharmaceutically acceptable salt thereof.

[0180]

[Item 152] The use according to any one of items 149 to 151, further having the characteristic(s) according to any one or more of items 100 to 133.

[0181]

Other than the above, the present invention also provides treatment methods, prevention or prophylaxis methods, uses, and the like using a compound of the present invention, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition thereof, a therapeutic agent, or a prophylactic agent, and further details and embodiments of these methods and uses can be understood by those skilled in the art from the description of the present specification.

10 [0182]

It is understood that one or a plurality of the above-mentioned characteristics can be further combined and used. These still further embodiments and advantages of the present invention will be recognized by those skilled in the art if the following detailed descriptions are read and understood as necessary.

[Advantageous Effects of Invention]

15 [0183]

Since 2-acetylnaphtho[2,3-b]furan-4,9-dione targets a cancer stem cell in addition to a conventional cancer cell, it is expected as a novel anticancer agent. However, since 2-acetylnaphtho[2,3-b]furan-4,9-dione has high crystallizability, its absorption in oral administration is an object as well as its use in parenteral administration. The compound represented by formula (1A) or (1) or a pharmaceutically acceptable salt thereof (optionally, also referred to as the present compound) is a water-soluble prodrug of 2-acetylnaphtho[2,3-b]furan-4,9-dione. Due to its high water-solubility, it is useful as a medicament to be successful in prevention or prophylaxis and/or treatment of cancer as an oral agent and an agent for intravenous administration.

- 100 -

[Description of Embodiments]

[0184]

5 Since the compound of the present invention may be present in the form of a hydrate and/or a solvate, hydrates and/or solvates of the compound represented by formula (1A) or (1) or a pharmaceutically acceptable salt thereof are also encompassed by the present compound.

[0185]

10 Since the compound represented by formula (1A) or (1) may have one, or optionally one or more, asymmetric carbon atom(s), and may result in geometrical isomerism or axial chirality, it may be present as several types of stereoisomers. In the present invention, these stereoisomers, and mixtures and racemates thereof are also 15 encompassed by the present compound.

[0186]

20 Further, a deuterated form in which any one or two or more ¹H of a compound represented by formula (1A) or (1) has been converted to ²H (D) is encompassed by the compound represented by formula (1A) or (1).

[0187]

25 Compounds represented by formula (1A) or (1) or pharmaceutically acceptable salts thereof obtained as crystal may be present as crystalline polymorphism, and those in any crystalline forms are encompassed by the present compound.

[0188]

Next, the terms in the present specification are described below.

30 [0189]

In the present specification, the number of substituents of a group defined by "optionally substituted" or "substituted" is not particularly limited if it is

substitutable, and is one or plural. In addition, unless otherwise indicated, the description for each group is also applied when the group is one part of or a substituent on other groups.

5 Examples of the substituents in the present invention include a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a guanidine group, a cyano group, a nitro group, a halogen atom, an alkyl group, an alkylthio group, an alkenyl group, an alkynyl group, a 10 cycloalkyl group, a cycloalkylcarbonyl group, a cycloalkylsulfinyl group, an alkoxy group, a cycloalkoxy group, an alkoxycarbonyl group, an alkylcarbonyl group, an aryl group, an arylcarbonyl group, a heteroaryl group, a heterocyclic group, an amino group, an aminocarbonyl group, 15 an aminosulfinyl group, an aminosulfonyl group, a heterocyclxy group, a heterocyclthio group, a heterocyclxy carbonyl group, a heterocyclsulfinyl group, a heterocyclsulfonyl group, a heterocyclcarbonyl group, an alkylsulfonyl group, an arylsulfonyl group, an alkoxy carbonyloxy group, an aminocarbonyloxy group, and alkoxycarbonylamino group. 20 The substituents may be further substituted with a substituent(s) described above.

[0190]

25 In the present specification, examples of a "halogen atom" include a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom. Preferred is a fluorine atom or a chlorine atom. Further preferred is a fluorine atom.

[0191]

30 An "alkyl group" means a linear or branched, saturated hydrocarbon group, and for example, a "C₁₋₄alkyl group" or a "C₆alkyl group" means an alkyl group having one to four or six carbon atoms. The same applies to cases of other

numbers.

A "C₁₋₁₀alkyl group" includes, preferably a "C₁₋₆alkyl group", and further preferably a "C₁₋₄alkyl group". Specific examples of the "C₁₋₁₀alkyl group" include, for example, a methyl group, an ethyl group, a propyl group, a 1-methylethyl group, a butyl group, a 2-methylpropyl group, a 1-methylpropyl group, a 1,1-dimethylethyl group, a pentyl group, a 3-methylbutyl group, a 2-methylbutyl group, a 2,2-dimethylpropyl group, a 1-ethylpropyl group, a 1,1-dimethylpropyl group, a hexyl group, a 4-methylpentyl group, a 3-methylpentyl group, a 2-methylpentyl group, a 1-methylpentyl group, a hexyl group, a heptyl group, an octyl group, a nonyl group, a decyl group, and the like. Specific examples of the "C₁₋₆alkyl group" include examples of those having one to six carbon atoms in the specific examples of the "C₁₋₁₀alkyl group". Specific examples of the "C₁₋₄alkyl group" include examples of those having one to four carbon atoms in the specific examples of the "C₁₋₁₀alkyl group".

[0192]

The "C₁₋₆alkyl" moiety of the "C₁₋₆alkylthio group", the "C₁₋₆alkylsulfinyl group", and the "C₁₋₆alkylsulfonyl group" is defined the same as the above-described "C₁₋₆alkyl group". Specific examples of the "C₁₋₆alkylthio group" include, for example, a methylthio group and the like. Specific examples of the "C₁₋₆alkylsulfinyl group" include, for example, a methylsulfinyl group and the like. Specific examples of the "C₁₋₆alkylsulfonyl group" include, for example, a methylsulfonyl group and the like.

[0193]

A "C₂₋₁₀alkenyl group" means a linear or branched, unsaturated hydrocarbon group having two to ten carbon atoms and containing one to five double bonds. Examples of the "C₂₋₁₀alkenyl group" include, preferably, a "C₂₋₆alkenyl

group". Specific examples of the "C₂₋₁₀alkenyl group" include, for example, a vinyl group, a propenyl group, a methylpropenyl group, a butenyl group, a methylbutenyl group, a pentenyl group, a hexenyl group, a heptenyl group, a octenyl group, a nonenyl group, a decenyl group, and the like.

[0194]

A "C₂₋₁₀alkynyl group" means a linear or branched, unsaturated hydrocarbon group having two to ten carbon atoms and containing one triple bond. The "C₂₋₁₀alkynyl group" includes, preferably, a "C₂₋₆alkynyl group". Specific examples of the "C₂₋₁₀alkynyl group" include, for example, propynyl, methylpropynyl, butynyl, methylbutynyl, a pentynyl group, a hexynyl group, a heptynyl group, an octynyl group, a nonynyl group, a decynyl group, and the like.

[0195]

A "C₁₋₁₀alkylene" means a linear or branched, saturated hydrocarbon having one to ten carbon atoms. The "C₁₋₁₀alkylene" includes, preferably, "C₁₋₆alkylene". Specific examples of the "C₁₋₁₀alkylene" include, for example, methylene, ethylene, propylene, 1-methylethylene, butylene, 2-methylpropylene, 1-methylpropylene, 1,1-dimethylethylene, pentylene, 3-methylbutylene, 2-methylbutylene, 2,2-dimethylpropylene, 1-ethylpropylene, 1,1-dimethylpropylene, hexylene, 4-methylpentylene, 3-methylpentylene, 2-methylpentylene, 1-methylpentylene, heptylene, octylene, nonylene, decylene, and the like.

[0196]

A "C₂₋₁₀alkenylene" means a linear or branched, unsaturated hydrocarbon having two to ten carbon atoms and containing one to five double bonds. The "C₂₋₁₀alkenylene" includes, preferably, "C₂₋₆alkenylene". Specific examples of the "C₂₋₁₀alkenylene" include, for example, vinylene,

propenylene, methylpropenylene, butenylene, methylbutenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene, and the like.

[0197]

5 A " C_{2-10} alkynylene" means a linear or branched, unsaturated hydrocarbon having two to ten carbon atoms and containing one triple bond. The " C_{2-10} alkynylene" includes, preferably, " C_{2-6} alkynylene". Specific examples of the " C_{2-10} alkynylene" include, for example, propynylene, 10 methylpropynylene, butynylene, methylbutynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene, and the like.

[0198]

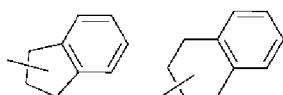
15 A " C_{3-10} cycloalkyl group" means a cyclic alkyl having three to ten carbon atoms, and includes those cyclic alkyl having a partially bridged structure. The " C_{3-10} cycloalkyl group" includes, preferably a " C_{3-7} cycloalkyl group", and more preferably a " C_{4-6} cycloalkyl group". Specific examples of the " C_{3-10} cycloalkyl group" include, for example, 20 a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, an adamantyl group, and the like. Specific examples of the " C_{3-7} cycloalkyl group" include, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl 25 group, a cycloheptyl group, and the like.

[0199]

The above-described " C_{3-10} cycloalkyl group" encompasses those compounds in which it is fused to an aromatic ring. Specific examples thereof include, for example, groups 30 represented by the following and the like.

[0200]

[Chem. 11]

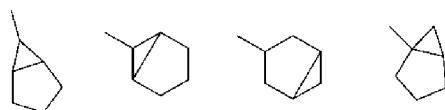


[0201]

5 The above-described “C₃₋₁₀cycloalkyl group” also encompasses a saturated bicyclo ring. Specific examples thereof include, for example, groups represented by the following group and the like.

[0202]

[Chem. 12]



10 [0203]

The “C₃₋₁₀cycloalkyl” moiety of the “C₃₋₁₀cycloalkylcarbonyl group”, the “C₃₋₁₀cycloalkylthio group”, the “C₃₋₁₀cycloalkylsulfinyl group”, and the “C₃₋₁₀cycloalkylsulfonyl group” is defined the same as the 15 above-described “C₃₋₁₀cycloalkyl group”. The “C₃₋₁₀cycloalkylcarbonyl group”, the “C₃₋₁₀cycloalkylthio group”, the “C₃₋₁₀cycloalkylsulfinyl group”, and the “C₃₋₁₀cycloalkylsulfonyl group” include, preferably, those 20 groups in which the “C₃₋₁₀cycloalkyl” moiety is the “C₃₋₇cycloalkyl group”. Specific examples of the “C₃₋₁₀cycloalkylcarbonyl group” include, for example, a cyclopropylcarbonyl group and the like. Specific examples of the “C₃₋₁₀cycloalkylthio group” include, for example, a cyclopropylthio group and the like. Specific examples of the 25 “C₃₋₁₀cycloalkylsulfinyl group” include, for example, a cyclopropylsulfinyl group and the like. Specific examples of the “C₃₋₁₀cycloalkylsulfonyl group” include, for example, a cyclopropylsulfonyl group and the like.

[0204]

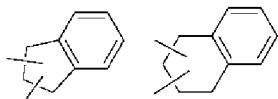
A "C₃₋₁₀cycloalkylene" means a cyclic alkylene having three to ten carbon atoms, and encompasses those cycloalkylene having a partially bridged structure. The "C₃₋₁₀cycloalkylene" includes, preferably, "C₄₋₇cycloalkylene". Specific examples of the "C₃₋₁₀cycloalkylene" include, for example, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, cyclooctylene, adamantylene, and the like. Specific examples of the "C₄₋₇cycloalkylene" include, for example, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and the like.

[0205]

The above-described "C₃₋₁₀cycloalkylene" and "C₄₋₇cycloalkylene" encompass those compounds in which it is fused to an aromatic ring. Specific examples thereof include, for example, groups represented by the following and the like.

[0206]

[Chem. 13]



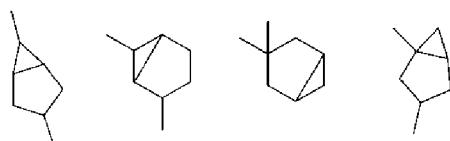
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[0207]

The above-described "C₃₋₁₀cycloalkylene" and "C₄₋₇cycloalkylene" encompass a saturated bicyclo ring. Specific examples thereof include, for example, groups represented by the following group and the like.

[0208]

[Chem. 14]



[0209]

A "C₁₋₆alkoxy group" refers to a "C₁₋₆alkyloxy group", and the "C₁₋₆alkyl" moiety is defined the same as the above-described "C₁₋₆alkyl group". The "C₁₋₆alkoxy group" includes, preferably, a "C₁₋₄alkoxy group" and the like. Specific examples of the "C₁₋₆alkoxy group" include, for example, a methoxy group, an ethoxy group, a propoxy group, a 1-methylethoxy group, a butoxy group, a 2-methylpropoxy group, a 1-methylpropoxy group, a 1,1-dimethylethoxy group, a pentyloxy group, a 3-methylbutoxy group, a 2-methylbutoxy group, a 2,2-dimethylpropoxy group, a 1-ethylpropoxy group, a 1,1-dimethylpropoxy group, a hexyloxy group, a 4-methylpentylloxy group, a 3-methylpentylloxy group, a 2-methylpentylloxy group, a 1-methylpentylloxy group, a 3,3-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 1,1-dimethylbutoxy group, a 1,2-dimethylbutoxy group, and the like.

[0210]

A "C₃₋₁₀cycloalkoxy group" refers to a "C₃₋₁₀cycloalkyloxy group", and the "C₃₋₁₀cycloalkyl" moiety is defined the same as the above-described "C₃₋₁₀cycloalkyl group". The "C₃₋₁₀cycloalkoxy group" includes, preferably, a "C₃₋₇cycloalkoxy group". Specific examples of the "C₃₋₁₀cycloalkyloxy group" include, for example, a cyclopropoxy group, a cyclobutoxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group, a cyclooctyloxy group, an adamantyloxy group, and the like. Specific examples of the "C₃₋₇cycloalkoxy group" include, for example, a cyclopropoxy group, a cyclobutoxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group, and the like.

[0211]

The "C₃₋₁₀cycloalkoxy" moiety of the

"C₃₋₁₀cycloalkoxycarbonyl group" are defined the same as the above-described "C₃₋₁₀cycloalkoxy group". The "C₃₋₁₀cycloalkoxycarbonyl group" includes, preferably, a "C₃₋₇cycloalkoxycarbonyl group". Specific examples of the "C₃₋₁₀cycloalkoxycarbonyl group" include a cyclopropoxycarbonyl group and the like.

5 [0212]

The "C₁₋₆alkoxy" moiety of the "C₁₋₆alkoxycarbonyl group" is defined the same as the above-described "C₁₋₆alkoxy group". The "C₁₋₆alkoxycarbonyl group" includes, preferably, a "C₁₋₄alkoxycarbonyl group". Specific examples of the "C₁₋₆alkoxycarbonyl group" include, for example, a methoxycarbonyl group, an ethoxycarbonyl group, and the like.

10 15 [0213]

The "C₁₋₆alkyl" moiety of the "C₁₋₆alkylcarbonyl group" is defined the same as the above-described "C₁₋₆alkyl group". The "C₁₋₆alkylcarbonyl group" includes, preferably, a "C₁₋₄alkylcarbonyl group". Specific examples of the "C₁₋₆alkylcarbonyl group" include, for example, a methylcarbonyl group, an ethylcarbonyl group, a propylcarbonyl group, a 1-methylethylcarbonyl group, a butylcarbonyl group, a 2-methylpropylcarbonyl group, a 1-methylpropylcarbonyl group, a 1,1-dimethylethylcarbonyl group, and the like.

20 25 [0214]

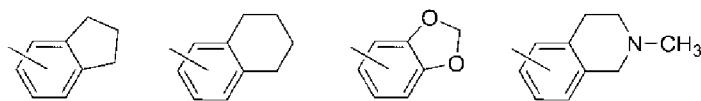
A "C₆₋₁₀aryl group" means an aromatic hydrocarbon having six to ten carbon atoms. Specific examples of the "C₆₋₁₀aryl group" include, for example, a phenyl group, a 1-naphthyl group, a 2-naphthyl group, and the like. Particularly preferably, it includes a phenyl group.

The "C₆₋₁₀aryl" also encompasses a 8- to 14-membered polycyclic group in which an aromatic ring is fused to a

5 C_{4-6} cycloalkyl, or a 9- to 14-membered polycyclic group in which an aromatic ring is fused to, for example, a 5- to 6-membered heterocyclic group having one to three homogeneous or heterogeneous atoms selected from a nitrogen atom, an oxygen atom, or a sulfur atom. Specific examples thereof include, for example, groups represented by the following and the like.

[0215]

[Chem. 15]



10

[0216]

15 The " C_{6-10} aryl" moiety of the " C_{6-10} arylcarbonyl group", the " C_{6-10} aryloxycarbonyl group", the " C_{6-10} arylthio group", the " C_{6-10} arylsulfinyl group", the " C_{6-10} arylsulfonyl group", and the " C_{6-10} aryloxy group" is defined the same as the above-described " C_{6-10} aryl group". For the " C_{6-10} aryl" moiety, a phenyl group is preferable. Specific examples of the " C_{6-10} arylcarbonyl group" include a phenylcarbonyl group and the like. Specific examples of the " C_{6-10} aryloxycarbonyl group" include a phenyloxycarbonyl group and the like. Specific examples of the " C_{6-10} arylthio group" include a phenylthio group and the like. Specific examples of the " C_{6-10} arylsulfinyl group" include a phenylsulfinyl group and the like. Specific examples of the " C_{6-10} arylsulfonyl group" include a phenylsulfonyl group and the like. Specific examples of the " C_{6-10} aryloxy group" include a phenoxy group and the like.

20

25

[0217]

30 An "arylene" means an aromatic hydrocarbon. The "arylene" includes, preferably, " C_{6-10} arylene". For the " C_{6-10} arylene", phenylene is preferable. Specific examples

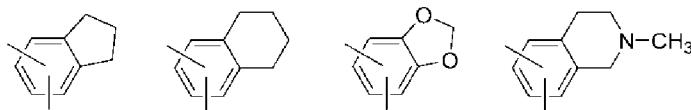
- 110 -

of the "C₆₋₁₀arylene" include, for example, phenylene, 1-naphthylene, 2-naphthylene, and the like.

The "C₆₋₁₀arylene" also encompasses a 8- to 14-membered polycyclic group in which an aromatic ring is fused to a C₄₋₆cycloalkyl, or a 9- to 14-membered polycyclic group in which an aromatic ring is fused to, for example, a 5- to 6-membered heterocyclic group having one to three homogeneous or heterogeneous atoms selected from a nitrogen atom, an oxygen atom, or a sulfur atom. Specific examples thereof include, for example, groups represented by the following and the like.

[0218]

[Chem. 16]



15 [0219]

A "C₅₋₁₀heteroaryl group" includes a 5- to 7-membered monocyclic aromatic heterocyclic group ("C₅₋₇ heteroaryl group") and an 8- to 10-membered bicyclic aromatic heterocyclic group ("C₈₋₁₀ heteroaryl group"), which contain one to four atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. The "C₅₋₁₀heteroaryl group" includes, preferably, a 5- to 7-membered monocyclic aromatic heterocyclic group ("C₅₋₇ heteroaryl group"), and further preferably, a 5- or 6-membered monocyclic aromatic heterocyclic group ("C₅₋₆ heteroaryl group").

Specific example of the "C₅₋₁₀heteroaryl" include a pyridyl group, a pyridazinyl group, an isothiazolyl group, a pyrrolyl group, a furyl group, a thienyl group, a thiazolyl group, an imidazolyl group, a pyrimidinyl group, a thiadiazolyl group, a pyrazolyl group, an oxazolyl group,

an isoxazolyl group, a pyrazinyl group, a triazinyl group, a triazolyl group, an imidazolidinyl group, an oxadiazolyl group, a triazolyl group, a tetrazolyl group, an indolyl group, an indazolyl group, a quinolyl group, an isoquinolyl group, 5 a benzofuranyl group, a benzothienyl group, a benzoxazolyl group, a benzothiazolyl group, a benzisoxazolyl group, a benzisothiazolyl group, a benzotriazolyl group, a benzimidazolyl group, a 6,11-dihydrodibenzo[b,e]thiepinyl group, and the like. It 10 is preferably a pyridyl group, a pyrimidinyl group, a quinolyl group and an isoquinolyl group, and further preferably a pyridyl group.

[0220]

A "C₅₋₁₀heteroarylene" includes a 5- to 7-membered 15 monocyclic aromatic heterocycle and an 8- to 10-membered bicyclic aromatic heterocycle, which contain one to four atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. The "C₅₋₁₀heteroarylene" includes, preferably, "C₅₋₇ heteroarylene". Specific examples thereof include 20 pyridylene, pyridazinylene, isothiazolylene, pyrrolylene, furylene, thienylene, thiazolylene, imidazolylene, pyrimidinylene, thiadiazolylene, pyrazolylene, oxazolylene, isoxazolylene, pyrazinylene, triazinylene, 25 triazolylene, imidazolidinylene, oxadiazolylene, triazolylene, tetrazolylene, indolylene, indazolylene, quinolylene, isoquinolylene, benzofuranylene, benzothienylene, benzoxazolylene, benzothiazolylene, benzisoxazolylene, benzisothiazolylene, benzotriazolylene, 30 benzimidazolylene, 6,11-dihydrodibenzo[b,e]thiepinylene, and the like. It is preferably pyridylene, pyrimidinylene, quinolylene, and isoquinolylene, and further preferably pyridylene.

[0221]

A "3- to 12-membered monocyclic or polycyclic heterocyclic group" includes a monocyclic or polycyclic heterocyclic group and the like, which contain one to four atoms independently selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom. It is preferably a 3- to 10-membered group, more preferably a 3- to 8-membered group, and further preferably a 3- to 6-membered group. All of the nitrogen atom, oxygen atom, and sulfur atom are atoms constituting the ring. The heterocyclic group may be either saturated or partially unsaturated, and a saturated heterocyclic group is more preferable. Specific examples of the "heterocyclic group" include, an epoxy group, an aziridine group, an azetidine group, a pyranyl group, a tetrahydrofuryl group, a pyrrolidinyl group, an imidazolidinyl group, a piperidinyl group, a morpholinyl group, a thiomorpholinyl group, a dioxothiomorpholinyl group, a hexamethyleneiminy group, an oxazolidinyl group, a thiazolidinyl group, an imidazolidinyl group, an oxoimidazolidinyl group, a dioxoimidazolidinyl group, an oxooxazolidinyl group, a dioxooxazolidinyl group, a dioxothiazolidinyl group, a tetrahydrofuran group, a tetrahydropyridinyl group, an oxetanyl group, a tetrahydropyranyl group, and the like. It should be noted that the group also encompasses a heterocyclic group having a bridged structure. Regarding the group, a nitrogen atom constituting the ring cannot be at a position to be attached in "the group". That is, the group does not encompass ideas of, for example, a 1-pyrrolidino group and the like.

[0222]

The "3- to 12-membered monocyclic or polycyclic heterocyclic group" may form a fused ring with a 6-membered

aromatic hydrocarbon or a 6-membered heteroaryl. Examples thereof include a bicyclic "heterocycle" having nine or ten ring-constituting atoms in which the above-described 5- or 6-membered "heterocyclic group" is fused to a 6-membered aromatic hydrocarbon or a 6-membered heteroaryl. The 6-membered aromatic hydrocarbon includes benzene and the like. The 6-membered unsaturated heterocycle includes a pyridine group, a pyrimidine group, a pyridazine group, and the like. Specific examples of the fused ring include a 5 dihydroindolyl group, a dihydroisoindolyl group, a dihydropurinyl group, a dihydrothiazolopyrimidinyl group, a dihydrobenzodioxanyl group, an isoindolyl group, an 10 indazolyl group, a tetrahydroquinolinyl group, a tetrahydroisoquinolinyl group, a tetrahydronaphthyridinyl group, a tetrahydropyridoazepinyl group, and the like.

15 [0223]

Examples of an "optionally substituted amino group" include amino, and mono- or di-substituted amino.

[0224]

20 Examples of a substituent of the "mono- or di-substituted amino" include "C₁₋₆alkyl", "C₃₋₁₀cycloalkyl", "C₃₋₁₀cycloalkyl C₁₋₄alkyl", "C₃₋₇cycloalkyl C₁₋₄alkoxycarbonyl", "C₁₋₄alkylcarbonyl", "C₁₋₄alkyloxycarbonyl", a "3- to 8-membered saturated 25 heterocycle", "3- to 8-membered saturated heterocyclyl C₁₋₄alkyl", "3- to 8-membered saturated heterocyclylcarbonyl", "3- to 8-membered saturated heterocyclloxycarbonyl", "3- to 8-membered saturated heterocyclyl C₁₋₄alkylcarbonyl", "C₆₋₁₀aryl", "C₇₋₁₄aralkyl", "C₆₋₁₀arylcarbonyl", "C₆₋₁₀aryloxycarbonyl", "C₅₋₆heteroaryl", "C₅₋₆heteroaryl C₁₋₄alkyl", and the like.

30

As used herein, the "3- to 8-membered saturated heterocyclyl C₁₋₄alkyl" means a group in which the

"C₁₋₄alkyl group" is substituted with a "3- to 8-membered saturated heterocycle". The "3- to 8-membered saturated heterocyclylC₁₋₄alkylcarbonyl" means a group in which the "C₁₋₄alkyl group" is substituted with a "3- to 8-membered saturated heterocycle". The "C₇₋₁₄aralkyl" means a group in which the "C₁₋₄alkyl group" is substituted with a "C₆₋₁₀aryl group". The "C₅₋₆ heteroaryl C₁₋₄alkyl" means a group in which the "C₁₋₄alkyl group" is substituted with a "C₅₋₆ heteroaryl".

10 [0225]

Specific examples of the "mono-substituted amino" include, for example,

"C₁₋₆alkylamino" (e.g., methylamino, ethylamino, propylamino, 1-methylethylamino, butylamino,

15 2-methylpropylamino, 1-methylpropylamino, 1,1-dimethylethylamino, and the like),

"C₃₋₈cycloalkylamino" (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, and the like),

20 "(C₃₋₈cycloalkylC₁₋₄alkyl)amino" (e.g., cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, cyclohexylmethylamino, cycloheptylmethylamino, and the like),

25 "(C₃₋₈cycloalkylC₁₋₄alkoxycarbonyl)amino" (e.g., cyclopropoxycarbonylamino, cyclobutoxycarbonylamino, cyclopentoxycarbonylamino, cyclohexyloxycarbonylamino, cycloheptyloxycarbonylamino, and the like),

30 "(C₁₋₄alkylcarbonyl)amino" (e.g., methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, 1-methylpropylcarbonylamino, 2-methylpropylcarbonylamino, butylcarbonylamino, 2,2-dimethylethylcarbonylamino, and the like),

"(C₁₋₄alkyloxycarbonyl)amino" (e.g., methoxycarbonylamino,

ethoxycarbonylamino, propoxycarbonylamino,
1-methylpropoxycarbonylamino, butoxycarbonylamino,
2-methylpropoxycarbonylamino, 2,2-dimethylethoxycarbonylamino, and the like),
5 "C₅₋₁₀arylarnino" (e.g., phenylarnino, 1-naphthylarnino,
2-naphthylarnino, and the like),
"C₇₋₁₄aralkylarnino" (e.g., benzylarnino,
1-naphthylmethylnarnino, 2-naphthylmethylnarnino, and the
like),
10 "C₆₋₁₀arylcarbonylamino" (e.g., phenylcarbonylamino,
1-naphthylcarbonylamino, 2-naphthylcarbonylamino, and the
like),
"C₆₋₁₀aryloxycarbonylamino" (e.g., phenoxy carbonylamino,
1-naphthoxycarbonylamino, 2-naphthoxycarbonylamino, and
the like),
15 "3- to 8-membered saturated heterocyclarnino" (e.g.,
tetrahydropyranylarnino, tetrahydropyridinylarnino,
pyrrolidinylarnino, oxopyrrolidinylarnino,
tetrahydrofuranylarnino, piperidinylarnino, and the like),
20 "(3- to 8-membered saturated heterocyclC₁₋₄alkyl)arnino"
(e.g., tetrahydropyranylarnylmethylnarnino,
tetrahydropyridinylarnylmethylnarnino, pyrrolidinylarnylmethylnarnino,
oxopyrrolidinylmethylnarnino, tetrahydrofuranylarnylmethylnarnino,
piperidinylmethylnarnino, piperazinylmethylnarnino,
25 morpholinylmethylnarnino, and the like),
"3- to 8-membered saturated heterocyclcarbonylamino"
(e.g., tetrahydropyranylcarbonylamino,
tetrahydropyridinylcarbonylamino,
pyrrolidinylcarbonylamino, oxopyrrolidinylcarbonylamino,
30 tetrahydrofuranylcarbonylamino, piperidinylcarbonylamino,
and the like),
"3- to 8-membered saturated heterocyclloxycarbonylamino"
(e.g., tetrahydropyranylloxycarbonylamino,

tetrahydropyridinyloxycarbonylamino,
pyrrolidinyloxycarbonylamino,
oxopyrrolidinyloxycarbonylamino,
tetrahydrofuranyloxycarbonylamino,
5 piperidinyloxycarbonylamino, and the like),
“(C₅ - 6 heteroaryl)amino” (e.g., pyrrolylamino,
thienylamino, furylamino, oxazolylamino, thiazolylamino,
isoxazolylamino, isothiazolylamino, imidazolylamino,
pyrazolylamino, triazolylamino, oxadiazolylamino,
10 thiadiazolylamino, tetrazolylamino, pyridylamino,
pyrazylamino, pyrimidylamino, pyridazylamino,
triaziylamino, and the like),
“(C₅ - 6 heteroarylC₁ - 4 alkyl)amino” (e.g.,
pyrrolylmethylamino, thienylmethylamino, furylmethylamino,
15 oxazolylmethylamino, thiazolylmethylamino,
isoxazolylmethylamino, isothiazolylmethylamino,
imidazolylmethylamino, pyrazolylmethylamino,
triazolylmethylamino, oxadiazolylmethylamino,
thiadiazolylmethylamino, tetrazolylmethylamino,
20 pyridylmethylamino, pyrazylmethylamino,
pyrimidylmethylamino, pyridazylmethylamino,
triaziylmethylamino, and the like), and the like.

[0226]

Specific examples of the “di-substituted amino” include,
25 for example,
“di-C₁ - 6 alkylamino” (e.g., dimethylamino, diethylamino,
dipropylamino, di-1-methylethylamino, dibutylamino,
di-2-methylpropylamino, di-1-methylpropylamino,
di-1,1-dimethylethylamino, and the like),
30 “N-(C₁ - 6 alkyl)-N-(C₃ - 10 cycloalkyl)amino” (e.g.,
methylcyclopropylamino, methylcyclobutylamino,
methylcyclopentylamino, methylcyclohexylamino,
methylcycloheptylamino, and the like),

5 "N- (C₁₋₆alkyl) -N- (3- to 8-membered saturated heterocyclyl) amino" (e.g., methyltetrahydropyranyl amino, methyltetrahydropyridinyl amino, methylpyrrolidinyl amino, methyloxopyrrolidinyl amino, methyltetrahydrofuranyl amino, methylpiperidinyl amino, and the like), and the like.

10 [0227]

An "aminocarbonyl group" means a group in which the above-described "amino group" is bonded to a carbonyl group. As used herein, the "amino" means unsubstituted amino, mono-substituted amino, di-substituted amino, or 3- to 12-membered cyclic amino. Specific examples thereof include, for example, a methylaminocarbonyl group, a cyclopropylaminocarbonyl group, a dimethylaminocarbonyl group, a dicyclopropyl aminocarbonyl group, and the like.

15 [0228]

An "aminosulfinyl group" means a group in which the above-described "amino group" is bonded to a sulfinyl group. As used herein, the "amino" means unsubstituted amino, mono-substituted amino, di-substituted amino, or 3- to 12-membered cyclic amino. Specific examples thereof include, for example, a methylaminosulfinyl group, a cyclopropylaminosulfinyl group, a dimethylaminosulfinyl group, a dicyclopropylaminosulfinyl group, and the like.

20 [0229]

An "aminosulfonyl group" means a group in which the above-described "amino group" is bonded to a sulfonyl group. As used herein, the "amino" is unsubstituted amino, mono-substituted amino, di-substituted amino, or 3- to 12-membered cyclic amino. Specific examples thereof include, for example, a methylaminosulfonyl group, a cyclopropylaminosulfonyl group, a dimethylaminosulfonyl group, a dicyclopropylaminosulfonyl group, and the like.

25 [0230]

The "3- to 12-membered monocyclic or polycyclic heterocycle" moiety of the "3- to 12-membered monocyclic or polycyclic heterocyclxy group", the "3- to 12-membered monocyclic or polycyclic heterocyclthio group", the "3- to 12-membered monocyclic or polycyclic heterocyclxy carbonyl group", the "3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group", the "3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group", and the "3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group" is defined the same as the above-described "3- to 12-membered monocyclic or polycyclic heterocyclic group". It is preferably a 3- to 10-membered group, more preferably a 3- to 8-membered group, and further preferably a 3- to 6-membered group. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclxy group" include, for example, a pyridyloxy group and the like. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclthio group" include, for example, a pyridylthio group and the like. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclxy carbonyl group" include, for example, a pyridyloxycarbonyl group and the like. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group" include, for example, a pyridylsulfinyl group and the like. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group" include, for example, a pyridylsulfonyl group and the like. Specific examples of the "3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group" include, for example, a pyridylcarbonyl group and the like.

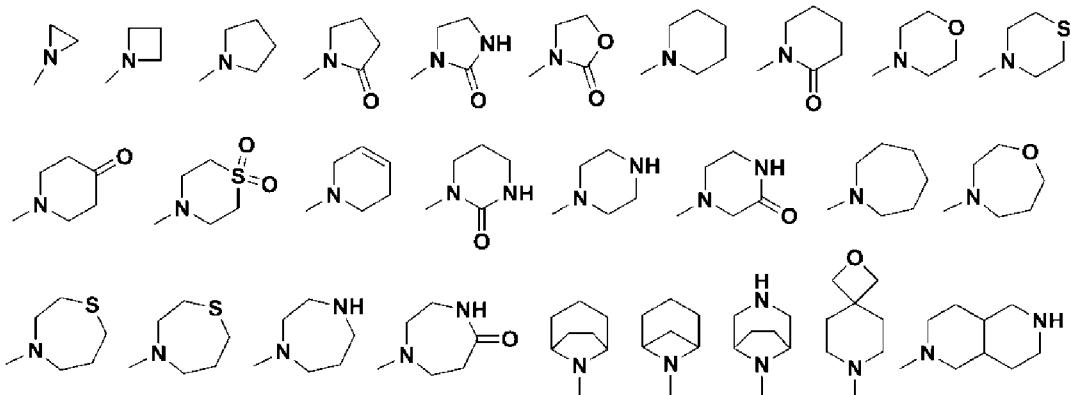
[0231]

5 A "3- to 12-membered cyclic amino group" means a 3- to 12-membered cyclic amino group in which the nitrogen atom in the ring is at a position to be directly attached in "the group", and also encompasses those amino groups having a partially bridged structure. It is preferably 3- to 8-membered, and further preferably 3- to 7-membered. It is most preferably 3- to 6-membered. Specific examples thereof include, for example, groups represented by the following, and the like. It should be noted that the group encompasses also a cyclic amino group containing a partially unsaturated ring.

10

[0232]

[Chem. 17]



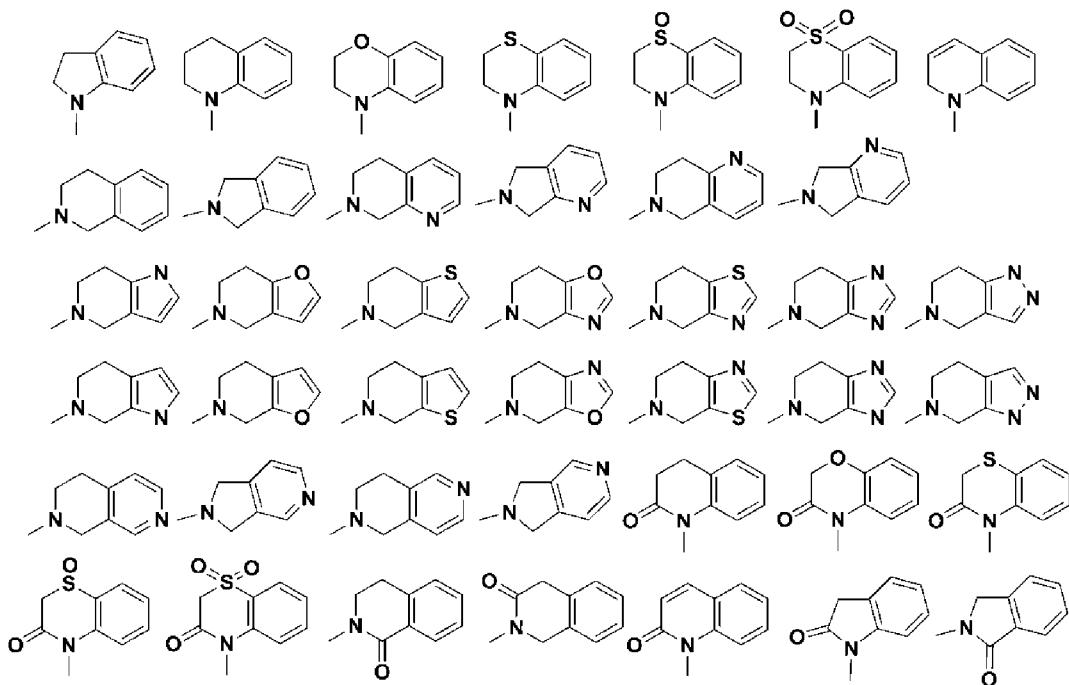
15 [0233]

The "3- to 12-membered cyclic amino group" may form a fused ring with a 6-membered aromatic hydrocarbon or a 5- or 6-membered heteroaryl. Specific examples thereof include, "the groups" represented by the following, and the like.

20

[0234]

[Chem. 18]



[0235]

The "3- to 12-membered cyclic amino" moiety of the "3- to 12-membered cyclic aminocarbonyl group", the "3- to 12-membered cyclic aminosulfinyl group", and the "3- to 12-membered cyclic aminosulfonyl group" is defined the same as the above-described "3- to 12-membered cyclic amino group". It is preferably 3- to 8-membered, and further preferably 3- to 7-membered. It is most preferably 3- to 6-membered. Specific examples of the "3- to 12-membered cyclic aminocarbonyl group" include, for example, a 1-piperidinylcarbonyl group and the like. Specific examples of the "3- to 12-membered cyclic aminosulfinyl group" include, for example, a 1-piperidinylsulfinyl group and the like. Specific examples of the "3- to 12-membered cyclic aminosulfonyl group" include, for example, a 1-piperidinylsulfonyl group and the like.

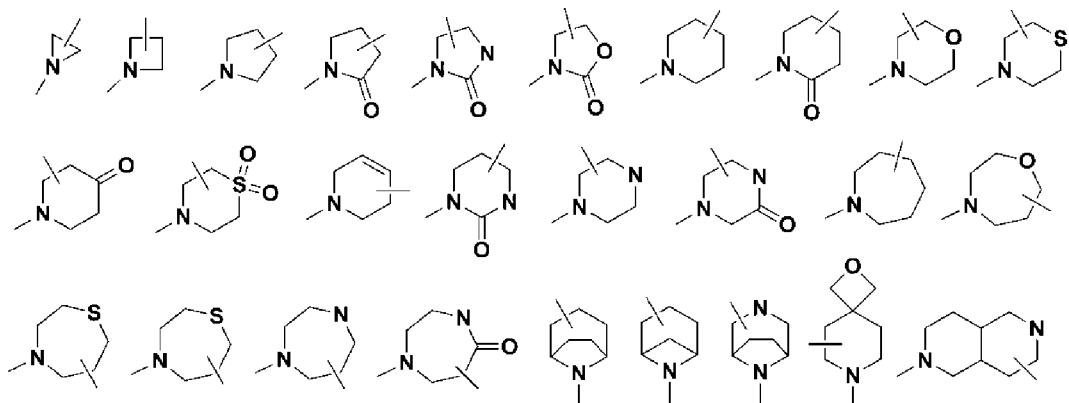
[0236]

A "3- to 12-membered cyclic aminyl linker group" means

5 a 3- to 12-membered cyclic amino in which the nitrogen atom in the ring is at a position to be directly attached in "the ring", and also encompasses those cyclic aminyl linker group having a partially bridged structure. It is preferably 3-
10 to 8-membered, and further preferably 3- to 7-membered. It is most preferably 3- to 6-membered. Specific examples thereof include, for example, groups represented by the following, and the like. It should be noted that the group also encompasses a cyclic amino group containing a partially unsaturated ring.

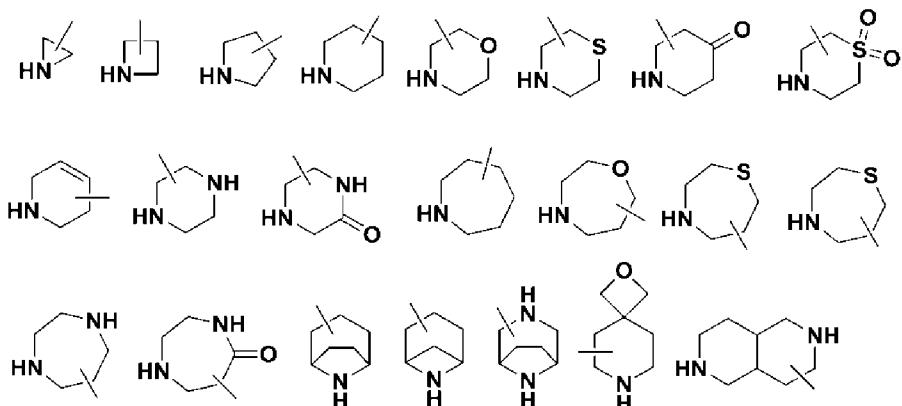
[0237]

[Chem. 19]



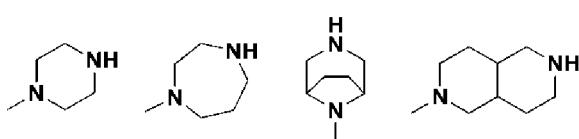
15 Specific examples of the 3- to 12-membered monocyclic or polycyclic heterocyclic group having at least one or more secondary nitrogen atoms in the ring include, for example, groups represented by the following, and the like.

[Chem. 20]



Specific examples of the 3- to 12-membered cyclic amino group having at least one or more secondary nitrogen atoms in the ring include, for example, groups represented by the following, and the like.

5 [Chem. 21]



[0238]

In the compound of the present invention represented by formula (1A) or (1), the following is preferable for A^1 , A^2 , B, R^1 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{4A} , R^{4B} , R^5 , R^6 , R^7 , R^8 , X, Y, Z, V, and n. However, the technical scope of the present invention is not limited to the scope of compounds set forth below.

15 [0239]

Preferably, A^1 and A^2 are identical or different and each independently include $-C(=O)B$, $-C(=O)CR^{3A}R^{3B}B$, $-CO_2B$, $-CONR^{3C}B$, and a hydrogen atom.

More preferably, A^1 and A^2 are identical or different, and each independently include $-CO_2B$, $-CONR^{3C}B$, and a hydrogen atom.

Further preferably, A^1 and A^2 are identical or different,

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and each independently $-\text{CONR}^3\text{B}$, or a hydrogen atom.

Most preferably, A^1 and A^2 include $-\text{CONR}^3\text{B}$.

[0240]

B includes, preferably,

5 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$),

10 (2) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$), and

15 (3) a group represented by the formula (B).

20 As used herein, the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

[0241]

25 B is, more preferably,

30 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

(2) a group represented by the formula (B),
wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group has at least one or more secondary

nitrogen atoms in the ring.

[0242]

B is, further preferably, a 3- to 6-membered monocyclic heterocyclic group optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-\text{CO}_2\text{R}^6$, or a group represented by the formula (B), wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

[0243]

B includes, most preferably, a 3- to 6-membered monocyclic heterocyclic group, or a group represented by the formula (B). As used herein, the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

[0244]

R^1 includes, preferably,

- (1) a hydrogen atom,
- (2) a halogen atom
- (3) a cyano group,
- (4) a hydroxyl group,

20 (5) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group),
25 (6) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered cyclic amino group),
30 (7) a C_{1-6} alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy

- 125 -

group, and a C_{3-10} cycloalkyl group),

(8) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group),

(9) a C_{1-6} alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered cyclic amino group),

(10) a carboxyl group,

(11) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

(a) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group),

(b) a C_{3-10} cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group), and

(c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group)), and

(12) a 3- to 12-membered cyclic aminocarbonyl group (the cyclic amino is optionally substituted with one to three C_{1-6} alkyl groups).

[0245]

R^1 includes, more preferably,

(1) a hydrogen atom,
(2) a hydroxyl group,
(3) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a C₃₋₁₀cycloalkyl group),
5 (4) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a C₃₋₁₀cycloalkyl group),
10 (5) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered cyclic amino group), and
15 (6) a carboxyl group.

[0246]

R¹ includes, further preferably, a hydrogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₁₋₆alkylcarbonyl group, and a carboxyl group.

[0247]

R¹ includes, most preferably, a hydrogen atom.

[0248]

Preferably, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently include

(1) a hydrogen atom,
(2) a halogen atom,
(3) a cyano group,
(4) a hydroxyl group,

25 (5) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of

30 (a) a C₁₋₆alkyl group (the alkyl group is optionally

substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a C₁₋₆alkoxy group),

5 (b) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and C₁₋₆alkoxy group),

10 (c) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

15 (d) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group)),

(6) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three C₁₋₆alkyl groups),

20 (7) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group),

25 (8) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group),

30 (9) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group),

(10) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group),

5 (11) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group),

10 (12) a C₃₋₁₀cycloalkylcarbonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group),

15 (13) a carboxyl group

(14) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

20 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

25 (b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

(c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl

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group, and a C₁₋₆alkoxy group)), and

(15) a sulfonate group.

[0249]

More preferably, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently include

(1) a hydrogen atom,

(2) a halogen atom,

(3) a hydroxyl group,

10 (4) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of a C₁₋₆alkyl group and a C₁₋₆alkylcarbonyl group),

15 (5) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a C₁₋₆alkoxy group),

(6) a C₃₋₁₀cycloalkyl group,

20 (7) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, and a C₁₋₆alkoxy group),

(8) a carboxyl group, and

25 (9) an aminocarbonyl group (the amino is optionally substituted with a C₁₋₆alkyl group).

[0250]

Further preferably, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently include a hydrogen atom, a halogen atom, a C₁₋₆alkyl group, a C₃₋₁₀cycloalkyl group, a C₁₋₆alkoxy group, and a carboxyl group.

[0251]

30 Most preferably, R^{2A}, R^{2B}, R^{2C}, and R^{2D} include the case where they all are hydrogen atoms.

[0252]

Preferably, R^{3A}, R^{3B}, and R^{3C} are identical or different,

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and each independently include a hydrogen atom, and a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷.

More preferably, R^{3A}, R^{3B}, and R^{3C} are identical or different, and each independently include a hydrogen atom, and a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶.

Further preferably, R^{3A}, R^{3B}, and R^{3C} are identical or different, and each independently include a hydrogen atom, and a C₁₋₆alkyl group optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶.

Most preferably, R^{3A}, R^{3B}, and R^{3C} include the case where they all are hydrogen atoms.

20 [0253]

Preferably, R^{4A} and R^{4B} are identical or different, and each independently include a hydrogen atom, and a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷.

More preferably, R^{4A} and R^{4B} are identical or different, and each independently include a hydrogen atom, and a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a C₁₋₆alkoxy group,

a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, and -CONR⁶R⁷.

Further preferably, R^{4A} and R^{4B} are identical or different, and each independently include a hydrogen atom, and a C₁₋₆alkyl group optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶.

Most preferably, R^{4A} and R^{4B} are identical or different, and each independently include a hydrogen atom, and a C₁₋₆alkyl group.

10 [0254]

R⁵ includes, preferably,

(1) a hydrogen atom,

(2) a C₁₋₁₀alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₆₋₁₀aryl group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, -SO₂NR⁶R⁷, -OCO₂R⁶, -OCONR⁶R⁷, and -NR⁶CO₂R⁷),

(3) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), and

(4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

[0255]

R^5 includes, more preferably,

(1) a hydrogen atom and

5 (2) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{6-10} aryl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, $-OCO_2R^6$, $-OCONR^6R^7$, and $-NR^6CO_2R^7$).

10

[0256]

R^5 includes, further preferably, a hydrogen atom, and a C_{1-6} alkyl group optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, a C_{6-10} aryl group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, $-OCO_2R^6$, $-OCONR^6R^7$, and $-NR^6CO_2R^7$.

15

[0257]

20

R^5 includes, most preferably, a hydrogen atom, and a C_{1-6} alkyl group optionally substituted with one to two carboxyl groups.

[0258]

25

30

Preferably, R^6 and R^7 are identical or different, and each independently include a hydrogen atom, and a C_{1-10} alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group. As used herein, R^6 and R^7 , when both are optionally substituted C_{1-10} alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

More preferably, R^6 and R^7 are identical or different, and each independently include a hydrogen atom, and a C_{1-6} alkyl group optionally substituted with one to two groups

selected from the group consisting of a halogen atom and a carboxyl group. As used herein, R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached 5 to form a 3- to 12-membered cyclic amino group.

Further preferably, R⁶ and R⁷ are identical or different, and each independently include a hydrogen atom, and a C₁₋₆alkyl group optionally substituted with one to two groups selected from the group consisting of a carboxyl group. As 10 used herein, R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered cyclic amino group.

Most preferably, R⁶ and R⁷ include a C₁₋₆alkyl group 15 optionally substituted with one to two carboxyl groups.

[0259]

R⁸ includes, preferably, a C₁₋₁₀alkyl group optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a 20 C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group.

R⁸ includes, more preferably, a C₁₋₁₀alkyl group 25 optionally substituted with one to three groups selected from the group consisting of a halogen atom, -NR⁶R⁷, a C₁₋₆alkoxy group, and a C₃₋₁₀cycloalkyl group.

R⁸ includes, further preferably, a C₁₋₆alkyl group optionally substituted with one to three halogen atoms.

R⁸ includes, further preferably, a methyl group.

30 [0260]

X includes, preferably,

- (1) a single bond,
- (2) C₁₋₆alkylene (the alkylene is optionally substituted

with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

5 (3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

10 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), and

15 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

20 [0261]

X includes, more preferably,

(1) a single bond,

25 (2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶),

(3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally

substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶), and

(5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶).

[0262]

X includes, further preferably, a single bond, and C₁₋₆alkylene optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and -CO₂R⁶.

[0263]

X includes, most preferably, a single bond, and C₁₋₆alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group, and -CO₂R⁶.

[0264]

Y includes, preferably, a single bond, an oxygen atom, -OCO₂- , -OCONR^{4A}- , -CONR^{4A}- , -NR^{4A}- , -NR^{4A}CO- , -NR^{4A}CO₂- , -NR^{4A}CONR^{4B}- , -NR^{4A}SO₂- , -NR^{4A}SO₂NR^{4B}- , a sulfur atom, -SO₂- , -SO₂NR^{4A}- , and an optionally substituted 3- to 12-membered cyclic aminyl linker group.

Y includes, more preferably, a single bond, an oxygen atom, -CONR^{4A}- , -NR^{4A}CO- , and a sulfur atom.

Y includes, most preferably, a single bond and an oxygen atom.

[0265]

Z include, preferably,

(1) a single bond,

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), and

(5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

[0266]

Z includes, more preferably,

(1) a single bond,

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and

$-\text{CO}_2\text{R}^6$),

(3) $\text{C}_{3-10}\text{cycloalkylene}$ (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, 5 $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), and

10 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$).

[0267]

15 Z includes, further preferably, a single bond, or $\text{C}_{1-6}\text{alkylene}$ optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-\text{CO}_2\text{R}^6$.

[0268]

20 Z includes, most preferably, a single bond, and $\text{C}_{1-6}\text{alkylene}$ optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$.

[0269]

25 V includes, preferably,

(1) $-\text{NHR}^5$,

(2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-8}\text{cycloalkoxy}$ group, 30 $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$), and

(3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, 5 a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷). As used herein, the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 10 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

[0270]

V includes, more preferably,

(1) -NHR⁵,

15 (2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶), and

20 (3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶). As used herein, the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at 25 least one or more secondary nitrogen atoms in the ring.

[0271]

V includes, further preferably, -NHR⁵, a 3- to 6-membered monocyclic heterocyclic group, and a 3- to 30 6-membered cyclic amino group. As used herein, the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

[0272]

V includes, most preferably, -NHR⁵ and a 3- to 6-membered monocyclic heterocyclic group. As used herein, the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring.

5 [0273]

Preferably, n includes 0, 1, and 2. More preferably, n includes 0 and 1. Most preferably, n includes 0.

[0274]

10 In the compound represented by formula (1A), preferable compounds include compounds as described below, and pharmaceutically acceptable salts.

[0275]

In the compound represented by formula (1A), preferable embodiments include the following (A).

15 (A)

A compound or a pharmaceutically acceptable salt thereof, wherein

20 A¹ and A² are identical or different, and each independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -CONR^{3C}B, or a hydrogen atom, wherein A¹ and A² are not both hydrogen atoms,

wherein

B is

25 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

30 (2) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a

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sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

(3) a group represented by the formula (B),

5 wherein

X is

(1) a single bond,

10 (2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

15 (3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

20 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

25 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group,

-NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

Y is a single bond, an oxygen atom, -OCO₂-, -OCONR^{4A}-, -CONR^{4A}-, -NR^{4A}-, -NR^{4A}CO-, -NR^{4A}CO₂-, -NR^{4A}CONR^{4B}-, -NR^{4A}SO₂-, -NR^{4A}SO₂NR^{4B}-, a sulfur atom, -SO₂-, -SO₂NR^{4A}-, or an optionally substituted 3- to 12-membered cyclic aminyl linker group,

R^{4A} and R^{4B} are identical or different, and each independently a hydrogen atom, or C₁₋₆alkyl optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶,

Z is

(1) a single bond,

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

(5) a 3- to 12-membered cyclic aminyl linker

group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷),

5 n is 0, 1, or 2,

V is

(1) -NHR⁵,

10 (2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), or

15 (3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷), wherein the 3- to 20 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one 25 or more secondary nitrogen atoms in the ring,

R⁵ is

(1) a hydrogen atom, or

30 (2) a C₁₋₁₀alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₆₋₁₀aryl group, a

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C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, $-SO_2NR^6R^7$, $-OCO_2R^6$, $-OCONR^6R^7$, and $-NR^6CO_2R^7$), and

5 R^6 and R^7 are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R^6 and R^7 , when both are optionally substituted C_{1-6} alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered 10 cyclic amino group, and

 wherein

15 the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

20 R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$;

R^1 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylcarbonyl group, or a carboxyl group;

25 R^{2A} , R^{2B} , R^{2C} , and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a C_{3-10} cycloalkyl group, a C_{1-6} alkoxy group, or a carboxyl group; and

30 R^8 is a C_{1-10} alkyl group optionally substituted with one to three groups selected from the group consisting of a halogen atom, $-NR^6R^7$, a C_{1-6} alkoxy group, and a C_{3-10} cycloalkyl group.

[0276]

 In the compound represented by formula (1A), more

preferable embodiments include the following (B).

(B)

A compound or a pharmaceutically acceptable salt thereof, wherein

5 A^1 and A^2 are identical or different, and each independently $-CO_2B$, $-CONR^3C^3B$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms,

wherein

10 B is a 3- to 6-membered monocyclic heterocyclic group optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-CO_2R^6$, or a group represented by the formula (B),

wherein

15 X is

(1) a single bond,

20 (2) C_{1-6} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

25 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$), or

30 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-NR^6R^7$, and $-CO_2R^6$),

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Y is a single bond, an oxygen atom, $-\text{CONR}^{4A}-$, $-\text{NR}^{4A}\text{CO}-$, or a sulfur atom;

R^{4A} is a hydrogen atom or $\text{C}_{1-6}\text{alkyl}$,

Z is

5 (1) a single bond,

(2) $\text{C}_{1-6}\text{alkylene}$ (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

10 (3) $\text{C}_{3-10}\text{cycloalkylene}$ (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

15 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

20 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$),

n is 0 or 1,

V is

25 (1) $-\text{NHR}^5$,

(2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), or

30 (3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of

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a halogen atom, a carboxyl group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$), wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring,

5 R^5 is

(1) a hydrogen atom or

10 (2) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{6-10} aryl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{OCO}_2\text{R}^6$, $-\text{OCONR}^6\text{R}^7$, and $-\text{NR}^6\text{CO}_2\text{R}^7$), and

15 R^6 and R^7 are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two groups selected from the group consisting of a carboxyl group, wherein R^6 and R^7 , when both are optionally substituted C_{1-6} alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 6-membered cyclic amino group, and wherein

20 the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring, and

25 R^{3C} is a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$;

30 R^1 is a hydrogen atom;

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms;

R^8 is a C_{1-6} alkyl group optionally substituted with one

to three halogen atoms.

[0277]

In the compound represented by formula (1A), further preferable embodiments include the following (C).

5 (C)

A compound or a pharmaceutically acceptable salt thereof, wherein

10 A^1 and A^2 are identical or different, and each independently $-CONR^3C_6H_4B$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms,

wherein

B is 3- to 6-membered monocyclic heterocyclic group, or a group represented by the formula (B),

wherein

15 X is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-CO_2R^6$,

Y is a single bond or an oxygen atom,

20 Z is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, and $-CO_2R^6$,

n is 0 or 1,

25 V is $-NHR^5$, 3- to 6-membered monocyclic heterocyclic group, or a 3- to 6-membered cyclic amino group, wherein the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring,

30 R^5 is a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two substituents selected from the group consisting of a fluorine atom, a carboxyl group, a C_{6-10} aryl group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$,

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$-\text{SO}_2\text{R}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{OCO}_2\text{R}^6$, $-\text{OCONR}^6\text{R}^7$, and $-\text{NR}^6\text{CO}_2\text{R}^7$, and
 R^6 is a C_{1-6} alkyl group optionally substituted with one to two carboxyl groups, and
wherein

5 the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring, and

$\text{R}^{3\text{C}}$ is a hydrogen atom;

R^1 is a hydrogen atom;

10 $\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{2\text{C}}$, and $\text{R}^{2\text{D}}$ are all hydrogen atoms; and

R^8 is a methyl group.

[0278]

In the compound represented by formula (1A), most preferable embodiments include the following (D).

15 (D)

A compound or a pharmaceutically acceptable salt thereof, wherein

A^1 and A^2 are $-\text{CONR}^{3\text{C}}\text{B}$,

wherein

20 B is 3- to 6-membered monocyclic heterocyclic group, or a group represented by the formula (B),

wherein

25 X is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and $-\text{CO}_2\text{R}^6$,

V is $-\text{NHR}^5$ or a 3- to 6-membered monocyclic heterocyclic group, wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring,

30 R^5 is a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two carboxyl groups, and

R^6 is a C_{1-6} alkyl group, and

wherein

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the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring, and

5 R^{3C} is a hydrogen atom;
 R^1 is a hydrogen atom;
 R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms; and
 R^8 is a methyl group.

[0279]

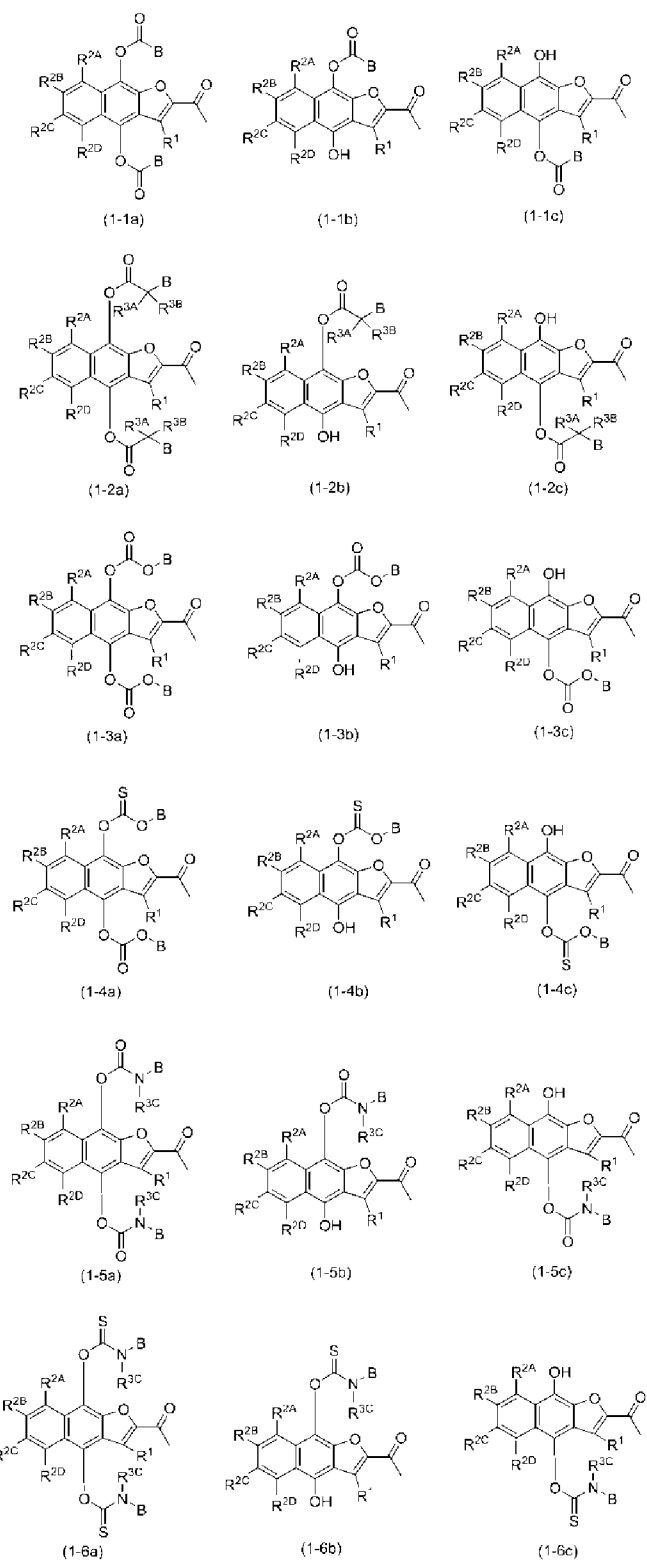
10 Preferable embodiments of the present invention include compounds represented by the following formulas (1-1a)-(3-4c).

[0280]

15 A compound represented by the following formula (1-1a), (1-1b), (1-1c), (1-2a), (1-2b), (1-2c), (1-3a), (1-3b), (1-3c), (1-4a), (1-4b), (1-4c), (1-5a), (1-5b), (1-5c), (1-6a), (1-6b), or (1-6c), or a pharmaceutically acceptable salt thereof:

[0281]

[Chem. 22]



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[0282]

[each symbol in the formulas is defined the same as item 1 or 2].

5 Preferable embodiments of respective symbols in the compounds represented by the above-described formulas (1-1a), (1-1b), (1-1c), (1-2a), (1-2b), (1-2c), (1-3a), (1-3b), (1-3c), (1-4a), (1-4b), (1-4c), (1-5a), (1-5b), (1-5c), (1-6a), (1-6b), and (1-6c) are the same as the preferable embodiments in the compound represented by
10 formula (1A) or (1).

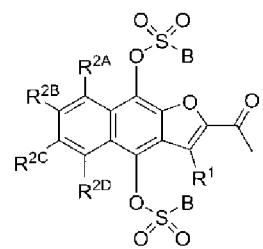
[0283]

15 A compound represented by the following formula (2-1a), (2-1b), (2-1c), (2-2a), (2-2b), (2-2c), (2-3a), (2-3b), (2-3c), (2-4a), (2-4b), or (2-4c), or a pharmaceutically acceptable salt thereof:

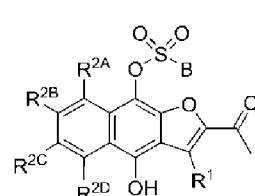
[0284]

[Chem. 23]

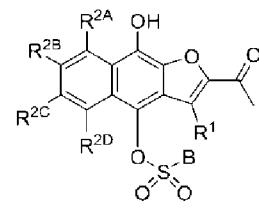
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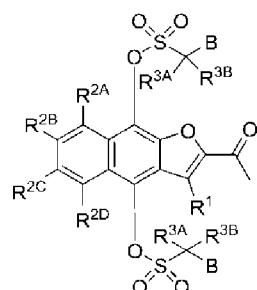
(2-1a)



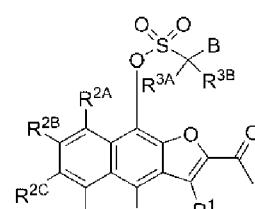
(2-1b)



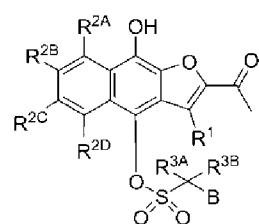
(2-1c)



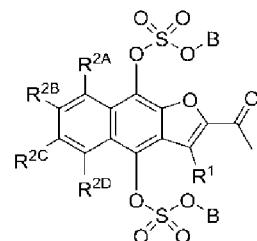
(2-2a)



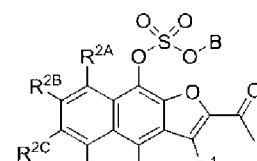
(2-2b)



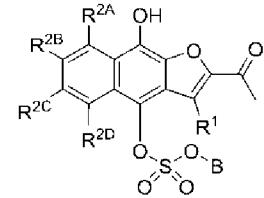
(2-2c)



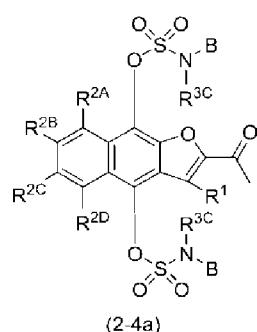
(2-3a)



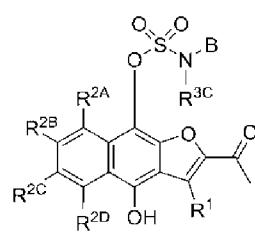
(2-3b)



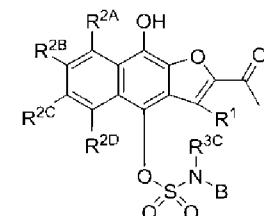
(2-3c)



(2-4a)



(2-4b)



(2-4c)

[0285]

[each symbol in the formulas is defined the same as item 1 or 2].

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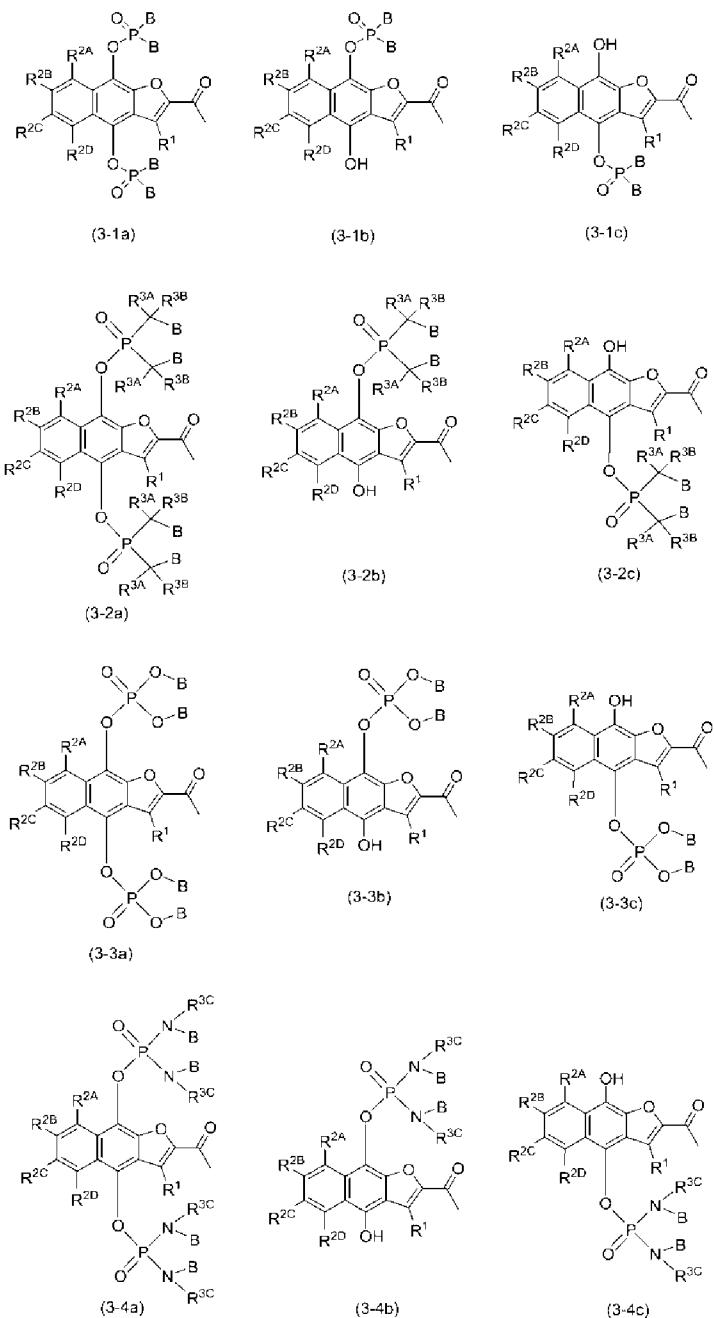
compounds represented by the above-described formulas (2-1a), (2-1b), (2-1c), (2-2a), (2-2b), (2-2c), (2-3a), (2-3b), (2-3c), (2-4a), (2-4b), and (2-4c) are the same as the preferable embodiments in the compound represented by formula (1A) or (1).

5 [0286]

A compound represented by the following formula (3-1a), (3-1b), (3-1c), (3-2a), (3-2b), (3-2c), (3-3a), (3-3b), (3-3c), (3-4a), (3-4b), or (3-4c), or a pharmaceutically acceptable salt thereof:

10 [0287]

[Chem. 24]



[0288]

[each symbol in the formulas is defined the same as item 1 or 2].

5 Preferable embodiments of respective symbols in the compounds represented by the above-described formulas

(3-1a), (3-1b), (3-1c), (3-2a), (3-2b), (3-2c), (3-3a), (3-3b), (3-3c), (3-4a), (3-4b), and (3-4c) are the same as the preferable embodiments in the compound represented by formula (1A) or (1).

5 [0289]

A "pharmaceutically acceptable salt" includes acid addition salts and base addition salts. Examples of acid addition salts include: inorganic acid salts such as hydrochlorides, hydrobromides, sulfates, hydroiodides, nitrates, phosphates, and the like; and organic acid salts such as citrate, oxalate, phthalate, fumarate, maleate, succinate, malate, acetate, formate, propionate, benzoate, trifluoroacetate, methanesulfonate, benzenesulfonate, para-toluenesulfonate, camphorsulfonate, and the like; and examples of base addition salts include inorganic base salts such as sodium, potassium, calcium, magnesium, barium, and aluminum salts, and the like, organic base salts such as trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, tromethamine [tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, dicyclohexylamine, and N,N-dibenzylethylamine, and the like, and further salts of an amino acid such as basic and acidic amino acids including 25 arginine, lysine, ornithine, aspartic acid, glutamic acid, and the like.

Suitable salts and pharmaceutically acceptable salts of starting compounds and target compounds are conventional nontoxic salts. They include acid addition salts such as 30 organic acid salts (e.g., acetate, trifluoroacetate, maleate, fumarate, citrate, tartrate, methanesulfonate, benzenesulfonate, formate, para-toluenesulfonate, or the like) and inorganic acid salts (e.g., hydrochloride,

hydrobromide, hydroiodide, sulfate, nitrate, phosphate, or the like), salts with an amino acid (e.g., arginine, aspartic acid, glutamic acid, or the like), metal salts such as alkali metal salts (e.g., sodium salt, potassium salt, or the like),
5 alkali earth metal salts (e.g., calcium salt, magnesium salt, or the like), and the like, ammonium salts, organic base salts (e.g., trimethylamine salts, triethylamine salts, pyridine salts, picoline salts, dicyclohexylamine salts, N,N'-dibenzylethylene diamine salts, or the like), or the
10 like, and additionally those skilled in the art can appropriately select them.

[0290]

When it is desired to obtain a salt of the present compound, if the present compound is obtained in a salt form,
15 it may be purified as it is, or if it is obtained in free form, it may be dissolved or suspended in a suitable organic solvent, and an acid or a base is added thereto to form a salt in accordance with a general method.

In addition, although the present compounds and pharmaceutically acceptable salts thereof may be present in an adduct form with water or any kind of solvent, these adducts are also encompassed by the present invention.

[0291]

In addition, the present invention encompasses compounds represented by formula (1A) or (1), or pharmaceutically acceptable salts thereof. It also encompasses hydrates or solvates (such as ethanol solvates and the like) thereof. Further, the present invention encompasses all tautomers and all present stereoisomers of the present compound (1A) or (1) as well as those in all modes of crystal forms.

[0292]

Among the present compounds (1A) or (1), there are

compounds that may be present as enantiomers based on an optically-active center, atropisomers based on axial or planar chirality caused by restriction of intramolecular rotation, other stereoisomers, tautomers, geometric isomer, 5 and the like. However, all possible isomers and mixtures thereof, including these, are encompassed within the scope of the present invention.

[0293]

In particular, an enantiomer and an atropisomer can be 10 obtained as a racemic body, or an optically-active substance when an optically-active starting material or intermediate is used, respectively. If necessary, in an appropriate step of the above-described production method, a corresponding starting material, intermediate, or racemic body as a final 15 product can be physically or chemically resolved into their optical enantiomers by a known separation method, such as a method using an optically active column, a fractional crystallization method, or the like. Specifically, for example, in a diastereomer method, two types of 20 diastereomers are formed from a racemic body by reaction using an optical active resolving agent. Since these different diastereomers generally have different physical properties, they can be separated by a known method such as fractional crystallization and the like.

25 [0294]

Production methods of compounds relating to the present invention are described below. The compounds relating to the present invention represented by formula (1A) or (1) or pharmaceutically acceptable salts thereof can be 30 produced from known compounds, for example, the following production method A, B, C, D, E, F, G, H, I, and J, and methods in accordance therewith, or by appropriately combining synthesis methods well-known to those skilled in the art.

It should be noted that a compound in a reaction includes the case where it forms a salt, for example, salts similar to salts in compound (1A) or (1) and the like are used as such a salt.

5 In addition, a compound obtained in each step can be used in a next reaction as a reaction solution or as a composition. However, it can be isolated from a reaction mixture in accordance with a routine method, and readily purified by a separation means such as recrystallization, 10 distillation, chromatography, and the like.

Each symbol of compounds in the following reactions is defined the same as above, unless specifically indicated.

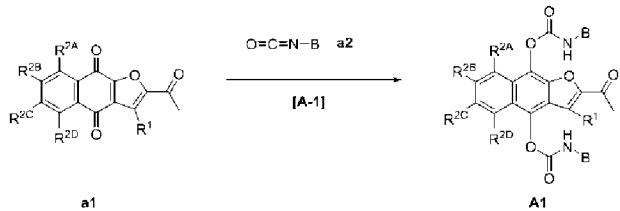
[0295]

Production method A

15 Of the compound represented by formula (1), Compound A1 represented by formula [A1] wherein A¹ and A² are -CONHB can be produced, for example, by the following production method.

[0296]

20 [Chem. 25]



[0297]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are as defined in item 1 or 2, and B is as defined in item 31.

25 [0298]

Compound a1 can be produced by a method described in a Patent Literature (e.g., WO2009/036059 or the like).

[0299]

[A-1 step]

This step is a step of obtaining Compound A1 by reacting Compound a1 with Compound a2, which is obtained by the following production method, in the presence of an additive, a base, and a reductant in suitable solvent. The additive 5 includes tetra-n-butylammonium chloride, tetra-n-butylammonium bromide, tetra-n-butylammonium iodide, and the like, and preferably, tetra-n-butylammonium bromide. The following can be used as the base: for example, basic salts such as sodium carbonate, potassium carbonate, 10 cesium carbonate, sodium acetate, sodium hydride, calcium hydride, and the like; aromatic amines such as pyridine, lutidine, 4-dimethylaminopyridine, N,N-dimethylaniline, and the like; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 15 N,N-diisopropylethylamine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, and the like; and the like. In particular, triethylamine or N,N-diisopropylethylamine is preferable. The reductant includes iron(II) ion, tin(II) ion, sodium, zinc, formic acid, oxalic acid, sodium dithionite, and the like, and preferably a mixed reductant of zinc and sodium dithionite. Solvent used in this step is selected from solvent and the like illustrated below. However, it includes aprotic 20 solvent such as N,N-dimethylformamide, N-methyl-2-pyrrolidone, dimethyl sulfoxide, acetonitrile, propionitrile, and the like; ether-based solvent such as tetrahydrofuran, 1,4-dioxane, and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, chlorobenzene, and the like; hydrocarbons such as toluene, benzene, and the like; water; 25 and mixed solvent thereof; and the like, and includes preferably N,N-dimethylformamide. The amount of a reductant used is generally 2 equivalents to 20 equivalents, 30

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preferably 4 equivalents to 8 equivalents, relative to one equivalent of Compound a1. The reaction time is generally about 0.5 hour to about 48 hours, and preferably about 0.5 hour to about 2 hours. The reaction temperature is 5 generally about -20°C to about 180°C, and preferably about 0°C to about 50°C.

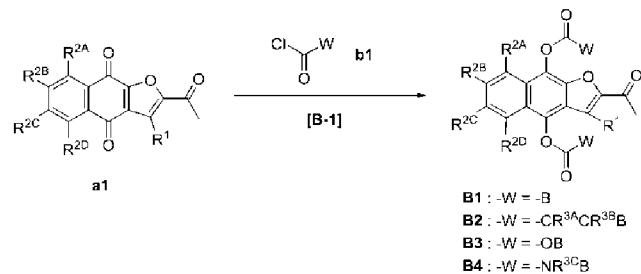
[0300]

Production method B

Of the compound represented by formula (1), Compound 10 B1, B2, B3, or B4 represented by formulas [B1], [B2], [B3] and [B4] wherein A¹ and A² are -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, or -CONR^{3C}B can be produced, for example, by the following production method.

[0301]

15 [Chem. 26]



[0302]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, and R^{3C} are as defined in item 1 or 2, B is as defined in item 31, and 20 W means -B, -CR^{3A}R^{3B}B, -OB, or -NR^{3C}B.

[0303]

[B-1 step]

This is a step of obtaining Compound B1, B2, B3, or B4 by reacting Compound a1 with Compound b1, which is obtained 25 by the following production method, under a condition in accordance with the above-described A-1 step.

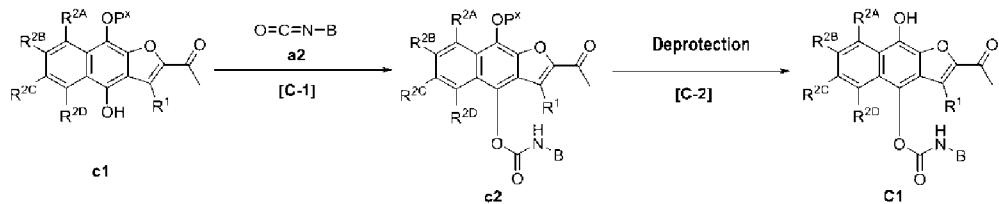
[0304]

Production method C

Of the compound represented by formula (1), Compound C1 represented by formula [C1] wherein A¹ is a hydrogen atom and A² is -CONHB can be produced, for example, by the following production method.

5 [0305]

[Chem. 27]



[0306]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are as defined in item 1 or 2, B is as defined in item 31, and P^X means a protecting group for a phenolic hydroxyl group.

10 [0307]

Protecting group P^X is described as a protecting group for a phenolic hydroxyl group in Protective Groups in Organic 15 Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley & Sons, Inc., 1999).

[0308]

Compound c1 can be produced from Compound a1, for example, by the same method as a method and the like described in 20 a Patent Literature (e.g., WO2012/119265, WO2013/120229, WO2013/128037, or the like).

[0309]

[C-1 step]

This step is a step of obtaining Compound c2 by reacting 25 Compound c1 with Compound a2, which is obtained by the following production method, in the presence of a base in suitable appropriate solvent. Solvent used in the reaction may be any solvent as long as it is inactive in the reaction, and is not particularly limited. However, for example,

tetrahydrofuran, 1,4-dioxane, dimethoxyethane, benzene, toluene, xylene, N,N-dimethylformamide, N-methyl-2-pyrrolidone, dimethyl sulfoxide, and the like can be used alone or as a mixture thereof, and in particular, 5 tetrahydrofuran or N,N-dimethylformamide is preferable. The following can be used as the base: for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium acetate, sodium hydride, calcium hydride, and the like; aromatic amines such as pyridine, lutidine, 10 4-dimethylaminopyridine, N,N-dimethylaniline, and the like; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, N,N-diisopropylethylamine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, and the like; and 15 the like. In particular, triethylamine or N,N-diisopropylethylamine is preferable.

The reaction temperature is generally a temperature between about 0°C and the boiling point of a solvent used, and preferably, 0 to 80°C. The reaction time is generally 20 0.5 to 24 hours, and preferably about 0.5 hour to about 2 hours.

[0310]

[C-2 step]

This step is a step of obtaining Compound C1 by 25 deprotecting a protecting group P^X for the phenolic hydroxyl group of Compound c2, which is obtained in the above-described production method C-1. This step can be carried out in accordance with a method or the like described in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley 30 & Sons, Inc., 1999).

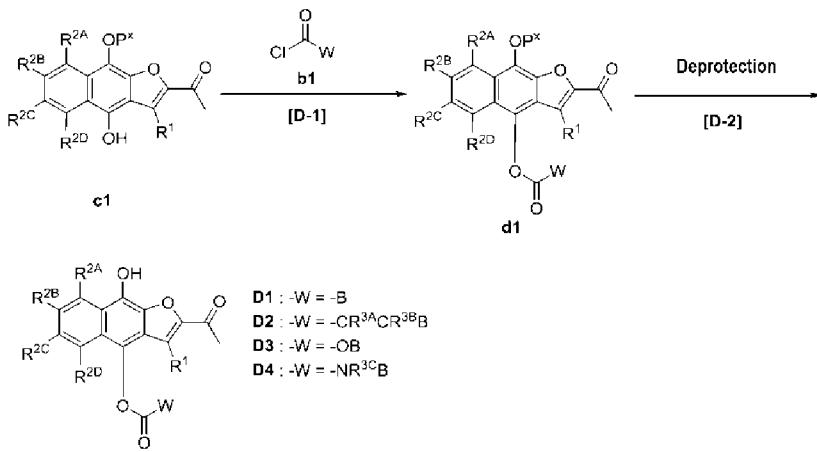
[0311]

Production method D

Of the compound represented by formula (1), Compound D1, D2, D3, or D4 represented by formula [D1], [D2], [D3], or [D4] wherein A¹ is a hydrogen atom and A² is -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, or -CONR^{3C}B can be produced, for example, by the following production method.

[0312]

[Chem. 28]



[0313]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, and R^{3C} are as defined in item 1 or 2, B is as defined in item 1 or 2, W means -B, -CR^{3A}R^{3B}B, -OB, or -NR^{3C}B.

[0314]

The protecting group P^X is described as a protecting group for a phenolic hydroxyl group in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley & Sons, Inc., 1999).

[0315]

Compound c1 can be produced from Compound 1 by the same method as a method or the like described in a Patent Literature (e.g., WO2012/119265, WO2013/120229, WO2013/128037, or the like).

[0316]

[D-1 step]

This step is a step of obtaining Compound d1 by reacting Compound c1 with Compound b1, which is obtained by the following production method, under a condition in accordance with the above-described C-1 step.

5 [0317]

[D-2 step]

10 This step is a step of obtaining Compound D1, D2, D3, or D4 by deprotecting a protecting group P^X for the phenolic hydroxyl group of Compound d1, which is obtained by the above-described production method D-1, under a condition in accordance with the above-described C-2 step.

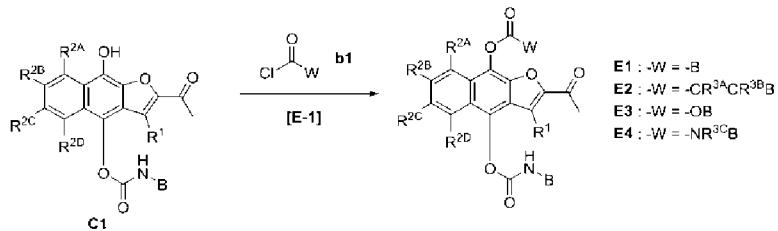
[0318]

Production method E

15 Of the compound represented by formula (1), Compound E1, E2, E3, or E4 represented by formula [E1], [E2], [E3], or [E4] wherein A¹ is -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, or -CONR^{3C}B and A² is -CONHB can be produced, for example, by the following production method.

[0319]

20 [Chem. 29]



[0320]

25 In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, and R^{3C} are as defined in item 1 or 2, B is as defined in item 1 or 2, and W means -B, -CR^{3A}R^{3B}B, -OB, or -NR^{3C}B.

[0321]

[E-1 step]

This step is a step of obtaining Compound E1, E2, E3, or E4 by reacting Compound C1, which is obtained in the

above-described C-2 step, with Compound b1, which is obtained by the following production method, under a condition in accordance with the above-described C-1 step.

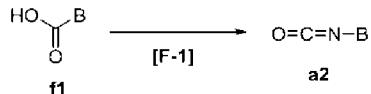
[0322]

5 Production method F (Production method of a synthetic intermediate)

A synthetic intermediate represented by the above-described a2 can be produced, for example, the following production method.

10 [0323]

[Chem. 30]



[0324]

In the formulas, B is as defined in item 31.

15 [0325]

[F-1 step]

This step is a step of converting Compound f1 to Compound a2.

20 Compound a2 can be produced from Compound f1 by the same method as a method or the like described in a Non Patent Literature {e.g., J. Am. Chem. Soc., 6203, vol. 94 (1972), Tetrahedron, 2151, vol. 30 (1974), or the like}.

[0326]

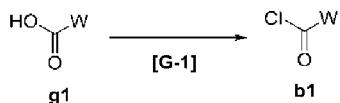
25 Production method G (production method of a synthetic intermediate)

A synthetic intermediate represented by the above-described b1 can be produced, for example, by the following production method.

[0327]

30 [Chem. 31]

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[0328]

In the formulas, W means -B or -CR^{3A}R^{3B}B, wherein B is as defined in item 31.

5 [0329]

[G-1 step]

This step is a step of converting Compound g1 to Compound b1.

10 Compound b1 can be produced from Compound f1 by the same method as a method or the like described in a document {e.g., J. Am. Chem. Soc., 7442, vol. 135 (2013), J. Org. Chem., 4506, vol. 68 (2003), J. Med. Chem., 3582, vol. 44 (2001), or the like}.

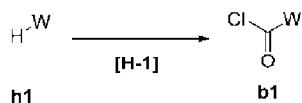
[0330]

15 Production method H (production method of a synthetic intermediate)

A synthetic intermediate represented by the above-described b1 can be produced, for example, by the following production method.

20 [0331]

[Chem. 32]



[0332]

25 In the formulas, W means -OB or -NR^{3C}B, wherein B is as defined in item 31.

[0333]

[H-1 step]

This step is a step of converting Compound h1 to Compound b1.

Compound b1 can be produced from Compound h1 by the same method as a method or the like described in a document {e.g., J. Am. Chem. Soc., 5505, vol. 106 (1984), J. Org. Chem., 5342, vol. 72 (2007), Tetrahedron, 9153, vol. 63 (2007), 5 J. Org. Chem., 5325, vol. 45 (1980), J. Org. Chem., 3787, vol. 69 (2004), or the like}.

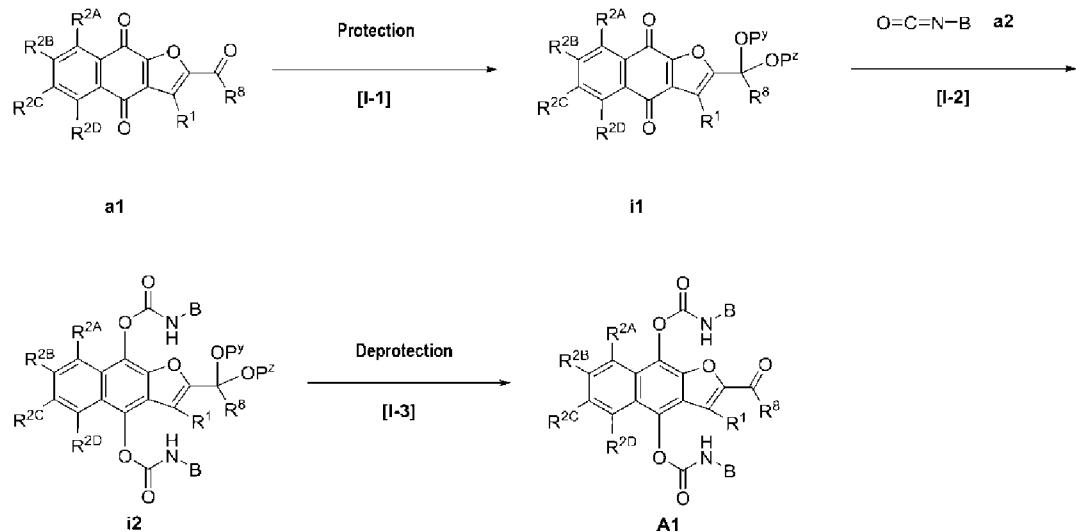
[0334]

Production method I

Of the compound represented by formula (1A), Compound A1 represented by formula [A1] wherein A¹ and A² are -CONHB can be produced, for example, by the following production method.

[0335]

[Chem. 33]



[0336]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, and R⁸ are as defined in item 1 or 2 and B is as defined in item 31.

[0337]

20 Protecting groups P^Y and P^Z are described as a protecting group for a ketone group in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts,

published by John Wiley & Sons, Inc., 1999).

[0338]

Compound a1 can be produced, for example, by a method described in a Patent Literature (e.g., WO2009/036059, or 5 the like).

[0339]

[I-1 step]

This step is a step of obtaining Compound i1 by protecting a ketone group of Compound a1 with an acetal. 10 This step can be carried out in accordance with a method or the like described in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley & Sons, Inc., 1999).

[0340]

15 [I-2 step]

This step is a step of obtaining Compound i2 by reacting Compound a2, which is obtained by the above-described production method, with Compound i1, which is obtained in the above-described production method I-1, under a 20 condition in accordance with the A-1 step.

[0341]

[I-3 step]

This step is a step of obtaining Compound A1 by deprotecting protecting groups P^Y and P^Z for the ketone group 25 of Compound i2, which is obtained in the above-described production method I-2. This step can be carried out in accordance with a method or the like described in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley & Sons, Inc., 1999).

30 [0342]

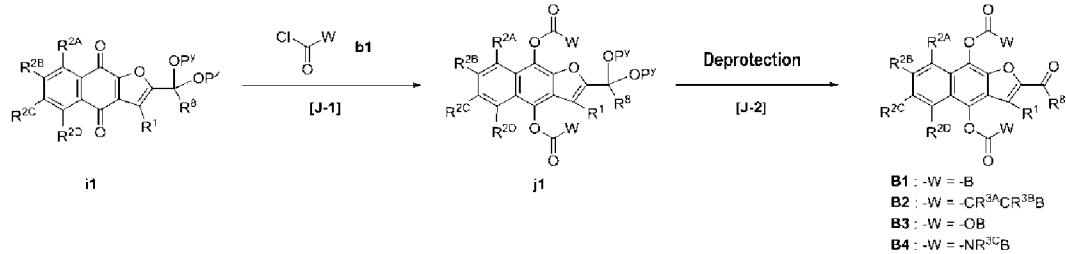
Production method J

Of the compound represented by formula (1A), Compound B1, B2, B3, or B4 represented by formula [B1], [B2], [B3],

or [B4] wherein A¹ and A² are -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, or -CONR^{3C}B can be produced, for example, by the following production method.

[0343]

5 [Chem. 34]



[0344]

In the formulas, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, and R⁸ are as defined in item 1 or 2, B is as defined in item 31, and W means -B, -CR^{3A}R^{3B}B, -OB, or -NR^{3C}B.

10 [0345]

Protecting groups P^Y and P^Z are described as a protecting group for a ketone group in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, 15 published by John Wiley & Sons, Inc., 1999).

[0346]

[J-1 step]

This step is a step of obtaining Compound j1 by reacting Compound b1, which is obtained by the above-described production method, with Compound i1, which is obtained by the above-described production method, under a condition in accordance with the above-described A-1 step.

[0347]

[J-2 step]

25 This step is a step of obtaining Compound B1, B2, B3, or B4 by deprotecting protecting groups P^Y and P^Z for a ketone group of Compound j1, which is obtained in the above-described production method J-1. This step can be

carried out in accordance with a method or the like described in Protective Groups in Organic Synthesis (written by Theodora W. Greene, Peter G. M. Wuts, published by John Wiley & Sons, Inc., 1999).

5 [0348]

In respective reactions of the production methods described above, even in a case other than the case where the use of a protecting group is specifically and explicitly indicated, if any functional group other than a reaction point is modified under a described reaction condition or is unsuitable for performing the described method, a target compound can be obtained by protecting any point other than the reaction point as necessary, and unprotecting after the reaction is finished or a series of reactions are performed.

10 15 [0349]

Conventional protecting groups can be used as the protecting group, such as those described in a document (e.g., Protective Groups in Organic Synthesis, 3rd ed., T. W. Greene, John Wiley & Sons Inc. (1999), or the like). Further specifically, examples of protecting groups for an amino group include benzyloxycarbonyl, tert-butoxycarbonyl, acetyl, benzyl, and the like, and examples of the protecting groups for a hydroxyl group include trialkylsilyl groups such as trimethylsilyl, tert-butyldimethylsilyl, or the like; acetyl, benzyl, and the like, respectively.

20 25 Introduction and elimination of a protecting group can be carried out by a method commonly used in synthetic organic chemistry (refer to, for example, the aforementioned Protective Groups in Organic Synthesis) or a method in accordance therewith.

30 [0350]

Bases used in the respective steps described above should be appropriately selected depending on the types of

reaction and a raw material compound, and the like. However examples thereof include alkali bicarbonates such as sodium bicarbonate and potassium bicarbonate; alkali carbonates such as sodium carbonate and potassium carbonate; metal hydrides such as sodium hydride and potassium hydride; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; alkali metal alkoxides such as sodium methoxide and sodium tert-butoxide; organic metal bases such as butyl lithium and lithium diisopropylamide; organic bases such as triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine (DMAP), and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU).

[0351]

Solvents used in the respective steps described above should be appropriately selected depending on the types of reaction and a raw material compound, and the like. However, examples thereof include alcohols such as methanol, ethanol, and isopropanol; ketones such as acetone and ethyl methyl ketone; halogenated hydrocarbons such as methylene chloride and chloroform; ethers such as tetrahydrofuran (THF) and dioxane; aromatic hydrocarbons such as toluene and benzene; aliphatic hydrocarbons such as hexane and heptane; esters such as ethyl acetate and propyl acetate; amides such as N,N-dimethylformamide (DMF) and N-methyl-2-pyrrolidone; sulfoxides such as dimethyl sulfoxide (DMSO); nitriles such as acetonitrile. These solvents can be used alone or as a mixture of two or more thereof. In addition, according to the type of reaction, organic bases may be used as solvent.

[0352]

The present compound represented by formula (1A) or (1) or an intermediate therefor can be separated and purified by a known method to those skilled in the art. Examples thereof include extraction, distribution, reprecipitation,

column chromatography (e.g., silica gel column chromatography, ion exchange column chromatography, or preparative liquid chromatography), recrystallization, and the like.

5 The following can be used as recrystallization solvent: for example, alcohol-based solvent such as methanol, ethanol, 2-propanol, or the like; ether-based solvent such as diethyl ether or the like; ester-based solvent such as ethyl acetate or the like; aromatic-hydrocarbon-based solvent such as benzene, toluene, or the like; ketone-based solvent such as acetone or the like; halogen-based solvent such as dichloromethane, chloroform, or the like; hydrocarbon-based solvent such as hexane or the like; aprotic solvent such as dimethylformamide, acetonitrile, or the like; water; or mixed solvent thereof; or the like. Other purification method can be used, such as methods described in *Jikken Kagaku Koza* (The Chemical Society of Japan ed., Maruzen), vol. 1, or the like. In addition, the determination of molecular structure of the present compound is easily performed with referencing structures derived from respective raw material compounds, and by spectrophotometric techniques such as the nuclear magnetic resonance method, the infrared absorption method, the circular dichroism spectrum analysis, and mass spectrometry.

25 [0353]

30 In addition, intermediates or final products in the above-described production methods can be derived to other compounds encompassed by the present invention by appropriately converting a functional group thereof, and in particular, extend any kind of side chain using an amino group, a hydroxyl group, a carbonyl group, a halogen group, or the like as an aid, and at this time, as necessary,

performing the above-described protection and deprotection. Conversion of a functional group and extension of a side chain can be performed by a routine, general method (refer to, e.g., *Comprehensive Organic Transformations*, R. C. 5 Larock, John Wiley & Sons Inc. (1999), and the like).

[0354]

In the present compounds represented by formula (1A) or (1) or pharmaceutically acceptable salts thereof, asymmetry may occur, or it may have a substituent having 10 an asymmetric carbon. In such compounds, optical isomers are present. The present compound also encompasses mixtures of these respective isomers, and isolated isomers, and can be produced according to a general method. Examples 15 of the production method include a method using a raw material having an asymmetric point, and a method in which an asymmetry is introduced in a half way. For example, in the case of an optical isomer, an optical isomer can be obtained by using an optically active raw material or performing optical resolution or the like in a suitable stage 20 of a production step. Examples of optical resolution methods include a diastereomer method of forming a salt, when the compound represented by formula (1A) or (1) or intermediates therefor have a basic functional group, in inactive solvent (alcohol-based solvent such as methanol, 25 ethanol, 2-propanol, or the like; ether-based solvent such as diethyl ether or the like; ester-based solvent such as ethyl acetate or the like; hydrocarbon-based solvent such as toluene or the like; aprotic solvent such as acetonitrile or the like; or mixed solvent thereof) using an optically active acid (e.g., monocarboxylic acid such as mandelic acid, 30 N-benzyloxy-alanine, lactic acid, or the like, dicarboxylic acid such as tartaric acid, ortho-diisopropylidene tartaric acid, malic acid, or the like, sulfonic acid such as camphor

sulfonic acid, bromocamphor sulfonic acid, or the like).

When an intermediate for the present compound represented by formula (1A) or (1) has an acidic functional group such as carboxyl and the like, optical resolution can be performed by forming a salt using an optically active amine (e.g., organic amines such as 1-phenylethylamine, quinine, quinidine, cinchonidine, cinchonine, strychnine, or the like).

[0355]

A temperature to form a salt is selected from the range from room temperature to the boiling point of solvent. To improve the optical purity, it is desirable to increase a temperature to the vicinity of the boiling point of a solvent once. When a precipitated salt is collected by filtration, as necessary, it can be cooled to improve the yield. Regarding the amount of an optically active acid or amine used, the range from about 0.5 to about 2.0 equivalents, preferably the range of approximately 1 equivalent, relative to a substrate is suitable. As necessary, crystal can be recrystallized in inactive solvent (e.g., alcohol-based solvent such as methanol, ethanol, 2-propanol, or the like; ether-based solvent such as diethyl ether or the like; ester-based solvent such as ethyl acetate or the like; hydrocarbon-based solvent such as toluene or the like; aprotic solvent such as acetonitrile or the like; or mixed solvent thereof) to obtain an optically active salt in high purity. In addition, a salt that is optically resolved as necessary can be treated with an acid or a base by a general method to obtain its free form.

[0356]

Among starting materials and intermediates in respective production methods described above, those of which production methods are not particularly and

repeatedly described are commercially available compounds or can be synthesized from a commercially available compound by a known method to those skilled in the art or a method in accordance therewith.

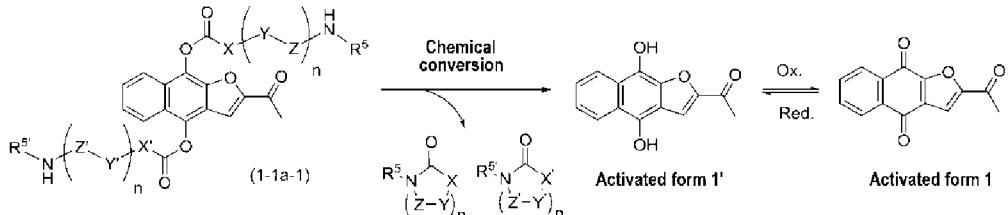
5 [0357]

Compounds represented by formulas (1A), (1), and (1-1a)-(3-4c) and pharmaceutically acceptable salts thereof exhibit high water-solubility suitable for oral administration and parenteral administration, and have at 10 least one or more primary or secondary nitrogen atoms at a terminal. Due to this structural feature, formulas (1A), (1), and (1-1a)-(3-4c) act as prodrugs that are converted to an active form by chemical conversion. As used herein, the chemical conversion means the conversion to an activated 15 form *in vivo* via a route other than the enzymatic conversion.

For example, as represented by the following formulas:

[0358]

[Chem. 35]



20 wherein each symbol is defined the same as item 1 or 2, a representative compound of formula (1A) or (1) represented by formula (1-1a-1), wherein A¹ and A² is -COB, R¹, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are hydrogen atoms, B is formula (B), and V is -NHR⁵, is chemically converted to an active form represented 25 by Activated form 1 as a result of that the nitrogen atoms respectively bound to terminal R⁵ and R^{5'}, attack the corresponding carbonyl carbons *in vivo*.

It should be noted that Activated form 1 is an isomer that can be equilibrated with Activated form 1', where they

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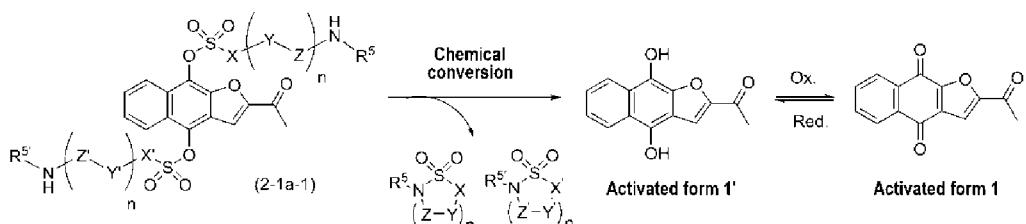
have a relationship between an oxidant and a reductant, and can be considered to be synonymous therewith.

[0359]

In a similar way to the above, as described below, a compound represented by formula (2-1a-1), wherein A¹ and A² are -SO₂B, R¹, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are hydrogen atoms, B is formula (B), and V is -NHR⁵, is chemically converted to an active form represented by Activated form 1 as a result of that the nitrogen atoms respectively bound to terminal R⁵ and R^{5'} attack the corresponding sulfur atoms *in vivo*. It should be noted that each symbol in the formulas is defined the same as item 1 or 2.

[0360]

[Chem. 36]



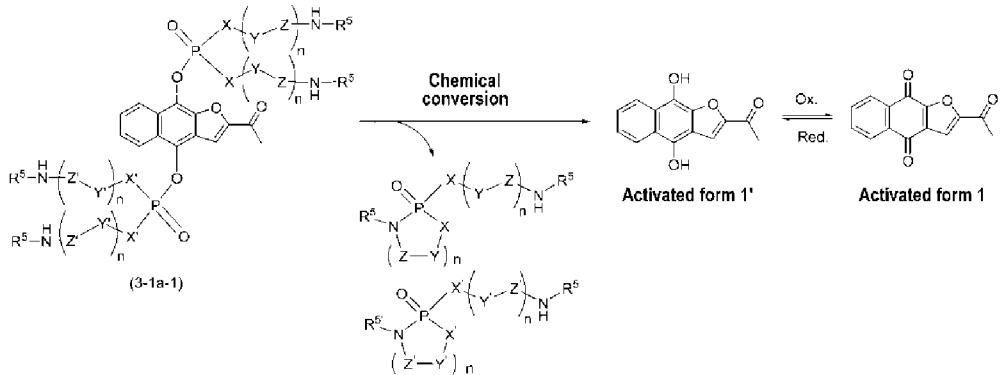
15

[0361]

In a similar way to the above, as described above, a compound represented by formula (3-1a-1), wherein A^1 and A^2 are $-P(=O)B_2$, R^1 , R^{2A} , R^{2B} , R^{2C} , and R^{2D} are hydrogen atoms, 20 B is formula (B), and V is $-NHR^5$, is chemically converted to an active form represented by Activated form 1 as a result of that the nitrogen atoms respectively bound to terminal R^5 and $R^{5'}$, attack the corresponding phosphorus atoms *in vivo*. It should be noted that each symbol in the formulas is defined 25 the same as item 1 or 2.

[0362]

[Chem. 37]



[0363]

Likewise the above-described formulas (1-1a-1), (2-1a-1), and (3-1a-1), also regarding formulas (1A), (1), 5 (1-1a), (1-1b), (1-1c), (1-2a), (1-2b), (1-2c), (1-3a), (1-3b), (1-3c), (1-4a), (1-4b), (1-4c), (1-5a), (1-5b), (1-5c), (1-6a), (1-6b), (1-6c), (2-1a), (2-1b), (2-1c), (2-2a), (2-2b), (2-2c), (2-3a), (2-3b), (2-3c), (2-4a), (2-4b), (2-4c), (3-1a), (3-1b), (3-1c), (3-2a), (3-2b), 10 (3-2c), (3-3a), (3-3b), (3-3c), (3-4a), (3-4b), and (3-4c), in a similar way to the above, the terminal primary or secondary nitrogen atoms attack the corresponding carbon, sulfur, or phosphorus atoms to produce Activated form 1 through chemical conversion.

[0364]

The present compound is provided, for example, as an anticancer agent. Although the type of cancer to which it is applied is not limited, specific examples thereof include acute leukemia, chronic lymphocytic leukemia, chronic 20 myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, 25 rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, endometrial cancer, cervical cancer,

urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma. Hematological cancer in the present invention is an idea encompassing lymphoma and leukemia, and has an effect to reduce or annihilate carcinoma or to inhibit the growth of carcinoma for the purposes of preventing /or treating cancer. It should be noted that in the present invention, "prevention (preventing)" or "prophylaxis" is an action to administer an active ingredient of the present invention to a healthy human that does not develop a disease, and a purpose thereof is, for example, to prevent the onset of a disease. "Treatment (treating)" is an action to administer an active ingredient of the present invention to a person (patient) diagnosed as developing a disease by a medical doctor, and a purpose thereof is, for example, to alleviate the disease and symptoms, to inhibit the growth of carcinoma, or to return it to a state prior to the onset of the disease. In addition, even when the purpose of administration is to prevent a disease or symptoms from deteriorating or carcinoma from growing, if it is administered to a patient, it is an action for therapy.

[0365]

When the present compound is administered, the amount of the compound used varies depending on symptoms, age, administration method, and the like. For example, in the case of intravenous injection, an effect is expected by administering to an adult 0.01 mg as the lower limit (preferably 0.1 mg) and 1000 mg as the upper limit (preferably 30 mg) once or in several batches daily depending on the symptoms. Examples of its administration schedule include single-dose administration, once a day

administration for three days in a row, and the like. Further, each administration described above can be repeated at intervals of about 7 days to about 60 days.

5 In the case of oral administration, it is desirable to administer to an adult 0.01 mg as the lower limit (preferably 1 mg) and 5000 mg as the upper limit (preferably 500 mg) once or in several batches daily depending on the symptoms. [0366]

10 The compound of the present invention can be formulated using a suitable dosage form to administer by parenteral administration or oral administration. Examples of the dosage form include, but not limited to, a tablet, a capsule, powder, granules, a solution, a suspension, an injection, a patch, a poultice, and the like. A formulation is produced 15 by a known method using a pharmaceutically acceptable additive.

20 The following can be used as an additive according to an object: excipient, disintegrator, binder, fluidizer, lubricant, coating agent, solvent, solubilizing agent, thickener, dispersing agent, stabilizing agent, sweetener, flavoring agent, and the like. Specific examples thereof include lactose, mannitol, crystalline cellulose, hydroxypropyl cellulose having low substitution degree, corn starch, partially pregelatinized starch, carmellose 25 calcium, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, magnesium stearate, sodium stearyl fumarate, polyethylene glycol, propylene glycol, titanium oxide, talc, and the like.

30 [0367]

A solution for injection includes solution, suspension, emulsion, and the like. Examples thereof include water-solution, water-propylene glycol solution, and the

like. The solution can be produced in form of a solution of polyethylene glycol or/and propylene glycol that may contain water. A solution suitable for oral administration can be produced by adding the present compound to water, 5 and as necessary adding a coloring agent, flavoring agent, stabilizing agent, sweetener, solvent, thickener, or the like. In addition, a solution suitable for oral administration can be produced by adding the present compound with a dispersing agent to water and thickening 10 it. Examples of the thickener include pharmaceutically acceptable naturally-occurring or synthetic gum, resin, methylcellulose, sodium carboxymethylcellulose, known suspending agent, and the like.

[0368]

15 It is possible to more effectively perform prophylactic treatment of cancer by combining one to three types selected from the group consisting of: (1) administering an effective amount of the present compound; and (2) (i) administering an effective amount of another anticancer agent, (ii) 20 administering an effective amount of a hormonal therapeutic agent; and (iii) non-pharmacological therapy. Examples of non-pharmacological therapy include surgery, radiotherapy, gene therapy, thermotherapy, cryotherapy, laser cauterization therapy, and the like. Two or more types of 25 these also can be combined.

[0369]

30 In one embodiment, a first active substance and a second active substance used in the present invention are administered in therapeutically and/or prophylactically effective amounts. Meanwhile, in another embodiment, the amount of the first active substance administered and/or the amount of the second active substance administered are less than a therapeutically and/or prophylactically

effective amount when administered alone, however, both may be administered in therapeutically and/or prophylactically effective amounts when they are combined. It is because the action mechanism of the first active substance of the present invention or the compound of the present invention or a pharmaceutically acceptable salt is different from that of anticancer agents and the like used as the second active substance and thus synergic action greater than that of the combination of general anticancer agents is expected.

5 10 [0370]

The present compound can be used in combination with another drug for purpose of enhancing its effect. Specifically, the present compound can be used in combination with a drug selected from the group consisting of a hormonal therapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, a biological agent, a cell growth factor inhibitor, a cell growth factor receptor inhibitor, a radiotherapeutic agent, an adjuvant agent, and an auxiliary agent. Hereinafter, a drug that may be used in combination with the present compound is abbreviated to a combination drug.

20 25 The present compound, even when used as a single agent, exhibits excellent anticancer effect, and further the combination use with one or several of the above-described combination drugs (polypharmacy) can further enhance its effect or improve the QOL of a patient.

[0371]

30 Examples of "hormonal therapeutic agents" include an adrenal cortical hormone-based agent (e.g., a steroid-based anti-inflammatory drug, an estrogen formulation, a progesterone formulation, an androgen formulation, and the like), an antiestrogen agent, an estrogen adjusting agent, an estrogen synthesis inhibitor, an anti-androgen agent,

an androgen adjusting agent, an androgen synthesis agent, a LH-RH agonist formulation, a LH-RH antagonist formulation, an aromatase inhibitor, a steroid lactonase inhibitor, a pill formulation, retinoid and a pharmaceutical agent to 5 delay the metabolism of retinoid, and the like.

[0372]

Examples of "hormonal therapeutic agents" include Fosfestrol, Diethylstilbestrol, Fluoxymesterone, Chlorotrianisene, Medroxyprogesterone acetate, Megestrol acetate, Chlormadinone acetate, Cyproterone acetate, Danazol, Dienogest, Asoprinsil, Allylestrenol, Gestrinone, Nomegestrol, Tadenan, Mepartricin, Raloxifene, Ormeloxifene, Levormeloxifene, Tamoxifen citrate, Toremifene citrate, Idoxifene, a pill formulation, 15 Mepitiostane, Testololactone, Aminoglutethimide, Goserelin acetate, Buserelin, Leuprorelin, Leuprolide, Droloxifene, Epitiostanol, ethynodiol estradiol sulfonate, Fadrozole hydrochloride, Anastrozole, Tetrazole, Ketoconazole, Letrozole, Exemestane, Vorozole, Formestane, 20 Exemestane, Flutamide, Bicalutamide, Nilutamide, Enzalutamide, Mifepristone, Finasteride, Dexamethasone, Prednisolone, Betamethasone, Triamcinolone, Abiraterone, and Liarozole, Bexarotene, DN101, and the like.

[0373]

25 As "chemotherapeutic agents", for example, alkylating agents, antimetabolites, topoisomerase inhibiting drugs, DNA intercalators, antimitotic agents, anticancer antibiotics, plant-derived anticancer agents, epigenome drugs, immunomodulators, molecule-targeting therapeutic drugs, angiogenesis inhibitors, and other chemotherapeutic agents, and the like are used. Representative examples are 30 described below.

[0374]

Examples of "alkylating agents" include Nitrogen mustard, Nitrogen mustard N-oxide hydrochloride, Chlorambucil, Cyclophosphamide, Ifosfamide, Thiotapec, Carboquone, Imrosulfan tosylate, Busulfan, Nimustine hydrochloride, Mitobronitol, Melphalan, Dacarbazine, Ranimustine, Estramustine phosphate sodium, Triethylenemelamine, Carmustine, Lomustine, Streptozocin, Pipobroman, Etoglucide, Carboplatin, Cisplatin, Miboplatin, Nedaplatin, Oxaliplatin, Altretamine, Ambamustine, Dibrospidium chloride, Fotemustine, Prednimustine, Pumitepa, Ribomustin, Temozolomide, Treosulfan, Trofosfamide, Zinostatin stimalamer, Adozelesin, Cystemustine, Bizelesin, Mechlorethamine, Uracil mustard, Streptozocin, Satraplatin, Trabectedin, Bevacizumab, Chlormethine, Bendamustine, Uramustine, Semustine, Triplatin tetranitrate, Mannosulfan, Triaziquone, Procarbazine, Canfosfamide, Nitrosourea, and DDS formulations thereof, and the like.

[0375]

Examples of "antimetabolites" include "a folic acid antagonist", "a pyrimidine metabolism-inhibiting drug", "a purine metabolism-inhibiting drug", "a ribonucleotide reductase inhibiting drug", and "a nucleotide analog".

[0376]

Examples of "antimetabolites" include Mercaptopurine, 6-Mercaptopurine riboside, Thioinosine, Methotrexate, Pemetrexed, Enocitabine, Cytarabine, Cytarabin ocfosfate, Ancitabine hydrochloride, 5-FU type pharmaceutical agent (e.g., Fluorouracil, Tegafur, UFT, Doxifluridine, Carmofur, Galocitabine, Emitefur, Capecitabine, and the like), Aminopterin, Nelzarabine, Leucovorin calcium, tabloid, Butocin, calcium folinate, calcium levofolinate, Cladribine, Emitefur, Fludarabine, Gemcitabine,

hydroxycarbamide, Pentostatin, Piritrexim, Idoxuridine, Mitoguazone, Tiazofurin, Ambamustine, Bendamustine, Floxuridine, Nelarabine, Leucovorin, Hydroxyurea, Thioguanine, Asparaginase, Bortezomib, Raltitrexed, 5 Clofarabine, Enocitabine, Sapacitabine, Azacytidine, Sulfadiazine, Sulfamethoxazole, Trimethoprim, and DDS formulations thereof, and the like.

[0377]

Examples of topoisomerase inhibiting drugs include Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Anthracenedione, Mitoxantrone, Mitomycin C, Bleomycin, Dactinomycin, Plicamycin, Irinotecan, Camptothecin, Rubitecan, Belotecan, Etoposide, Teniposide, Topotecan, Amsacrine, and DDS formulations thereof, and the like.

15 [0378]

Examples of DNA intercalators include Proflavine, Doxorubicin (Adriamycin), Daunorubicin, Dactinomycin, Thalidomide, and DDS formulations thereof, and the like.

[0379]

20 Examples of antimitotic agents include Paclitaxel, Paclitaxel derivatives (e.g., DHA Paclitaxel, Paclitaxel Polyglutamate, Nab-paclitaxel, Paclitaxel Micelle, 7α -Glucosyloxyacetylpaclitaxel, BMS-275183, and the like), Docetaxel, Vinorelbine, Vincristine, Vinblastine, 25 Vindesine, Vinzolidine, Etoposide, Teniposide, Ixabepilone, Larotaxel, Orataxel, Tesetaxel, Ispinesib, Colchicine, Vinflunine, and DDS formulations thereof, and the like.

[0380]

30 Examples of "anticancer antibiotics" include Actinomycin D, Actinomycin C, Mitomycin C, Chromomycin A3, Bleomycin hydrochloride, Bleomycin sulfate, Peplomycin sulfate, Daunorubicin hydrochloride, Doxorubicin hydrochloride, Aclarubicin hydrochloride, Pirarubicin

hydrochloride, Epirubicin hydrochloride, Neocarzinostatin, Mithramycin, Sarkomycin, Carzinophilin, Mitotane, Zorubicin hydrochloride, Mitoxantrone hydrochloride, Idarubicin hydrochloride, Mithramycin, and DDS formulations thereof, and the like.

5

[0381]

Examples of "plant-derived anticancer agents" include Etoposide, Etoposide phosphate, Vinblastine sulfate, Vincristine sulfate, Vindesine sulfate, Teniposide, 10 Paclitaxel, Docetaxel, DJ-927, Vinorelbine, Irinotecan, Topotecan, and DDS formulations thereof, and the like.

[0382]

Examples of "epigenome drugs" include a histone deacetylase (HDAC) inhibitor, a DNA methyltransferase (DNMT) inhibitor, and the like.

15

[0383]

Examples of "epigenome drugs" include Vorinostat, Belinostat, Entinostat, Romidepsin, Azacytidine, Decitabine, and DDS formulations thereof, and the like.

20

[0384]

Examples of "immunomodulators" include Thalidomide, Lenalidomide, Pomalidomide, and DDS formulations thereof, and the like.

[0385]

25

"A molecule-targeting therapeutic drug" may be a low molecular compound or an antibody. Examples of "molecule-targeting therapeutic drugs" include a kinase inhibitor, a proteasome inhibitor, a monoclonal antibody, a mTOR inhibitor, a TNF inhibiting drug, and a T-cell 30 inhibiting drug, and the like.

[0386]

Examples of "kinase inhibitors" include a tyrosine kinase inhibitor, a serine/threonine kinase inhibitor, a

Raf kinase inhibitor, a CDK (cyclin-dependent kinase) inhibitor, a MEK (mitogen-activated protein kinase) inhibitor, and the like.

[0387]

5 Examples of "kinase inhibitors" include Imatinib, Gefitinib, Erlotinib, Afatinib, Dasatinib, Bosutinib, Vandetanib, Sunitinib, Axitinib, Pazopanib, Lenvatinib, Lapatinib, Nintedanib, Nilotinib, Crizotinib, Ceritinib, Alectinib, Ruxolitinib, Tofacitinib, Ibrutinib, Sorafenib, 10 Vemurafenib, Dabrafenib, Palbociclib, Trametinib, Regorafenib, Cediranib, Lestaurtinib, Vandetinib, Vatalanib, Seliciclib, Tivantinib, Canertinib, Pelitinib, Tesevatinib, Cediranib, Motesanib, Midostaurin, Foretinib, Cabozantinib, Selumetinib, Neratinib, Volasertib, 15 Saracatinib, Enzastaurin, Tandutinib, Semaxanib, Alvocidib, ICR-62, AEE788, PD0325901, PD153035, TK787, BBI503, and DDS formulations thereof, and the like.

[0388]

20 Examples of "proteasome inhibitors" include Bortezomib, Carfilzomib, and DDS formulations thereof, and the like.

[0389]

25 Examples of "monoclonal antibodies" include an anti-CD22 antibody, an anti-CD20 antibody, an anti-CD25 antibody, an anti-CD30 antibody, an anti-CD33 antibody, an anti-CD5 antibody, an anti-CD52 antibody, an anti-epidermal growth factor receptor antibody (an EGFR antibody), an anti-endothelial cell growth factor antibody (an VEGF antibody), an anti-TNF- α antibody, an anti-IL-1 receptor antibody, an anti-IL-2 receptor antibody, an anti-IL-5 receptor antibody, an anti-IL-6 receptor antibody, an anti-HER2 antibody, an anti-IgE antibody, an anti-IgG antibody, an anti-RS virus antibody, an anti-CCR4 antibody, 30 an anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen

4, CD152) antibody, an anti-PD-1 antibody, an anti-RANKL (receptor activator of nuclear factor κ B ligand) antibody, an anti-c-Met antibody, and the like.

[0390]

5 Examples of "monoclonal antibodies" include Ibrutumomab tiuxetan, Rituximab, Cetuximab, Infliximab, Basiliximab, Brentuximab vedotin, Tocilizumab, Trastuzumab, Bevacizumab, Omalizumab, Mepolizumab, Gemtuzumab, ozogamicin, Palivizumab, Ranibizumab, Certolizumab, 10 Ocrelizumab, Mogamulizumab, Eculizumab, Pertuzumab, Alemtuzumab, Inotuzumab, Panitumumab, Ofatumumab, Golimumab, Adalimumab, Ramucirumab, Nivolumab, Infliximab, Anakinra, Denosumab, Ipilimumab, Pembrolizumab, matuzumab, and DDS formulations thereof, and the like.

15 [0391]

Examples of "mTOR inhibitors" include Everolimus, Rapamycin (Sirolimus), Temsirolimus, and DDS formulations thereof, and the like.

[0392]

20 Examples of "TNF inhibiting drugs" include Etanercept and the like.

[0393]

Examples of "T-cell inhibiting drugs" include Abatacept and the like.

25 [0394]

Examples of "angiogenesis inhibitors" include CM101, IFN- α , IL-12, platelet factor-4, Suramin, Semaxanib, Thrombospondin, a VEGFR antagonist, an angiogenesis inhibiting steroid plus heparin, cartilage-derived 30 angiogenesis inhibitory factor, a matrix metalloproteinase inhibitor, Batimastat, Marimastat, Angiostatin, Endostatin, 2-methoxyestradiol, Tecogalan, Thrombospondin, an α V β 3 inhibitor, Linomide, ADH-1, and DDS formulations thereof,

and the like.

[0395]

Examples of "other chemotherapeutic agents" include Sobuzoxane, Obatoclax, Efaproxiral, Tipifarnib, Lonafarnib, 5 and the like.

[0396]

Examples of "immunotherapeutic agents (BRM)" include Picibanil, Krestin, Sizofiran, Lentinan, Ubenimex, interferon, interleukin, macrophage colony stimulating factor, 10 granulocyte-colony stimulating factor, Erythropoietin, Lymphotoxin, BCG vaccine, Corynebacterium parvum, Levamisole, polysaccharide K, Procodazole, anti-CTLA4 antibody, PD-1 antibody, Toll-like Receptors agonist (e.g., TLR7 agonist, TLR8 agonist, TLR9 agonist, 15 and the like).

[0397]

Examples of "biological agents" include Interleukin-2 (Aldesleukin), Interferon- α , Interferon- β , Interferon- γ , Erythropoietin (EPO), granulocyte CSF (Filgrastim), 20 granulocytes, macrophage CSF (Sargramostim), IL13-PE38QQR, Bacillus Calmette-Guerin, Levamisole, Octreotide, CPG7909, Provence, GVAX, Myvax, Favld, Lenalidomide, Trastuzumab, Rituximab, Gemtuzumab ozogamicin, Alemtuzumab, Endostatin, Ibritumomab tiuxetan, Tositumomab, Cetuximab, Zanolimumab, 25 Ofatumumab, HGS-ETR1, Pertuzumab, M200, SGN-30, matuzumab, Adecatumumab, Denosumab, Zalutumumab, MDX-060, Nimotuzumab, MORAb-003, Vitaxin, MDX-101, MDX-010, a DPC4 antibody, a NF-1 antibody, a NF-2 antibody, a Rb antibody, a p53 antibody, 30 a WT1 antibody, a BRCA1 antibody, a BRCA2 antibody, Ganglioside (GM2), a prostate-specific antigen (PSA), α -Fetoprotein (AFP), a carcinoembryonic antigen (CEA), a melanoma-associated antigen (MART-1, gap 100, MAGE 1,3 tyrosine), and Papilloma virus E6 and E7 fragments, and DDS

formulations thereof, and the like.

[0398]

A cell growth factor may be any substance as long as it promotes cell growth. Generally, they include a factor 5 that is a peptide having a molecular weight of 20,000 or less and exhibits an effect at a low concentration by binding with a receptor. Examples of "cell growth factors" include epidermal growth factor (EGF), insulin-like growth factor (IGF) (e.g., insulin, IGF-1, IGF-2, and the like), 10 transforming growth factor (TGF) (e.g., TGFalpha, TGF-beta), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vesicular endothelial growth factor (VEGF), colony stimulating factor (CSF) (e.g., Granulocyte-colony stimulating factor (G-CSF)), 15 granulocyte-macrophage-colony stimulating factor (GM-CSF), platelet-derived growth factor (PDGF), erythropoietin (EPO), fibroblast growth factor (FGF) (e.g., acidic FGF, basic FGF, KGK (keratinocyte growth factor), FGF-10, and the like), hepatocyte growth factor (HGF), heregulin, 20 angiopoietin, and the like. It should be noted that cell growth factor is synonymous with growth factor.

[0399]

Examples of "cell growth factor inhibitors" include an epidermal growth factor inhibitor (an EGF inhibitor), an 25 insulin-like growth factor inhibitor (an IGF inhibitor), a nerve growth factor inhibitor (a NGF inhibitor), a brain-derived neurotrophic factor inhibitor (a NGF inhibitor), a vesicular endothelial growth factor inhibitor (a VEGF inhibitor), a colony stimulating factor inhibitor (a CSF inhibitor), a platelet-derived growth factor inhibitor (a PDGF inhibitor), an erythropoietin inhibitor (a EPO inhibitor), a fibroblast growth factor inhibitor (a FGF inhibitor), a hepatocyte growth factor inhibitor (a HGF

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inhibitor), a heregulin inhibitor, an angiopoietin inhibitor, and the like. It should be noted that cell growth factor inhibitor is synonymous with growth factor inhibitor.

5 [0400]

Examples of "cell growth factor receptor inhibitors" include an epidermal growth factor receptor inhibitor (an EGFR inhibitor), an insulin-like growth factor receptor inhibitor (an IGFR inhibitor), a nerve growth factor receptor inhibitor (a NGFR inhibitor), a brain-derived neurotrophic factor receptor inhibitor (a NGFR inhibitor), a vesicular endothelial growth factor receptor inhibitor (a VEGFR inhibitor), a colony stimulating factor receptor inhibitor (a CSFR inhibitor), a platelet-derived growth factor receptor inhibitor (a PDGFR inhibitor), an erythropoietin receptor inhibitor (an EPOR inhibitor), a fibroblast growth factor receptor inhibitor (a FGFR inhibitor), a hepatocyte growth factor receptor inhibitor (a HGFR inhibitor), a heregulin receptor inhibitor, an angiopoietin receptor inhibitor, and the like. It should be noted that cell growth factor receptor inhibitor is synonymous with growth factor receptor inhibitor.

10 [0401]

Examples of "radiotherapeutic agents" include a radioactive substance, a radioactive sensitizer, and the like.

15 [0402]

Examples of "auxiliary agents" include Aprepitant, Ondansetron, Lorazepam, Dexamethason, Diphenhydramine, Ranitidine, Cimetidine, Ranitidine, Famotidine, Cimetidine, Procrit, Epoetin alfa, Filgrastim, Oprelvekin, Leucovorin, granulocyte·macrophage colony stimulating factor, and the like.

[0403]

As another embodiment, the present compound can be used in combination with Decitabine, Canfosfamide, Efaproxiral, Tipifarnib, Lonafarnib, Tamoxifen, Toremifene, Raloxifene, 5 Droloxifene, Idoxifene, Megestrol Acetate, Anastrozole, Letrozole, Vorozole, Exemestane, Flutamide, Nilutamide, Bicalutamide, Cyproterone Acetate, Goserelin Acetate, Leuprolide, Finasteride, a metalloprotease inhibitor, a 10 urokinase plasminogen activator receptor function inhibitor, a growth factor inhibitor, a growth factor receptor inhibitor, Bevacizumab, Cetuximab, a serine/threonine kinase inhibitor, Methotrexate, Fluorouracil, a purine and adenosine analogue, Cytarabine, Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, 15 Mitomycin C, Dactinomycin, Mithramycin, Cisplatin, Carboplatin, Nitrogen mustard, Melphalan, Chlorambucil, Busulfan, Cyclophosphamide, Ifosfamide, Nitrosourea, Thiotepa, Vincristin, Vinorelbine, Vinblastine, Vinflunine, Paclitaxel, Docetaxel, an Epothilone analogue, a 20 Discodermolide analogue, an Eleutherobin analogue, Etoposide, Teniposide, Amsacrine, Topotecan, Alvocidib, a proteasome inhibitor, an androgen receptor antagonist, a LH-RH derivative, a LH-RH antagonist, a Taxane analogue, an estrogen receptor antagonist, and DDS formulations 25 thereof, and the like.

[0404]

Examples of combination drugs with the present compound include, preferably, Cisplatin, Oxaliplatin, Temozolomide, Pemetrexed, Fluorouracil, Capecitabine, Gemcitabine, 30 Leucovorin, Bortezomib, Irinotecan, Paclitaxel, Imatinib, Ibrutinib, Sorafenib, Regorafenib, Bortezomib, Cetuximab, Bevacizumab, Panitumumab, Nivolumab, Ipilimumab, Pembrolizumab, and Dexamethasone.

[0405]

The period of administration of the present compound and a combination pharmaceutical agent is not limited, and these may be administered concurrently or at intervals to 5 a subject to be administered. In addition, a mixture of the present compound and a combination pharmaceutical agent may be made. The dosage of a combination pharmaceutical agent can be appropriately selected using clinically used dose as criteria. In addition, the mixing ratio of the present 10 compound and a combination pharmaceutical agent can be appropriately selected depending on a subject to be administered, an administration route, target disease, symptoms, combinations, and the like. For example, when a subject to be administered is a human, 0.01 to 100 parts 15 by weight of a combination pharmaceutical agent may be used relative to one part by weight of the present compound. In addition, for purpose of inhibiting its side effect, they can be used in combination with a pharmaceutical agent (a combination pharmaceutical agent) such as an antiemetic 20 agent, a sleep-inducing agent, an anticonvulsant, and the like.

[0406]

Hereinafter, the present invention is further specifically described with reference examples, Examples, 25 and test examples set forth. However, these do not limit to the present invention. It should be noted that the identification of a compound was performed with an elemental analysis value, a mass spectrum, a high performance liquid chromatography mass spectrometer; LC-MS, IR spectra, NMR 30 spectra, high performance liquid chromatography (HPLC), and the like.

[0407]

Hereinafter, the present invention is more specifically

described with reference examples, Examples, and test examples. However, the scope of the present invention is certainly not limited to these examples. It should be noted that compound names shown in the following reference 5 examples and Examples do not always follow the IUPAC nomenclature. It should be noted that although abbreviations are sometimes used to simplify a description, these abbreviations are defined the same as the above descriptions.

10 In the present specification, the following abbreviations are sometimes used.

In NMR and MS data of reference examples and Examples, the following abbreviations are used.

[0408]

15 Me: a methyl group

Et: an ethyl group

Ns: a 2-nitrobenzenesulfonyl group

Ts: a para-toluenesulfonyl group

tert: tertiary

20 t - Bu: a tert - butyl group

Boc: a tert-butoxycarbonyl group

DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

25 HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N''-tetramethyluronium hexafluorophosphate

HOBT: 1-hydroxybenzotriazole

NMP: N-methylpyrrolidone

THF: tetrahydrofuran

30 WSC•HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

s: singlet

brs: broad singlet

d: doublet

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dd: double doublet
t: triplet
q: quartet
m: multiplet
5 br: broad
J: coupling constant
Hz: Hertz
CDCl₃: deuterated chloroform
DMSO-d₆: deuterated dimethyl sulfoxide
10 [0409]

High performance chromatography mass spectrometry; The measurement condition of LC-MS is as described below, an observed mass analysis value [MS (m/z)] is shown as [M+H]⁺, [M+2H]²⁺, [M+Na]⁺, or [M+2Na]²⁺, and a retention time is shown
15 as Rt (minute(s), min).

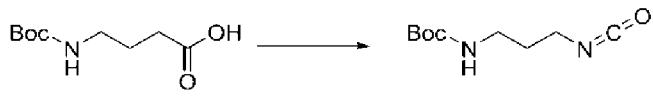
[0410]

Measurement condition

Detection instrument: ACQUITY (registered trademark) SQ
detector (WATERS)
20 HPLC: ACQUITY UPLC (registered trademark) system
Column: WATERS ACQUITY UPLC (registered trademark) BEH C18
(1.7 um, 2.1 mm X 30 mm)
Solvent: Solution A: 0.06% formic acid/H₂O, Solution B:
0.06% formic acid/MeCN
25 Gradient condition: 0.0-1.3 min linear gradient from B 2%
to 96%
Flow rate: 0.8 mL/min
UV: 220 nm and 254 nm
[Examples]
30 [0411]
Reference example 1
tert-Butyl (3-isocyanatopropyl)carbamate
[0412]

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[Chem. 38]



Reference example 1

[0413]

5 Diisopropylethylamine (4.35 mL) and diphenylphosphoryl azide (4.71 mL) were added to a solution of 4-((tert-butoxycarbonyl)amino)butanoic acid (4.23 g) in toluene (41.6 mL). The reaction mixture was then stirred at room temperature for 15 minutes. After further stirring 10 at 80°C for 1 hour, the reaction solution was cooled to room temperature to yield a solution of Reference example 1 in toluene. The resulting solution was used in the next reaction as it was.

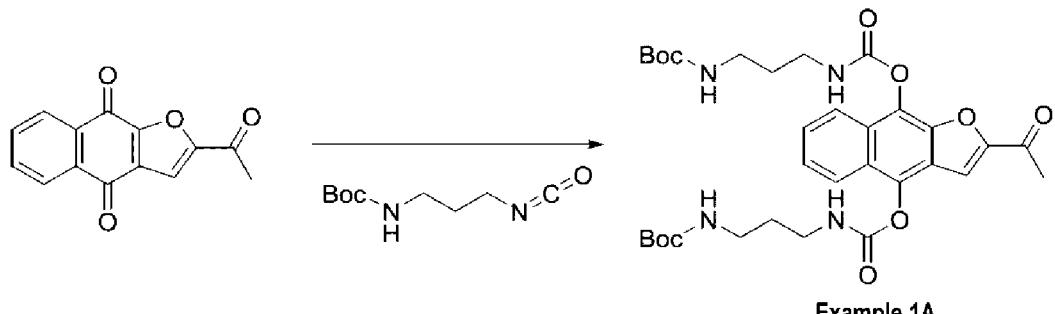
[0414]

Example 1A

15 2-Acetylnaphtho[2,3-b]furan-4,9-diy1 bis((3-((tert-butoxycarbonyl)amino)propyl)carbamate)

[0415]

[Chem. 39]



Example 1A

20 [0416]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (1.00 g), zinc (1.09 g), sodium dithionite (3.62 g), diisopropylethylamine (7.25 mL), tetra-n-butylammonium bromide (134 mg) in N,N-dimethylformamide (59.5 mL) was

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stirred under nitrogen atmosphere at room temperature for 1 hour. Then, the suspension was cooled to 0°C, and the solution of tert-butyl (3-isocyanatopropyl)carbamate in toluene, which was prepared in Reference example 1, was added dropwise thereto over 15 minutes. After further stirring at room temperature for 1 hour, ethyl acetate and aqueous saturated ammonium chloride solution were added to the reaction solution. After the resulting mixture was filtered through Celite, the filtrate was distributed between an organic layer and an aqueous layer. The aqueous layer was then extracted with ethyl acetate twice. The resulting organic layer was washed with water once and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1-1:4) to yield Example 1A (560 mg).

(LC-MS: $[M-t\text{-}Bu]^+/\text{Rt}$ (min)) = 587/1.05

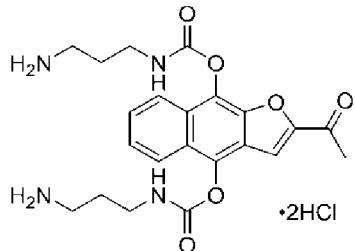
[0417]

20 Example 1

2-Acetylnaphtho[2,3-b]furan-4,9-diyl bis((3-aminopropyl)carbamate)dihydrochloride

[0418]

[Chem. 40]



25 **Example 1**

[0419]

A 4 mol/L hydrochloric acid/dioxane solution (20.0 mL)

was added to Example 1A (733 mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 1 (568 mg).

5 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 1.80-1.91 (4H, m), 2.63 (3H, s), 2.86-2.95 (4H, m), 3.21-3.29 (4H, m), 7.60-7.70 (2H, m), 7.87-7.99 (6H, m), 7.99-8.07 (2H, m), 8.07 (1H, s), 8.44-8.50 (2H, m).

(LC-MS: $[\text{M}+2\text{H}]^{2+}/\text{Rt}$ (min)) = 222/0.36

10 [0420]

Reference example 3

3-((tert-butoxycarbonyl)amino)propionic acid

[0421]

[Chem. 41]



15

[0422]

Cesium carbonate (861 mg) was added to a solution of 3-((tert-butoxycarbonyl)amino)propionic acid (1.00 g) in methanol (24.0 mL) and water (2.40 mL). The reaction mixture was then stirred at room temperature for 5 minutes. The reaction solution was concentrated, and then the residue was dissolved in N,N-dimethylformamide (18.0 mL). Benzyl bromide (0.62 mL) was added dropwise thereto, and then the reaction mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated, and then ethyl acetate and water were added to the residue to separate the organic layer. The aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure to yield benzyl-3-((tert-butoxycarbonyl)amino)propionate.

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(1.50 g). This was dissolved in acetonitrile (26.0 mL), di-tert-butyl-dicarbonate (2.31 g) and N,N-dimethylaminopyridine (65.0 mg) were added to the solution, and then it was stirred for 21 hours at room 5 temperature. The reaction solution was diluted with water, and then extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica 10 gel column chromatography (hexane/ethyl acetate = 1:0 to 4:1) to yield benzyl-3-(bis(tert-butoxycarbonyl)amino)propionate (1.74 g). This was dissolved in methanol (23.0 mL), 10% palladium on carbon (500 mg) was added to the solution, and then it 15 was stirred under hydrogen atmosphere at room temperature for 1.5 hours. The reaction solution was filtered through Celite, and then the Celite was washed with methanol. The filtrate was concentrated to yield Reference example 3 (1.25 g).

20 (LC-MS: $[M-t\text{-Bu}]^+/\text{Rt}$ (min)) = 234/0.86

[0423]

Example 2A

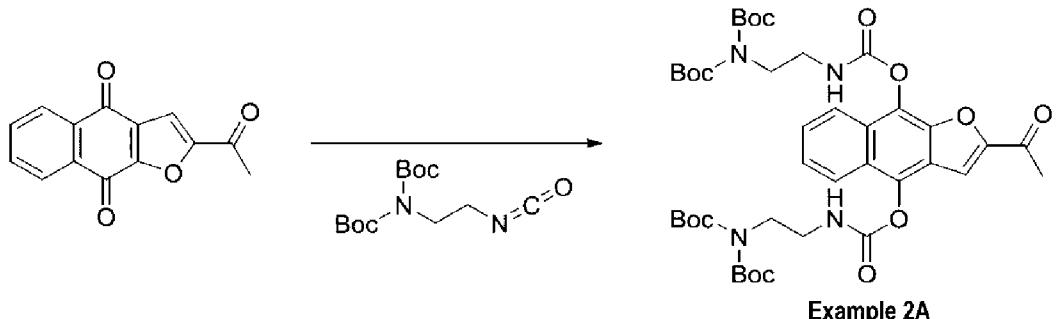
tert-Butyl

25 (2-(((2-acetyl-4-(((2-(bis(tert-butoxycarbonyl)amino)ethyl)carbamoyl)oxy)naphtho[2,3-b]furan-9-yl)oxy)carbonyl)amino)ethyl) (tert-butoxycarbonyl)carbamate

[0424]

[Chem. 42]

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[0425]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (100 mg), zinc (109 mg), sodium dithionite (362 mg), 5 diisopropylethylamine (0.73 mL), and tetra-n-butylammonium bromide (13.0 mg) in N,N-dimethylformamide (5.90 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of tert-butyl 10 N-((tert-butoxy)carbonyl)-N-(2-isocyanatoethyl)carbamate in toluene, which had been prepared from Reference example 3 (482 mg) by the same method as Reference example 1, was added dropwise thereto over 7 minutes. After stirring at 0°C for 30 minutes, the reaction solution was filtered 15 through Celite, and the Celite was washed with ethyl acetate. Aqueous saturated ammonium chloride solution was added to the filtrate, the organic layer was separated, and then the aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous 20 sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1-3:2) to yield Example 2A (97.0 mg). (LC-MS: [M+Na]⁺/Rt (min)) = 837/1.32

[0426]

Example 2

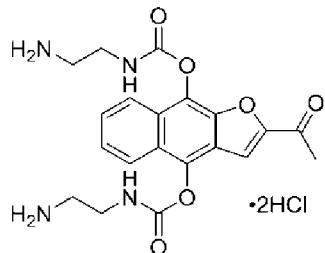
2-Acetylnaphtho[2,3-b]furan-4,9-diy1

- 200 -

bis((2-aminoethyl)carbamate) dihydrochloride

[0427]

[Chem. 43]



Example 2

5 [0428]

To Example 2A (40.0 mg) was added 4 mol/L hydrochloric acid/dioxane solution (2.00 mL). The reaction mixture was then stirred at room temperature for 1.5 hours. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 2 (20.0 mg).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.62 (3H, s), 2.98-3.07 (4H, m), 3.39-3.47 (4H, m), 7.59-7.71 (2H, m), 7.89-8.07 (6H, br), 8.07-8.20 (3H, m), 8.43-8.53 (2H, m).

(LC-MS: [M+2H]²⁺/Rt (min)) = 208/0.33

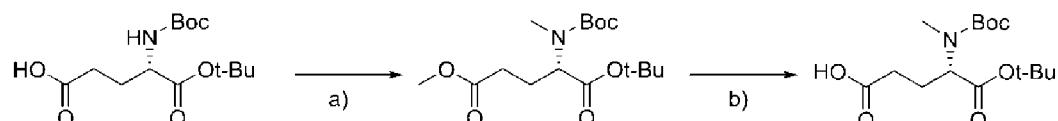
15 [0429]

Reference example 5

(S)-5-(tert-Butoxy)-4-((tert-butoxycarbonyl)(methyl)amino)-5-oxopentanoic acid

[0430]

20 [Chem. 44]



Reference example 5

[0431]

a) A suspension of sodium hydride (330 mg) in N,N-dimethylformamide (8.00 mL) was cooled to 0°C, and a

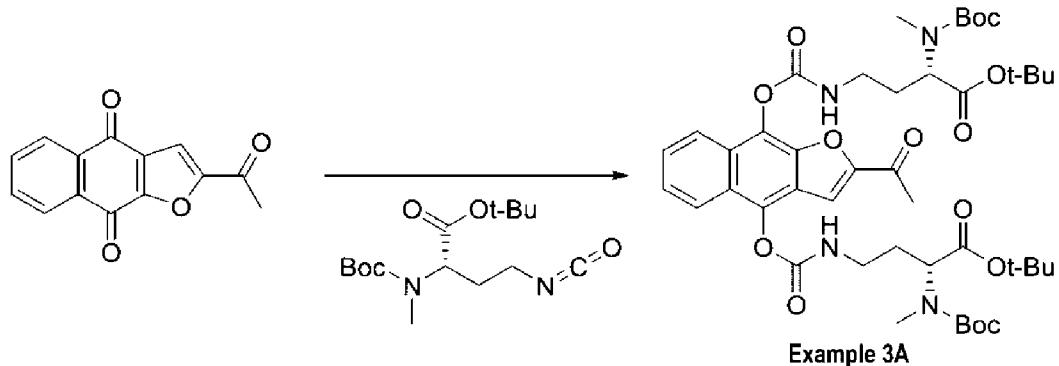
solution of ((S)-5-(tert-butoxy)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid (1.00 g) in N,N-dimethylformamide (8.00 mL) was added dropwise thereto. After stirring at 0°C for 5 30 minutes, a solution of methyl iodide (0.51 mL) in N,N-dimethylformamide (2.00 mL) was added dropwise thereto. After stirring at 0°C for 10 minutes, the reaction mixture was further stirred at room temperature for 3 hours. The reaction solution was diluted with aqueous saturated 10 ammonium chloride solution, and then extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure to yield 1-(tert-butyl)5-methyl 15 N-(tert-butoxycarbonyl)-N-methyl-L-glutamate (1.05 g). (LC-MS: [M+H]⁺/Rt (min)) = 332/1.07 [0432]
b) To a solution of 1-(tert-butyl) 5-methyl N-(tert-butoxycarbonyl)-N-methyl-L-glutamate (1.05 g) in 20 tetrahydrofuran (14.0 mL) and water (2.40 mL) was added lithium hydroxide•monohydrate (138 mg). The reaction mixture was then stirred at 50°C for 8 hours. The reaction solution was concentrated, and then suspended in methanol. The suspension was purified by a silica gel short column 25 to yield Reference example 5 (1.20 g). (LC-MS: [M+H]⁺/Rt (min)) = 318/0.90 [0433]

Example 3A
tert-Butyl
30 (S)-4-(((2-acetyl-4-(((R)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)(methyl)amino)-4-oxobutyl)carbamoyl)oxy)naptho[2,3-b]furan-9-yl)oxy)carbonyl)amino)-2-((tert-butoxycarbonyl)(methyl)amino)butanoate

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[0434]

[Chem. 45]



[0435]

5 A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (100 mg), zinc (109 mg), sodium dithionite (362 mg), diisopropylethylamine (0.725 mL), tetra-n-butylammonium bromide (13.0 mg) in N,N-dimethylformamide (5.90 mL) was stirred under nitrogen atmosphere at room temperature for 10 1 hour. The reaction mixture was then cooled to 0°C, and a solution of tert-butyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-isocyanato butanoate in toluene, which had been prepared from Reference example 5 (396 mg) by the same method as Reference example 15 1, was added dropwise thereto over 5 minutes. After stirring at 0°C for 1 hour, the reaction solution was filtered through Celite, and then the Celite was washed with 20 ethyl acetate. Aqueous saturated ammonium chloride solution was added to the filtrate, the organic layer was separated, and then the aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography 25 (hexane/ethyl acetate = 3:2-2:3) to yield Example 3A (141 mg).

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(LC-MS: $[M-\text{Boc}-\text{t-Bu}]^+/\text{Rt}$ (min)) = 715/1.34

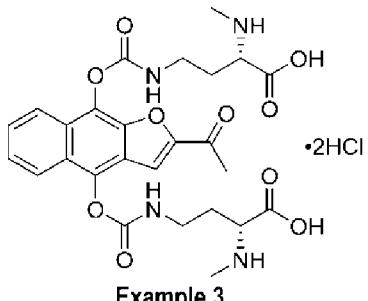
[0436]

Example 3

(S)-4-(((2-Acetyl-4-(((R)-3-carboxy-3-(methylamino)propyl)carbamoyl)oxy)naphtho[2,3-b]furan-9-yl)oxy)carbonyl amino)-2-(methylamino)butanoic acid dihydrochloride

[0437]

[Chem. 46]



Example 3

10 [0438]

A 4 mol/L hydrochloric acid/dioxane solution (10.0 mL) was added to Example 3A (140 mg). The reaction mixture was then stirred at 50°C for 1.5 hours. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 3 (102 mg).

¹H-NMR (400 MHz, D₂O) δ: 2.11-2.25 (4H, m), 2.52 (3H, s), 2.68 (6H, s), 3.31-3.50 (4H, m), 3.74-3.84 (2H, m), 7.50-7.64 (2H, m), 7.76 (1H, s), 7.95-8.03 (2H, m).

(LC-MS: $[M+2H]^{2+}/\text{Rt}$ (min)) = 280/0.38

20 [0439]

Reference example 7

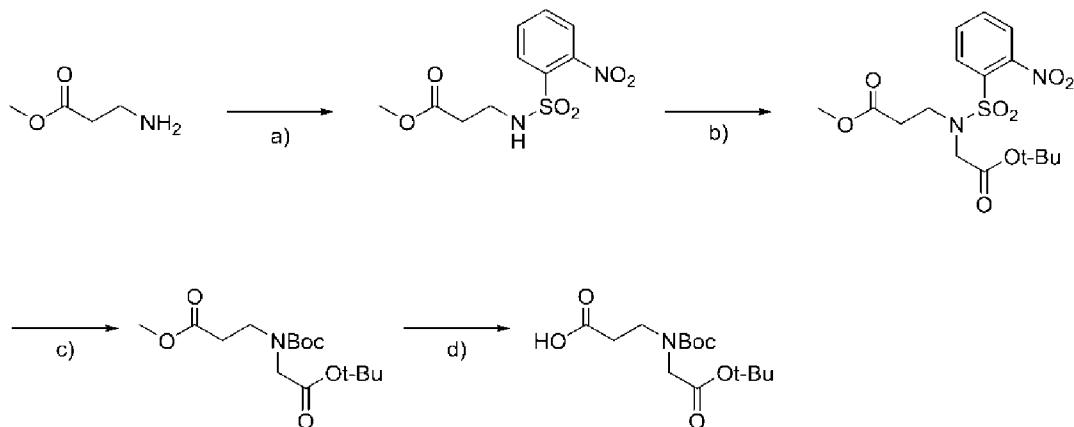
Methyl

3-((2-(tert-butoxy)-2-oxoethyl)(tert-butoxycarbonyl)amino)propionate

25 [0440]

[Chem. 47]

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**Reference example 7**

[0441]

a) Triethylamine (9.90 mL) and 2-nitrobenzenesulfonyl chloride (4.10 g) were added to a solution of methyl 3-aminopropionate (2.00 g) in methylene chloride (50.0 mL) at 0°C. The reaction mixture was then stirred at room temperature for 1 hour. The reaction solution was concentrated, ethyl acetate and saturated brine were added to the residue, and then the organic layer was separated. The aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure to yield 4-((3-methoxy-3-oxopropyl)amino)-3-nitrobenzenesulfonic acid (4.30 g).

[0442]

b) A suspension of 4-((3-methoxy-3-oxopropyl)amino)-3-nitrobenzenesulfonic acid (4.30 g), tert-butyl 2-bromoacetate (2.10 mL), and cesium carbonate (9.30 g) in acetonitrile (100 mL) was stirred at room temperature for 10 hours. The reaction solution was diluted with water, and then extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off

and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:2) to yield 4-((2-(tert-butoxy)-2-oxoethyl)(3-methoxy-3-oxopropyl)amino)-3-nitrobenzenesulfonic acid (5.00 g).

5 [0443]

c) A suspension of 4-((2-(tert-butoxy)-2-oxoethyl)(3-methoxy-3-oxopropyl)amino)-3-nitrobenzenesulfonic acid (5.00 g), benzenethiol (2.10 mL), and cesium carbonate (11.0 g) in N,N-dimethylformamide (100 mL) was stirred under nitrogen atmosphere at room temperature 2 hours. Di-tert-butyl-dicarbonate (10.0 g) was added to the reaction mixture, and then it was further stirred at room temperature 2 hours. The reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. The filtrate was concentrated, and then purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:2) to yield methyl 15 3-((2-(tert-butoxy)-2-oxoethyl)(tert-butoxycarbonyl)amino)propionate (2.40 g).

20 (LC-MS: [M+H]⁺/Rt (min)) = 318/1.06

d) A suspension of methyl 3-((2-(tert-butoxy)-2-oxoethyl)(tert-butoxycarbonyl)amino)propionate (2.40 g), and potassium trimethylsilyl anolate (1.89 g) in tetrahydrofuran (50.0 mL) was stirred under nitrogen atmosphere at room temperature for 10 hours. The reaction solution was diluted with water, and then extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-0:1) to yield Reference example 30

7 (450 mg).

(LC-MS: $[M+H]^+$ /Rt (min)) = 304/0.90

[0444]

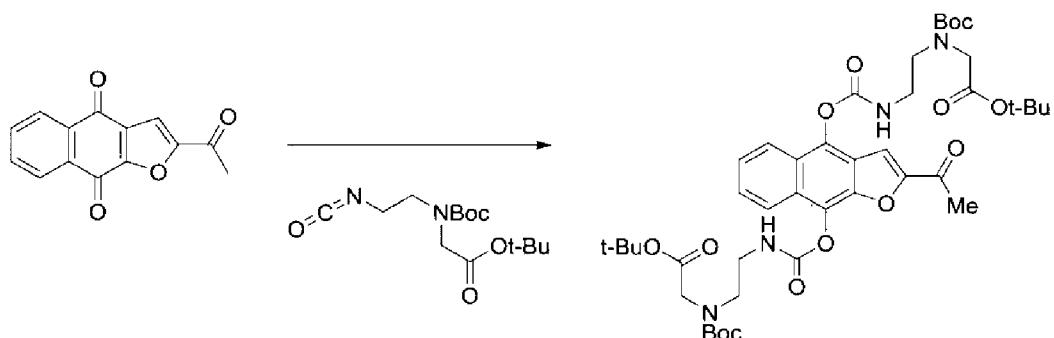
Example 4A

5 Di-tert-butyl

2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis((tert-butoxycarbonyl)azanediyl))diacetate

[0445]

10 [Chem. 48]



Example 4A

[0446]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (50.0 mg), zinc (54.0 mg), sodium dithionite (181 mg), diisopropylethylamine (0.36 mL), and tetra-n-butylammonium bromide (7.00 mg) in N,N-dimethylformamide (3.00 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of tert-butyl 20 N-(tert-butoxycarbonyl)-N-(2-isocyanatoethyl)glycinate in toluene, which had been prepared from Reference example 7 (253 mg) by the same method as Reference example 1, was added dropwise thereto over 5 minutes. After stirring at 0°C for 30 minutes, the reaction solution was filtered through Celite, and then the Celite was washed with ethyl 25

acetate. Aqueous saturated ammonium chloride solution was added to the filtrate, the organic layer was separated, and then the aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1-3:7) to yield Example 4A (102 mg).

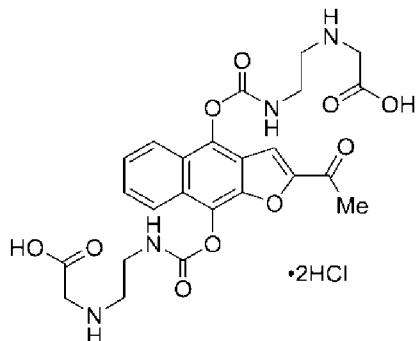
10 (LC-MS: $[M-Boc+H]^+$ /Rt (min)) = 743/1.37
[0447]

Example 4

15 2,2'-((((((2-Acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))diacetic acid dihydrochloride

[0448]

[Chem. 49]



Example 4

[0449]

20 A 4 mol/L hydrochloric acid/dioxane solution (10.0 mL) was added to Example 4A (101mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 4 (59.0 mg).

25 1H -NMR (400 MHz, DMSO-d₆) δ : 2.62 (3H, s), 3.13-3.22 (4H, m), 3.48-3.55 (4H, m), 3.96 (4H, s), 7.59-7.71 (2H, m),

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8.04-8.18 (3H, m), 8.47-8.57 (2H, m), 9.15 (4H, br).

(LC-MS: $[M+2H]^{2+}/R_t$ (min)) = 266/0.37

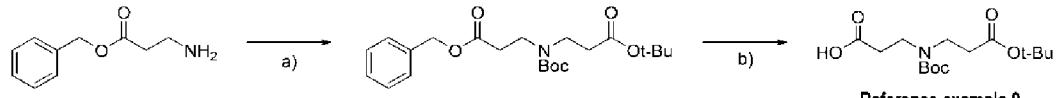
[0450]

Reference example 9

5 3-((3-(tert-Butoxy)-3-oxopropyl)(tert-butoxycarbonyl)amino)propionic acid

[0451]

[Chem. 50]



10 [0452]

a) Diisopropylethylamine (3.24 mL) and tert-butyl acrylate (1.35 mL) were added to a solution of benzyl 3-aminopropionate (2.00 g) in ethanol (20.0 mL). The reaction mixture was then stirred at room temperature for 15 10 hours. Di-tert-butyl-dicarbonate (5.00 g) was added to the reaction mixture, and it was further stirred at room temperature for 2 hours. The reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. The filtrate was concentrated and then purified 20 by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:1) to yield benzyl 3-((3-(tert-butoxy)-3-oxopropyl)(tert-butoxycarbonyl)amino)propionate (2.00 g).

(LC-MS: $[M+H]^+/R_t$ (min)) = 408/1.10

25 [0453]

b) A suspension of benzyl 3-((3-(tert-butoxy)-3-oxopropyl)(tert-butoxycarbonyl)amino)propionate (2.00 g), 10% palladium on carbon (500 mg), and ammonium formate (1.54 g) in methanol (20.0 mL) was stirred under nitrogen atmosphere at 50°C for 1.5 hours. The reaction solution was filtered through Celite, and then

the Celite was washed with methanol. The filtrate was concentrated, and then purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-0:1) to yield Reference example 9 (1.10 g).

5 (LC-MS: $[M+H]^+$ /Rt (min)) = 318/0.94

[0454]

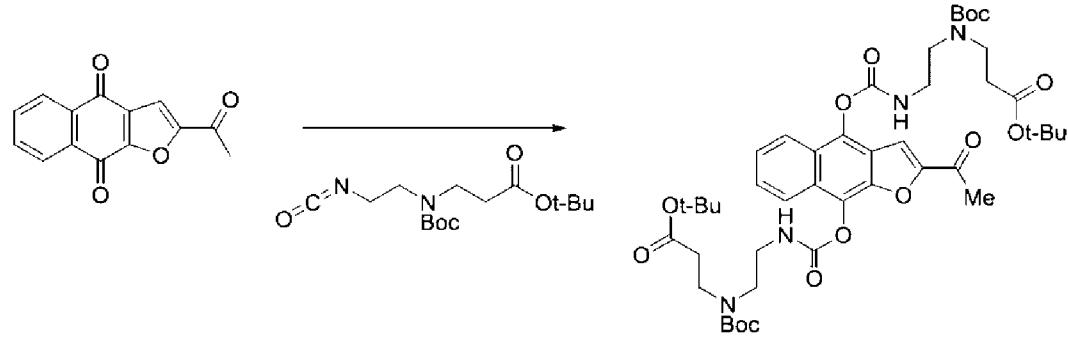
Example 5A

Di-tert-butyl

3,3'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl)bis(azanediyl))bis(ethane-2,1-diyl))bis((tert-butoxycarbonyl)azanediyl))dipropionate

10 [0455]

[Chem. 51]



Example 5A

15 [0456]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (59.0 mg), zinc (64.0 mg), sodium dithionite (214 mg), diisopropylethylamine (0.43 mL), and tetra-n-butylammonium bromide (8.00 mg) in N,N-dimethylformamide (3.50 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of tert-butyl 3-((tert-butoxycarbonyl)(2-isocyanatoethyl)amino)propanoate in toluene, which had been prepared from Reference example 9 (312 mg) by the same method as Reference example 1, was added dropwise thereto over 5 minutes. After

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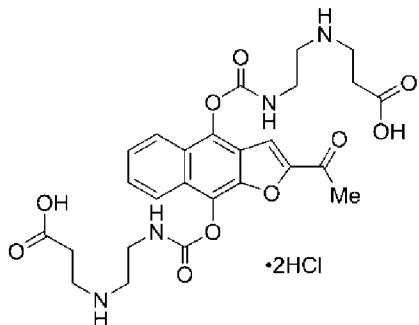
stirring at 0°C for 30 minutes, the reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. Aqueous saturated ammonium chloride solution was added to the filtrate, the organic layer was separated, and then the aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1-3:7) to yield Example 5A (105 mg).

(LC-MS: [M-t-Bu]⁺/Rt (min)) = 815/1.36
[0457]

Example 5

3,3'-((((2-Acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid dihydrochloride
[0458]

[Chem. 52]



Example 5

20

[0459]

A 4 mol/L hydrochloric acid/dioxane solution (10.0 mL) was added to Example 5A (103 mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 5 (65 mg).

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¹H-NMR (400 MHz, DMSO-d₆) δ: 2.62 (3H, s), 2.68-2.81 (4H, m), 3.10-3.24 (8H, m), 3.43-3.54 (4H, m), 7.58-7.71 (2H, m), 8.05-8.15 (2H, m), 8.21-8.29 (1H, m), 8.46-8.58 (2H, m), 8.75-9.16 (4H, m), 12.71 (2H, br).

5 (LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.37

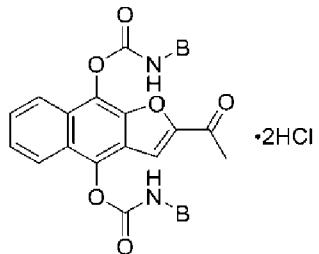
[0460]

Examples 6-13 (Compounds analogous to Example 1)

Compounds shown in Table 1 were obtained by using corresponding raw material compounds and performing the reactions/treatments described in Reference example 1, Example 1A, and Example 1.

[0461]

[Chem. 53]



15 [Table 1]

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Example	B	(LC-MS: $[M+2H]^{2+}$ / Rt (min))
6		252/0.32
7		262/0.41
8		248/0.36
9		252/0.43
10		220/0.36
11		280/0.38
12		266/0.37
13		236/0.43

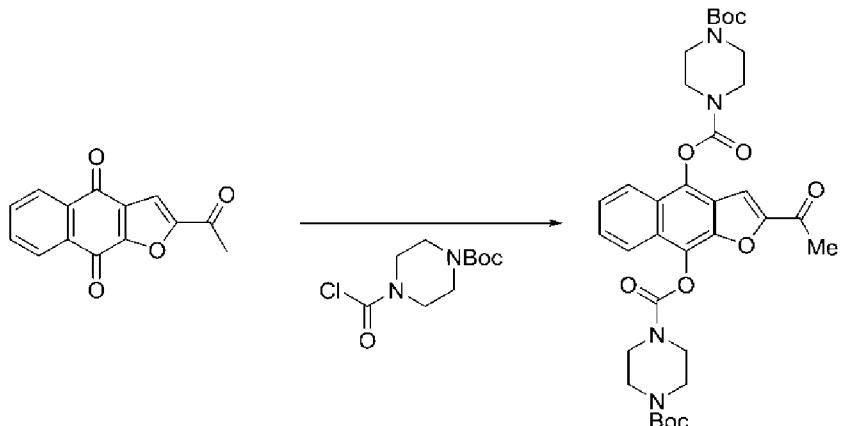
[0462]

Reference example 11

1-(2-Acetyl-4-((tert-butoxy)carbonyl)piperazine-1-carbonyloxy)naphtho[2,3-b]furan-9-yl)
4-tert-butylpiperazine-1,4-dicarboxylate

[0463]

[Chem. 54]

**Reference example 11**

[0464]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (100 mg), zinc (109 mg), sodium dithionite (362 mg), 5 diisopropylethylamine (0.36 mL), and tetra-n-butylammonium bromide (13.0 mg) in N,N-dimethylformamide (4.20 mL) was stirred under nitrogen atmosphere at room temperature for 10 minutes. Then, tert-butyl 4-(chlorocarbonyl)piperazine-1-carboxylate (259 mg) was 10 added to the reaction mixture, and it was stirred at 70°C for 4.5 hours. The reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. Aqueous saturated ammonium chloride solution was added to the filtrate, the organic layer was separated, and then the 15 aqueous layer was further extracted with ethyl acetate once. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:2-2:3) to yield Reference example 11 (55 mg).

(LC-MS: $[M-t\text{-Bu}]^+/\text{Rt (min)}$) = 611/1.24

[0465]

Example 14

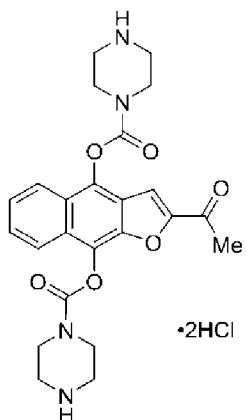
2-Acetylnaphtho[2,3-b]furan-4,9-diyI

- 214 -

bis (piperazine-1-carboxylate) dihydrochloride

[0466]

[Chem. 55]



Example 14

5 [0467]

A 4 mol/L hydrochloric acid/dioxane solution (5.00 mL) was added to Reference example 11 (55.0 mg). The reaction mixture was then stirred at 60°C for 30 minutes. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 14 (41.0 mg).

10 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 2.63 (3H, s), 3.24-3.30 (4H, br), 3.34-3.41 (4H, br), 3.70-3.78 (4H, br), 4.04-4.13 (4H, br), 7.60-7.71 (2H, m), 8.12 (2H, t, J = 8.9 Hz), 8.19 (1H, s), 9.18 (4H, br).

15 (LC-MS: $[\text{M}+2\text{H}]^{2+}/\text{Rt}$ (min)) = 234/0.35

[0468]

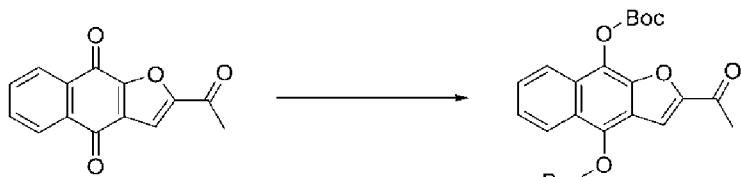
Reference example 12

2-Acetylnaphtho[2,3-b]furan-4,9-diyl di-tert-butyl bis(carbonate)

20 [0469]

[Chem. 56]

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Reference example 12

[0470]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (300 mg), zinc (327 mg), sodium dithionite (1.09 g), 5 diisopropylethylamine (2.18 mL), and tetra-n-butylammonium bromide (40.0 mg) in N,N-dimethylformamide (12.5 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and then a solution of di-tert-butyl-dicarbonate (3.69 g) in 10 N,N-dimethylformamide (8.30 mL) was added dropwise thereto over 5 minutes. After stirring at room temperature for 3.5 hours, the reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. The resulting filtrate was distributed between an organic layer 15 and an aqueous layer, and then the aqueous layer was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column 20 chromatography (chloroform) to yield Reference example 12 (370 mg).

(LC-MS: $[M-t-Bu]^+/Rt$ (min)) = 387/1.28

[0471]

Reference example 13

25 2-Acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl tert-butyl carbonate

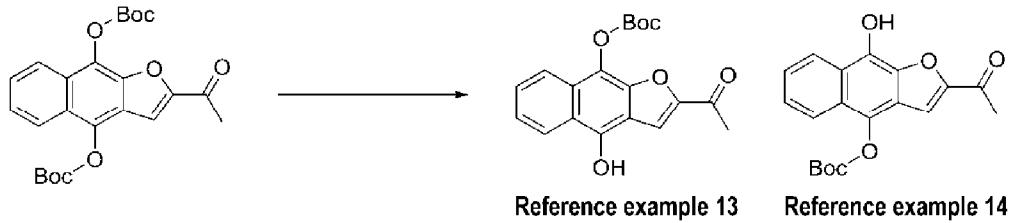
Reference example 14

2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl tert-butyl carbonate

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[0472]

[Chem. 57]



[0473]

5 A suspension of Reference example 12 (360 mg) and potassium carbonate (562 mg) in methanol (35.0 mL) and tetrahydrofuran (18.0 mL) was stirred at room temperature for 85 minutes. Aqueous saturated ammonium chloride solution was added to the reaction solution, and then it
10 was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1-3:2) to yield
15 Reference example 13 (157 mg) and Reference example 14 (68.0 mg).

Reference example 13: (LC-MS: $[M+H]^+/\text{Rt (min)}$) = 343/1.04

Reference example 14: (LC-MS: $[M-t\text{-Bu}]^+/\text{Rt (min)}$) = 287/1.03

20 [0474]

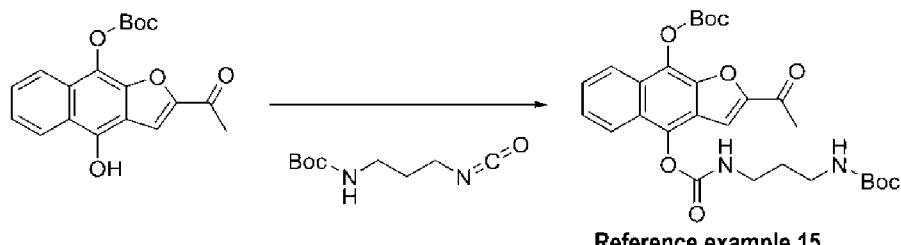
Reference example 15

2-Acetyl-9-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-4-yl tert-butyl propane-1,3-diyl dicarbamate

[0475]

25 [Chem. 58]

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Reference example 15

[0476]

A solution of Reference example 13 (50.0 mg), diisopropylethylamine (0.13 mL) in N,N-dimethylformamide (2.90 mL) was added dropwise under nitrogen atmosphere at 5 0°C to a solution of tert-butyl (3-isocyanatopropyl)carbamate in toluene (2.90 mL), which had been prepared from 4-((tert-butoxycarbonyl)amino)butanoic acid (119 mg) by the same method as Reference example 1. The reaction mixture was then stirred for 2 hours. Aqueous saturated ammonium chloride solution was added to the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1-1:1) to yield Reference example 15 (64.0 mg). (LC-MS: $[\text{M}-\text{Boc}+\text{H}]^+/\text{Rt}$ (min)) = 443/1.15

[0477]

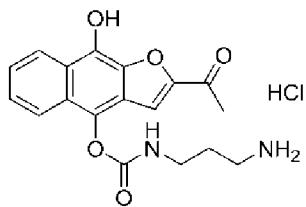
Example 15

2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl (3-aminopropyl)carbamate hydrochloride

[0478]

25 [Chem. 59]

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**Example 15**

[0479]

5 A 4 mol/L hydrochloric acid/dioxane solution (3.00 mL) was added to Reference example 15 (62.0 mg). The reaction mixture was stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 15 (37.0 mg).

10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 1.79-1.87 (2H, m), 2.63 (3H, s), 2.85-2.92 (2H, m), 3.19-3.25 (2H, m), 7.48-7.53 (2H, m), 7.73-7.82 (2H, br), 7.87-7.91 (2H, m), 8.24-8.29 (1H, m), 8.29-8.34 (1H, m), 10.78 (1H, s).

(LC-MS: $[\text{M}+\text{H}]^+/\text{Rt}$ (min)) = 343/0.53

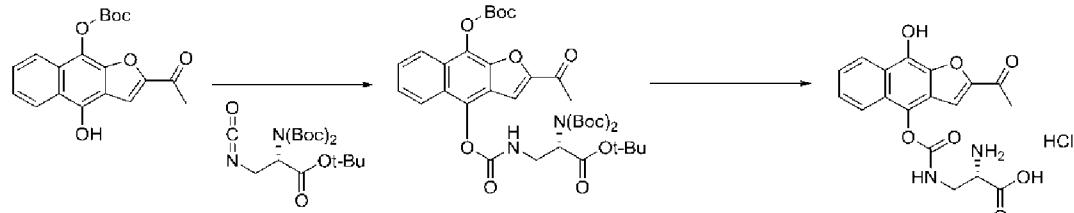
[0480]

Example 16

15 (S)-3-(((2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl)oxy)carbonyl)amino)-2-aminopropionic acid hydrochloride

[0481]

[Chem. 60]

**Example 16**

20 [0482]

A solution of Reference example 13 (50.0 mg) and diisopropylethylamine (0.13 mL) in $\text{N,N-dimethylformamide}$ (2.90 mL) was added dropwise under nitrogen atmosphere at

0°C to a solution of tert-butyl (2S)-2-(bis((tert-butoxy)carbonyl)amino)-3-isocyanatopr opionate in toluene, which had been prepared from (3S)-3-(bis((tert-butoxy)carbonyl)amino)-4-(tert-butoxy) -4-oxobutanoic acid (228 mg) by the same method as Reference example 1. The reaction mixture was stirred for 2 hours. Aqueous saturated ammonium chloride solution was added to the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1-7:3) to yield tert-butyl (S)-3-(((2-acetyl-9-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-4-yl)oxy)carbonyl)amino)-2-(bis(tert-butoxy carbonyl)amino)propionate (100 mg). Subsequently, 4 mol/L hydrochloric acid/dioxane solution (1.5 mL) was added to the above-described compound. The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 16 (37.0 mg).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.63 (3H, s), 3.60-3.72 (2H, m), 4.05-4.11 (1H, m), 7.46-7.54 (2H, m), 7.95-8.02 (2H, m), 8.28-8.34 (1H, m), 8.40-8.45 (1H, m), 8.54 (3H, br), 10.78 (1H, br).

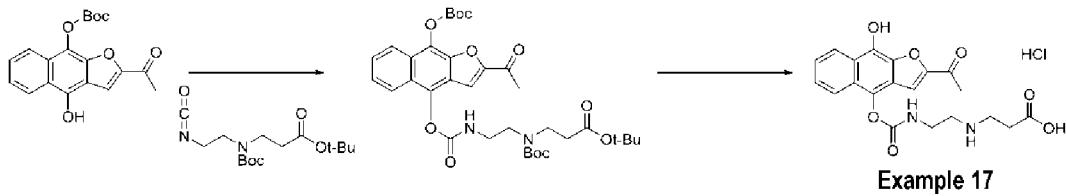
(LC-MS: [M+H]⁺/Rt (min)) = 373/0.48
[0483]

Example 17

3-((2-(((2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl)ox y)carbonyl)amino)ethyl)amino)propionic acid hydrochloride
[0484]

[Chem. 61]

- 220 -



[0485]

A solution of Reference example 13 (50.0 mg) and diisopropylethylamine (0.13 mL) in N,N-dimethylformamide (3.70 mL) was added dropwise under nitrogen atmosphere at 5 0°C to a solution of tert-butyl 3-((tert-butoxycarbonyl)amino)propionate in toluene, which had been prepared from 10 3-((3-(tert-butoxy)-3-oxopropyl) (tert-butoxycarbonyl)amino)propionic acid (185 mg) by the same method as Reference example 1. The reaction mixture was then stirred for 3 hours. Aqueous saturated ammonium chloride solution was added to 15 the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:3-1:1) to yield tert-butyl 3-((2-((2-acetyl-9-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-4-yl)oxy)carbonyl)amino)ethyl) (tert-butoxycarbonyl)amino)propionate (42.0 mg). Subsequently, 4 mol/L 20 hydrochloric acid/dioxane solution (5.00 mL) was added to the above-described compound. The reaction mixture was then stirred at 50°C for 30 minutes. The reaction solution was concentrated, and then the residue was washed with 25 diethyl ether to yield Example 17 (28.0 mg).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.60-2.65 (3H, m), 2.67-2.76 (2H, m), 3.11-3.24 (4H, m), 3.42-3.51 (2H, m), 7.47-7.55 (2H, m), 7.91-8.04 (2H, m), 8.26-8.35 (2H, m), 8.79 (1H, br), 10.79 (1H, br).

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(LC-MS: $[M+H]^+$ /Rt (min)) = 401/0.50

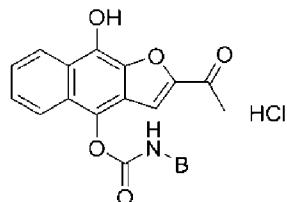
[0486]

Examples 18-19 (Compounds analogous to Example 15)

5 Compounds shown in Table 2 were obtained by using corresponding raw material compounds and performing the reactions/treatments described in Reference example 15 and Example 15.

[0487]

[Chem. 62]



10

[0488]

[Table 2]

Example	B	(LC-MS: $[M+H]^+$ /Rt (min))
18		329/0.48
19		387/0.51

[0489]

15

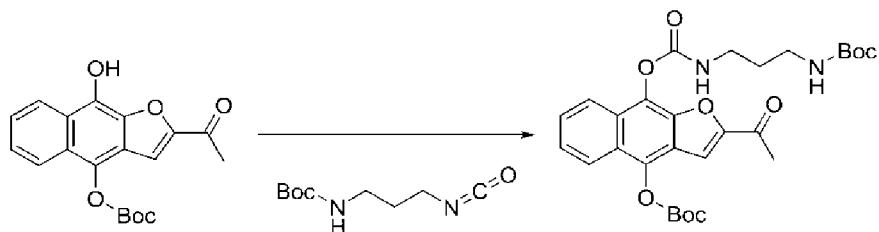
Reference example 16

2-Acetyl-4-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-9-yl tert-butyl propane-1,3-diyl dicarbamate

[0490]

[Chem. 63]

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Reference example 16

[0491]

A solution of Reference example 14 (44.0 mg) and diisopropylethylamine (0.11 mL) in N,N-dimethylformamide (2.50 mL) was added dropwise under nitrogen atmosphere at 0°C to a solution of tert-butyl (3-isocyanatopropyl) carbamate in toluene (2.50 mL), which had been prepared from 4-((tert-butoxycarbonyl)amino)butyric acid (104 mg) by the same method as Reference example 1. The reaction mixture was then stirred at 0°C for 3.5 hours. Aqueous saturated ammonium chloride solution was added to the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1-1:1) to yield Reference example 16 (49.0 mg).

20 (LC-MS: [M+H]⁺/Rt (min)) = 543/1.15

[0492]

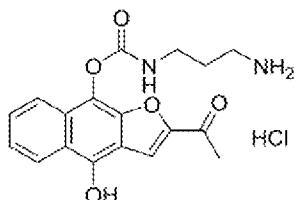
Example 20

2-Acetyl-4-hydroxynaphtho[2,3-b]furan-9-yl
(3-aminopropyl)carbamate hydrochloride

25 [0493]

[Chem. 64]

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Example 20

[0494]

A 4 mol/L hydrochloric acid/dioxane solution (3.00 mL) was added to Reference example 16 (48.0 mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 20 (20.0 mg).

¹H-NMR (400 MHz, DMSO-d₆) δ: 1.79-1.88 (2H, m), 2.56 (3H, s), 2.85-2.94 (2H, m), 3.18-3.26 (2H, m), 7.41-7.47 (1H, m), 7.56-7.62 (1H, m), 7.81-7.92 (4H, m), 8.25 (1H, s), 8.27-8.34 (2H, m), 11.31 (1H, s).

(LC-MS: [M+H]⁺/Rt (min)) = 343/0.54

[0495]

Reference example 17

15 4-((tert-Butoxycarbonyl)amino)butyl carbonochloridate

[Chem. 65]



Reference example 17

[0496]

20 Diisopropylethylamine (7.26 mL) and triphosgene (432 mg) were added to a solution of tert-butyl (4-hydroxybutyl) carbamate (788 mg) in tetrahydrofuran (10.0 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, and thereby a solution of Reference example 17 in tetrahydrofuran was produced. The resulting solution was used in the next reaction as it was.

[0497]

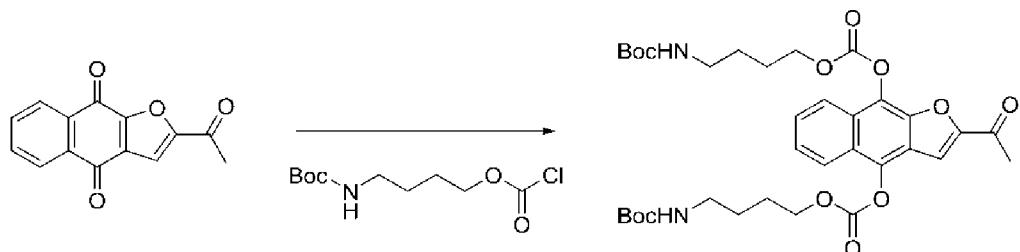
Reference example 18

Di-tert-butyl

((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)bis(carbonyl)bis(oxy))bis(butane-4,1-diyl))dicarbamate

5 [0498]

[Chem. 66]



Reference example 18

[0499]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (100 mg), zinc (108 mg), sodium dithionite (362 mg), diisopropylethylamine (7.25 mL), and tetra-n-butylammonium bromide (13.5 mg) in N,N-dimethylformamide (10 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of 4-((tert-butoxycarbonyl)amino)butyl carbonochloride in tetrahydrofuran, which had been prepared in Reference example 17, was added dropwise over 15 minutes. After further stirring at 0°C for 1 hour, ethyl acetate and aqueous saturated ammonium chloride solution were added to the reaction solution. After the resulting mixture was filtered through Celite, the filtrate was distributed between an organic layer and an aqueous layer, and then the aqueous layer was extracted with ethyl acetate twice. The resulting organic layer was washed with water once and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column

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chromatography (hexane/ethyl acetate = 1:1-1:4) to yield Reference example 18 (103 mg).

(LC-MS: $[M+H]^+/\text{Rt (min)}$) = 673/1.39

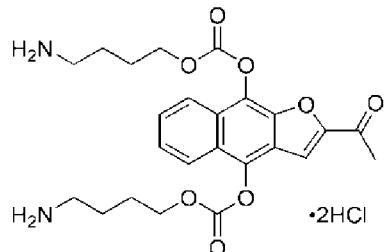
[0500]

5 Example 21

2-Acetylnaphtho[2,3-b]furan-4,9-diyl bis(4-aminobutyl)bis(carbonate) dihydrochloride

[0501]

[Chem. 67]



10 **Example 21**

[0502]

A 4 mol/L hydrochloric acid/dioxane (10 mL) solution was added to Reference example 18 (103 mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction 15 solution was concentrated, and then the residue was washed with diethyl ether to yield Example 21 (39.0 mg).

(LC-MS: $[M+H]^+/\text{Rt (min)}$) = 473/0.44

[0503]

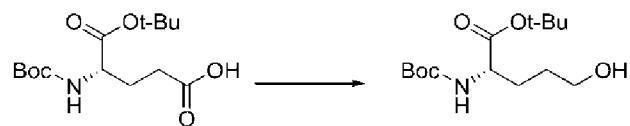
Reference example 19

20 tert-Butyl

(S)-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate

[0504]

[Chem. 68]



Reference example 19

[0505]

A 2.0 mol/L solution of dimethyl sulfide borane in tetrahydrofuran (5.40 mL) was added to a solution of (S)-5-(tert-butoxy)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid (3.00 g) in tetrahydrofuran (100 mL) at 0°C. The reaction mixture was stirred at room temperature for 10 hours. Ethyl acetate and saturated brine were added to the reaction solution. After the resulting mixture was filtered through Celite, the filtrate was distributed between an organic layer and an aqueous layer, and then the aqueous layer was extracted with ethyl acetate twice. The resulting organic layer was washed with water once and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:1) to yield Reference example 19 (450 mg).

(LC-MS: $[M+H]^+$ /Rt (min)) = 290/0.86

[0506]

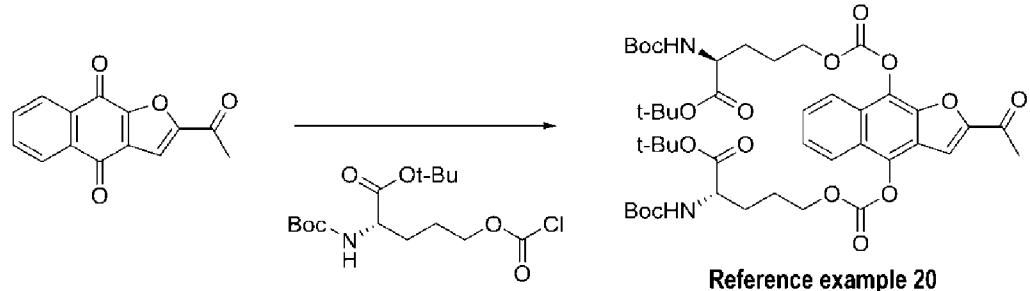
20 Reference example 20

Di-tert-butyl

5,5'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(oxy))(2S,2S')-bis(2-((tert-butoxycarbonyl)amino)pentanoate

25 [0507]

[Chem. 69]



[0508]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (62.0 mg), zinc (68.0 mg), sodium dithionite (221 mg), diisopropylethylamine (451 uL), and tetra-n-butylammonium bromide (8.30 mg) in N,N-dimethylformamide (10.0 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-5-((chlorocarbonyl)oxy)pentanoate in tetrahydrofuran, which had been prepared from (S)-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate (450 mg) by the same method as Reference example 17, was added dropwise thereto over 15 minutes. After further stirring at 0°C for 1 hour, ethyl acetate and aqueous saturated ammonium chloride solution were added to the reaction solution. After the resulting mixture was filtered through Celite, the filtrate was distributed between an organic layer and an aqueous layer, and then the aqueous layer was extracted with ethyl acetate twice. The resulting organic layer was washed with water once and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:2) to yield Reference example 20 (71.0 mg).

(LC-MS: [M+Na]⁺/Rt (min)) = 895/1.43

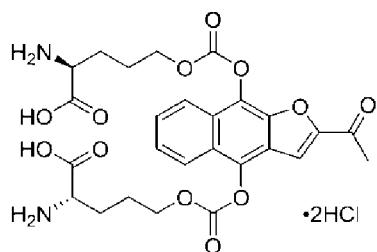
[0509]

Example 22

(2S,2S')-5,5'-((((2-Acetylnaphtho[2,3-b]furan-4,9-diyl) bis(oxy))bis(carbonyl)bis(oxy))bis(2-aminopentanoic acid) dihydrochloride

[0510]

[Chem. 70]



Example 22

[0511]

A 4 mol/L hydrochloric acid/dioxane (10.0 mL) solution was added to Reference example 20 (71.0 mg). The reaction mixture was stirred at 60°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 22 (29.0 mg).

(LC-MS: $[M+H]^+/\text{Rt}$ (min)) = 561/0.49

10

[0512]

Reference example 21

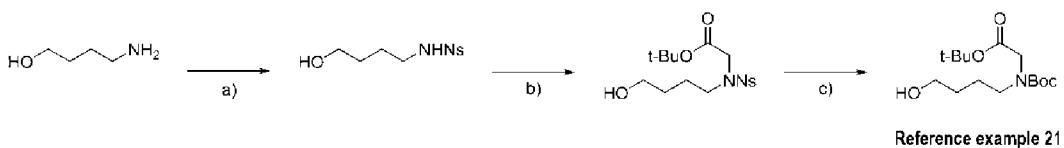
tert-Butyl

N-(tert-butoxycarbonyl)-N-(4-hydroxybutyl)glycinate

[0513]

15

[Chem. 71]



[0514]

a) Triethylamine (10.3 mL) and 2-nitrobenzenesulfonyl chloride (6.04 g) were added to a solution of 4-aminobutan-1-ol (2.21 g) in acetonitrile (50.0 mL) were added at 0°C. The reaction mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated, ethyl acetate and saturated brine were added to the residue, and then the organic layer was separated. The aqueous layer was further extracted with ethyl acetate

20

25

once. The resulting organic layer was dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure to yield 4-((4-hydroxybutyl)amino)-3-nitrobenzenesulfonic acid (2.70 g). The resulting compound was used in the next reaction as it was.

[0515]

10 b) A solution of 4-((4-hydroxybutyl)amino)-3-nitrobenzenesulfonic acid (7.00 g), tert-butyl 2-bromoacetate (4.10 mL), and potassium carbonate (10.0 g) in acetonitrile (100 mL) was stirred at room temperature for 10 hours. The reaction solution was diluted with water, and then extracted with ethyl acetate twice. After the resulting organic layer was 15 dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-0:1) to yield 4-((2-(tert-butoxy)-2-oxoethyl)(4-hydroxybutyl)amino)-3-nitrobenzenesulfonic acid (6.00 g).

(LC-MS: $[M+H]^+/\text{Rt (min)}$) = 389/0.90

[0516]

20 c) A suspension of 4-((2-(tert-butoxy)-2-oxoethyl)(4-hydroxybutyl)amino)-3-nitrobenzenesulfonic acid (6.00 g), benzenethiol (1.90 mL), and cesium carbonate (10.0 g) in acetonitrile (100 mL) was stirred under nitrogen atmosphere at room temperature for 2 hours. Di-tert-butyl-dicarbonate (6.80 g) was added to the reaction mixture, and it was further stirred at room 25 temperature for 2 hours. The reaction solution was filtered through Celite, and then the Celite was washed with ethyl acetate. The filtrate was concentrated, and then purified by silica gel column chromatography (hexane/ethyl acetate

- 230 -

= 1:0-0:1) to yield Reference example 21 (3.10 g).

(LC-MS: $[M+H]^+$ /Rt (min)) = 304/0.93

[0517]

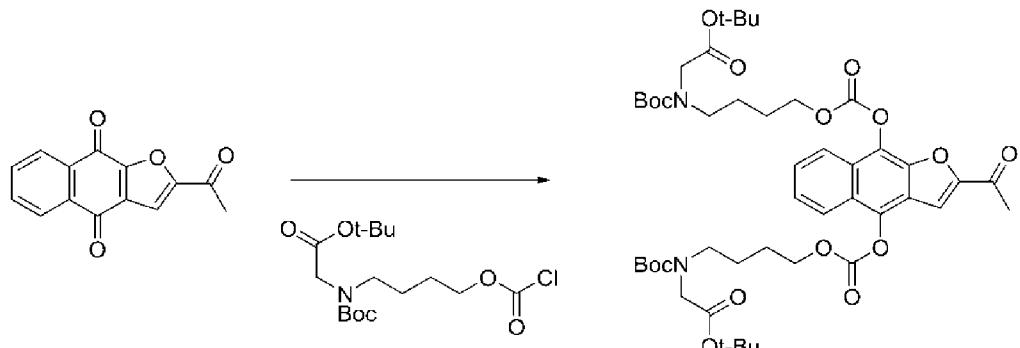
Reference example 22

5 Di-tert-butyl

2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)bis(carbonyl)bis(oxy))bis(butane-4,1-diyl))bis((tert-butoxycarbonyl)azanediyl))diacetic acid

[0518]

10 [Chem. 72]



Reference example 22

[0519]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (118 mg), zinc (125 mg), sodium dithionite (432 mg),

15 diisopropylethylamine (860 uL), and tetra-n-butylammonium bromide (16.0 mg) in N,N-dimethylformamide (20.0 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was then cooled to 0°C, and a solution of

20 N-(tert-butoxycarbonyl)-N-(4-chlorobutyl)glycinate in tetrahydrofuran, which had been prepared from tert-butyl

25 N-(tert-butoxycarbonyl)-N-(4-hydroxybutyl)glycinate (900 mg) in the same way as Reference example 17, was added dropwise thereto over 15 minutes. After further stirring

5 at 0°C for 1 hour, ethyl acetate and aqueous saturated ammonium chloride solution were added to the reaction solution. After the resulting mixture was filtered through Celite, the filtrate was distributed between an organic layer and an aqueous layer, and then the aqueous layer was extracted with ethyl acetate twice. The resulting organic layer was washed with water once and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was
10 purified by silica gel column chromatography (hexane/ethyl acetate = 1:0-1:1) to yield Reference example 22 (111 mg). (LC-MS: $[M+Na]^+/\text{Rt (min)}$) = 923/1.47

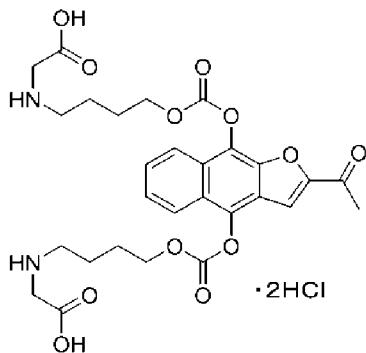
[0520]

Example 23

15 2,2'-((((2-Acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)bis(carbonyl))bis(oxy))bis(butane-4,1-diyl))bis(azanediyl)diacetic acid dihydrochloride

[0521]

[Chem. 73]



20 **Example 23**

[0522]

25 A 4 mol/L hydrochloric acid/dioxane (10.0 mL) solution was added to Reference example 22 (111 mg). The reaction mixture was stirred at 70°C for 1 hour. The reaction solution was concentrated, and then the residue was washed

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with diethyl ether to yield Example 23 (56.8 mg).

(LC-MS: $[M+2H]^{2+}/R_t$ (min)) = 295/0.55

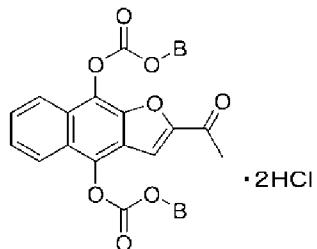
[0523]

Examples 24-28 (Compounds analogous to Example 21)

5 Compounds shown in Table 3 were obtained by using corresponding raw material compounds and performing the reactions and treatments described in Reference example 17, Reference example 18, and Example 21.

[0524]

10 [Chem. 74]



[0525]

[Table 3]

Example	B	(LC-MS: $[M+2H]^{2+}/R_t$ (min))
<u>24</u>		209/0.32
<u>25</u>		223/0.32
<u>26</u>		267/0.32
<u>27</u>		263/0.53
<u>28</u>		265/0.32

15

[0526]

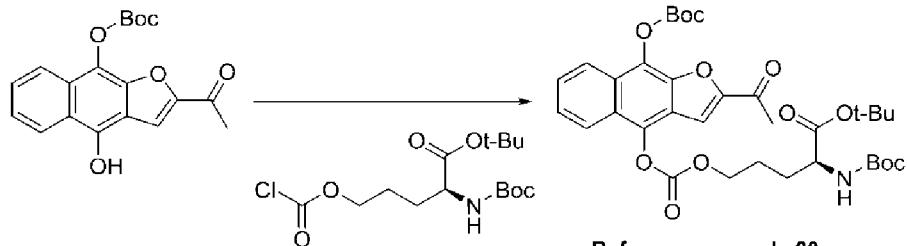
Reference example 23

tert-Butyl

(S)-5-(((2-acetyl-9-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-4-yl)oxy)carbonyl)oxy)-2-((tert-butoxycarbonyl)amino)pentanoate

5 [0527]

[Chem. 75]



Reference example 23

[0528]

A solution of Reference example 13 (70.0 mg) and diisopropylethylamine (0.50 mL) in N,N-dimethylformamide (10.0 mL) was added dropwise under nitrogen atmosphere at 10 0°C to a solution of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-5-((chlorocarbonyl)oxy)pentanoate in tetrahydrofuran (10.0 mL), which had been 15 prepared from tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate (500 mg) by the same method as Reference example 17. The reaction mixture was then stirred for 2 hours. Aqueous 20 saturated ammonium chloride solution was added to the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue 25 was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1-1:1) to yield Reference example 23 (101 mg).

(LC-MS: $[M+Na]^+/\text{Rt (min)}$) = 680/1.37

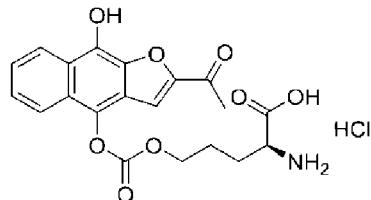
[0529]

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Example 29

(S)-5-(((2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl)oxy)carbonyloxy)-2-aminopentanoic acid hydrochloride
[0530]

5 [Chem. 76]



Example 29

[0531]

10 A 4 mol/L hydrochloric acid/dioxane (10.0 mL) solution was added to Reference example 23 (101 mg). The reaction mixture was then stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 29 (41.0 mg).

(LC-MS: $[M+H]^+/\text{Rt (min)}$) = 402/0.60

[0532]

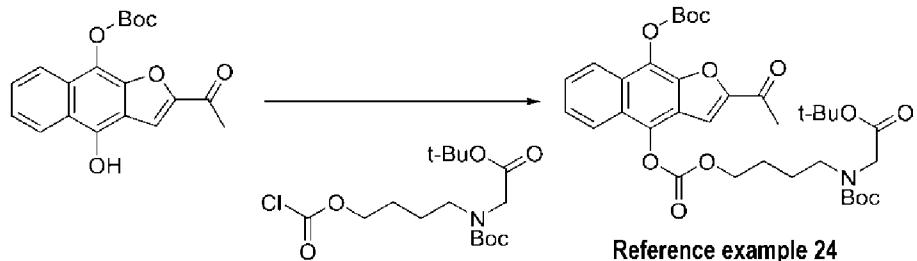
15 Reference example 24

tert-Butyl

N-(4-(((2-acetyl-9-((tert-butoxycarbonyl)oxy)naphtho[2,3-b]furan-4-yl)oxy)carbonyloxy)butyl)-N-(tert-butoxycarbonyl)glycinate

20 [0533]

[Chem. 77]



[0534]

- 235 -

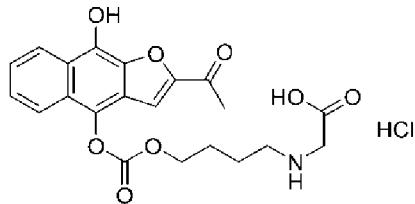
A solution of Reference example 13 (81.0 mg) and diisopropylethylamine (0.50 mL) in N,N-dimethylformamide (10.0 mL) was added dropwise under nitrogen atmosphere at 0°C to a solution of tert-butyl 5 N-(tert-butoxycarbonyl)-N-((chlorocarbonyl)oxy)butyl)glycinate in tetrahydrofuran (10.0 mL), which had been prepared from tert-butyl N-(tert-butoxycarbonyl)-N-(4-hydroxybutyl)glycinate (600 mg) by the same method as Reference example 17. The reaction 10 mixture was then stirred for 2 hours. Aqueous saturated ammonium chloride solution was added to the reaction solution, and then it was extracted with ethyl acetate twice. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was 15 evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1-1:1) to yield Reference example 24 (98.0 mg). (LC-MS: $[M+Na]^+/\text{Rt (min)}$) = 694/1.42
[0535]

20 Example 30

(4-(((2-Acetyl-9-hydroxynaphtho[2,3-b]furan-4-yl)oxy)carbonyl)oxy)butyl)glycine hydrochloride

[0536]

[Chem. 78]



25 Example 30

[0537]

A 4 mol/L hydrochloric acid/dioxane (10.0 mL) solution was added to Reference example 24 (98.0 mg). The reaction

- 236 -

mixture was stirred at 50°C for 1 hour. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 30 (51.0 mg).

(LC-MS: $[M+H]^+/\text{Rt}$ (min)) = 416/0.64

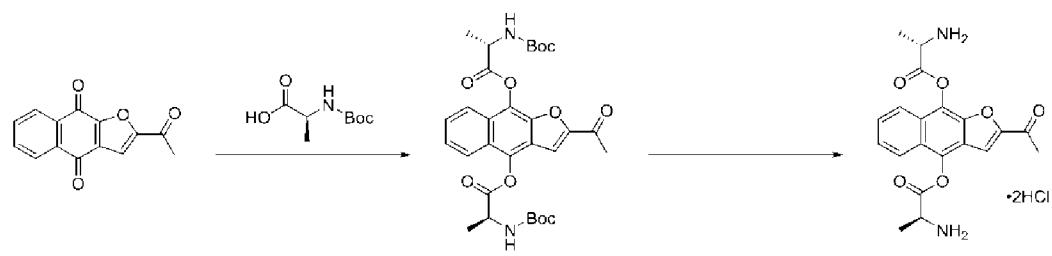
5 [0538]

Example 31

2-Acetylnaphtho[2,3-b]furan-4,9-diyi
(2S,2'S)-bis(2-aminopropanoate) dihydrochloride

[0539]

10 [Chem. 79]



Example 31

[0540]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (50.0 mg), sodium dithionite (109 mg), and tetra-n-butylammonium bromide (7.00 mg) in THF (1.30 mL) and water (0.70 mL) was stirred under nitrogen atmosphere at room temperature for 40 minutes. The reaction solution was diluted with ethyl acetate, and then washed with water twice. The resulting organic layer was concentrated, and then the resulting solid was dissolved in tetrahydrofuran (2.00 mL). Diisopropylethylamine (0.18 mL), dimethylaminopyridine (4.00 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (160 mg), and tert-butoxycarbonyl-L-alanine (158 mg) were added to the solution, and then it was stirred at room temperature for 16 hours. The reaction solution was diluted with water, and then extracted with ethyl acetate three times. The resulting organic layer was washed with

aqueous saturated sodium hydrogen carbonate solution twice and dried over anhydrous sodium sulfate, and then it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1-1:1) to yield 2-acetylnaphtho[2,3-b]furan-4,9-diyi⁵ (2S,2'S)-bis(2-((tert-butoxycarbonyl)amino)propanoate) (7.00 mg). Subsequently, 4 mol/L hydrochloric acid/dioxane (5.00 mL) solution was added to the above-described compound. The reaction mixture was stirred at room temperature for 4 hours. The reaction solution was concentrated, and then the residue was washed with diethyl ether to yield Example 10 31 (3.00 mg).

¹H-NMR (400 MHz, DMSO-d₆) δ: 1.99 (6H, d, J = 6.7 Hz), 2.66 (15 3H, s), 3.56-3.75 (2H, m), 7.66-7.76 (2H, m), 7.89 (1H, s), 8.15 (2H, t, J = 8.9 Hz).

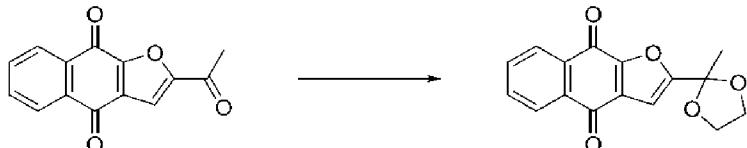
[0541]

Reference example 25

2-(2-methyl-1,3-dioxolan-2-yl)naphtho[2,3-b]furan-4,9-dione²⁰

[0542]

[Chem. 80]



Reference example 25

[0543]

²⁵ A solution of 2-acetylnaphtho[2,3-b]furan-4,9-dione (6.0 g), tosylic acid hydrate (0.48 g), and ethylene glycol (70 mL) in toluene (0.25 L) was heated to reflux for 3.5 hours. Then, water and ethyl acetate were added thereto and the organic layer was separated. After the resulting

organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by recrystallization operation (hexane-ethyl acetate) to yield Reference example 5 25 (5.4 g).

(LC-MS: $[M+H]^+$ /Rt (min)) = 285/0.92

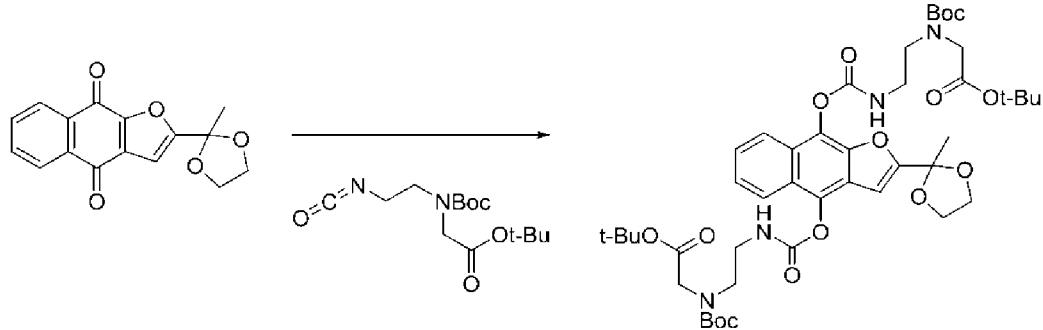
[0544]

Reference example 26

Di-tert-butyl

10 2,2'-((((((2-(2-methyl-1,3-dioxolan-2-yl)naphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis((tert-butoxycarbonyl)azanediyl))diacetate
[0545]

15 [Chem. 81]



Reference example 26

[0546]

A suspension of Reference example 25 (2.13 g), zinc (0.460 g), sodium dithionite (1.23 g), 20 diisopropylethylamine (1.23 mL), and tetra-n-butylammonium bromide (57.0 mg) in N,N-dimethylformamide (17.6 mL) was stirred under nitrogen atmosphere at room temperature for 2 hours. Then, the suspension was cooled to 0°C, and the solution of tert-butyl 25 N-(tert-butoxycarbonyl)-N-(2-isocyanatoethyl)glycinate in toluene, which was prepared from

N-(tert-butoxycarbonyl)-N-(2-tert-butoxy-2-oxoethyl)-b-alanine (0.500 g) according to the same method as in Reference example 1, was added dropwise thereto over 6 minutes. After stirring at 0°C for 1 hour, the reaction 5 solution was filtered through Celite, and the Celite was washed with ethyl acetate. Then, 0.1 mol/L hydrochloric acid was added to the filtrate and the organic layer was separated. The aqueous layer was then further extracted with ethyl acetate once. After the resulting organic layer 10 was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1-2:3) to yield Reference example 26 (1.22 g).

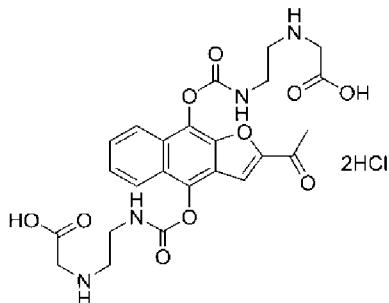
15 (LC-MS: [M-Boc+H]⁺/Rt (min)) = 787/1.38
[0547]

Example 4

2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) diacetic acid dihydrochloride

20 [0548]

[Chem. 82]



Example 4

[0549]

25 A 4 mol/L hydrochloric acid/dioxane solution (7.0 mL), water (20 uL), and acetonitrile (7.0 mL) were added to Reference example 26 (0.50 g). The reaction mixture was

- 240 -

stirred at 70°C for 1.5 hours. The precipitated solid was washed with acetonitrile and diethyl ether to yield Example 4 (0.33 g).

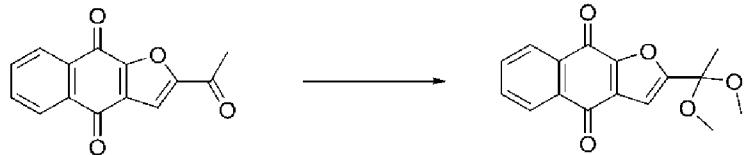
[0550]

5 Reference example 27

2-(1,1-dimethoxyethyl)naphtho[2,3-b]furan-4,9-dione

[0551]

[Chem. 83]



Reference example 27

10 [0552]

A solution of 2-acetylnaphtho[2,3-b]furan-4,9-dione (0.50 g), tosylic acid hydrate (0.40 g), and trimethyl orthoformate (0.64 mL) in methanol (30 mL) was heated to reflux for 3.5 hours. Then, ethyl acetate was added thereto 15 and the solution was washed with saturated saline and water. After the resulting organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl 20 acetate) to yield Reference example 27 (0.53 g).

(LC-MS: $[M-OMe+H]^+/\text{Rt (min)}$) = 255/1.00

[0553]

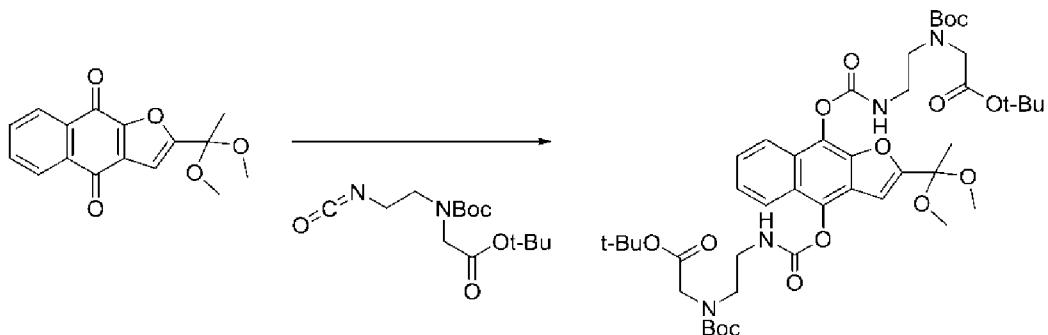
Reference example 28

Di-tert-butyl

25 $2,2'-(((2-(1,1-dimethoxyethyl)naphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis((tert-butoxycarbonyl)azanediyl))diacetate$

[0554]

[Chem. 84]



[0555]

5 A suspension of Reference example 27 (0.10 g), zinc (0.18 g), sodium dithionite (0.30 g), Diisopropylethylamine (0.24 mL), and tetra-*n*-butylammonium bromide (0.011 g) in *N,N*-dimethylformamide (6.0 mL) was stirred under nitrogen atmosphere at room temperature for 2 hours. Then, the suspension was cooled to 0°C and the solution of *tert*-butyl N-(*tert*-butoxycarbonyl)-N-(2-isocyanatoethyl)glycinate in toluene, which was prepared from N-(*tert*-butoxycarbonyl)-N-(2-*tert*-butoxy-2-oxoethyl)-*b*-alanine (0.37 g) according to the same method as in Reference example 1, was added dropwise over 10 minutes. After 10 stirring at 0°C for 1 hour, the reaction solution was filtered through Celite and the Celite was washed with ethyl acetate. Water was added to the filtrate and the organic layer was separated. Then, the aqueous layer was further extracted with ethyl acetate once. After the resulting 15 layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1-1:2) to yield Reference example 28 (0.23 g).

20 (LC-MS: $[M-OMe+H]^+/\text{Rt (min)}$) = 857/1.42

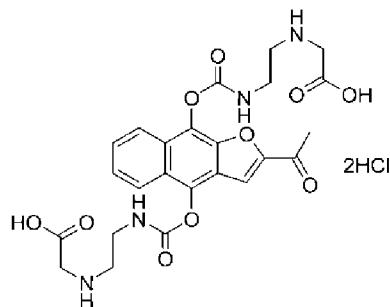
[0556]

Example 4

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) diacetic acid dihydrochloride

5 [0557]

[Chem. 85]



Example 4

[0558]

A 4 mol/L hydrochloric acid/dioxane solution (7.0 mL),
10 water (20 μ L), and acetonitrile (7.0 mL) were added to Reference example 28 (0.50 g), and the reaction mixture was stirred at 70°C for 1.5 hours. The precipitated solid was washed with acetonitrile and diethyl ether to yield Example 4 (0.33 g).

15 [0559]

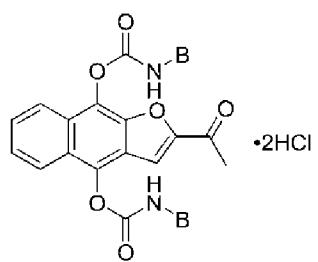
Examples 32 to 70 (Compounds analogous to Example 1)

Compounds shown in Table 4 were obtained by using corresponding raw material compounds prepared by reactions/treatments described in Reference example 7 and Reference example 9, and by performing reactions/treatments described in Reference example 1, Reference example 2, and Example 1.

20 [0560]

[Chem. 86]

- 243 -



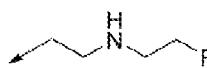
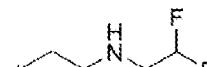
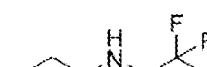
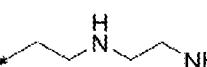
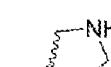
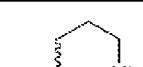
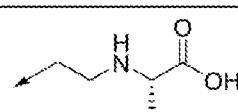
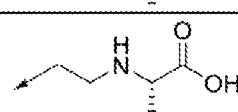
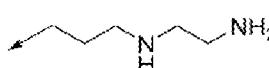
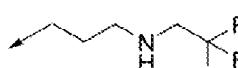
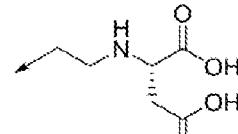
[Table 4-1]

- 244 -

Example	B	(LC-MS: $[M+2H]^{2+}$ /Rt (min))
32		266/0.44
33		450/0.44
34		321/0.50
35		308/0.50
36		280/0.54
37		264/0.50
38		278/0.55
39		292/0.90
40		280/0.40
41		323/0.40
42		294/0.35

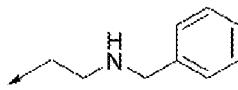
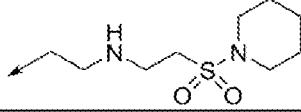
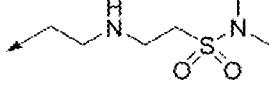
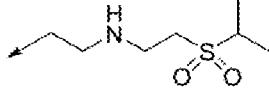
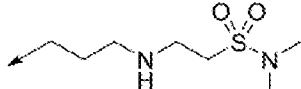
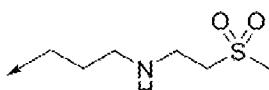
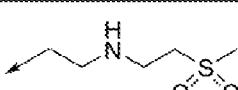
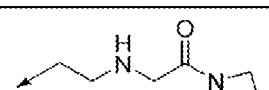
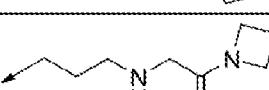
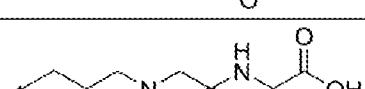
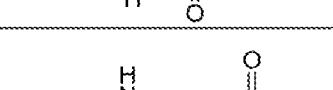
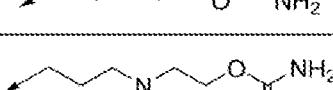
[Table 4-2]

- 245 -

43		254/0.32
44		272/0.34
45		290/0.69
46		251/0.19
47		294/0.37
48		234/0.34
49		248/0.37
50		280/0.37
51		294/0.39
52		265/0.22
53		304/0.51
54		324/0.37

[Table 4-3]

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55		298/0.50
56		383/0.67
57		343/0.52
58		342/0.60
59		357/0.52
60		328/ 0.39
61		314/0.39
62		305/0.38
63		319/0.40
64		337/0.38
65		295/0.33
66		309/0.37

[Table 4-4]

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67		309/0.37
68		323/0.39
69		296/0.33
70		324/0.42

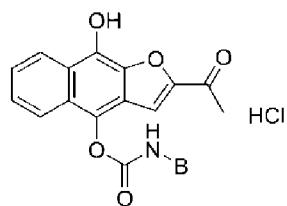
[0561]

Examples 71 to 77 (Compounds analogous to Example 15)

Compounds shown in Table 5 were obtained by using corresponding raw material compounds prepared by reactions/treatments described in Reference example 7 and Reference example 9, and by performing reactions/treatments described in Reference example 15 and Example 15.

[0562]

10 [Chem. 87]



[0563]

[Table 5]

Example	B	(LC-MS: [M+H] ⁺ /Rt (min))
71		387/0.51
72		371/0.54
73		399/0.61
74		357/0.52
75		413/0.70
76		429/0.57
77		401/0.52

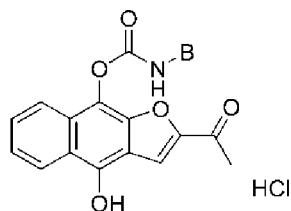
[0564]

Examples 78 to 92 (Compounds analogous to Example 20)

Compounds shown in Table 6 were obtained by using corresponding raw material compounds prepared by reactions/treatments described in Reference example 7 and Reference example 9, and by performing reactions/treatments described in Reference example 16 and Example 20.

[0565]

10 [Chem. 88]



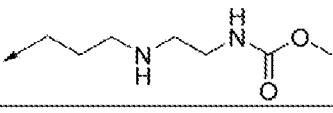
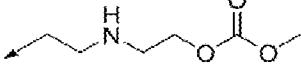
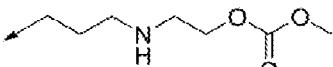
[0566]

[Table 6-1]

Example	B	(LC-MS: $[M+H]^+$ /Rt (min))
78		387/0.51
79		464/0.55
80		478/0.56
81		435/0.50
82		449/0.53
83		444/0.55
84		458/0.51
85		426/0.51
86		440/0.50
87		416/0.48
88		430/0.50
89		430/0.52

[Table 6-2]

- 250 -

90		440/0.54
91		431/0.58
92		445/0.56

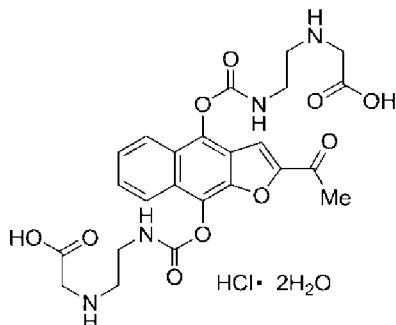
[0567]

Example 93

2,2'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl) diacetic acid monohydrochloride dihydrate

[0568]

[Chem. 89]

Example 93

10 [0569]

Example 4 (1.00 g) was recrystallized from 0.1% aqueous hydrochloric acid solution (5.00 mL) to yield Example 93 (689 mg).

15 $^1\text{H-NMR}$ (400 MHz, 0.1M DCl) δ 2.45 (3H, s), 3.35 (4H, t, J = 5.8 Hz), 3.64 (4H, t, J = 5.8 Hz), 3.99 (4H, s), 7.52-7.55 (1H, m), 7.58-7.62 (1H, m), 7.64 (1H, s), 7.97 (2H, d, J = 9.2 Hz).

[0570]

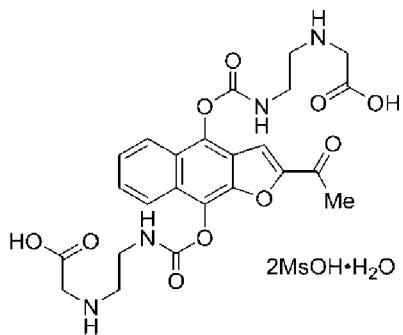
Example 94

- 251 -

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))diacetic acid dimethanesulfonate salt monohydrate

5 [0571]

[Chem. 90]



Example 94

[0572]

10 A solution of Example 4A (0.30 g) and methanesulfonic acid (0.23 mL) in THF (3.0 mL)-water (0.20 mL) was stirred at 70°C for 1.5 hours and then stirred at room temperature overnight. The precipitated solid was washed with THF to yield Example 94 (0.25 g).

15 ¹H-NMR (400 MHz, DMSO-d₆) δ 2.29 (6H, s), 2.63 (3H, s), 3.20 (4H, m), 3.53 (4H, m), 4.02 (4H, m), 7.11 (4H, d), 7.48 (4H, d), 7.67 (2H, m), 8.11 (2H, m), 8.12 (1H, s), 8.51 (2H, m), 9.05 (4H, m), 13.87 (2H, br).

(LC-MS: [M+2H]²⁺/Rt (min)) = 266/0.39

[0573]

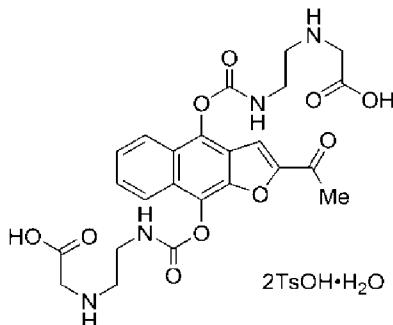
20 Example 95

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))diacetic acid ditoluenesulfonate salt monohydrate

25 [0574]

[Chem. 91]

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Example 95

[0575]

5 A solution of Example 4A (0.10 g) and toluenesulfonic acid (0.11 g) in acetonitrile (1.0 mL)-water (0.064 mL) was stirred at 70°C for 4 hours. Then, the solution was diluted with ethyl acetate and stirred at room temperature for 15 minutes. After ethyl acetate was removed, the residue was further washed with ethyl acetate twice to yield Example 95 (0.099 g).

10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 2.29 (6H, s), 2.63 (3H, s), 3.20 (4H, m), 3.53 (4H, m), 4.02 (4H, m), 7.11 (4H, d), 7.48 (4H, d), 7.67 (2H, m), 8.11 (2H, m), 8.12 (1H, s), 8.51 (2H, m), 9.05 (4H, m), 13.87 (2H, br).

(LC-MS: $[\text{M}+2\text{H}]^{2+}/\text{Rt}$ (min)) = 266/0.36

15 [0576]

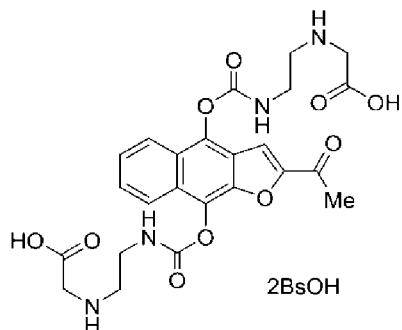
Example 96

2,2'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)diacetic acid dibenzenesulfonate salt

20 [0577]

[Chem. 92]

- 253 -

**Example 96**

[0578]

A solution of Example 4A (0.10 g) and benzenesulfonic acid (0.38 g) in THF (3.0 mL)-water (0.10 mL) was stirred at 70°C for 2.5 hours. Then, the solution was diluted with ethyl acetate and stirred at room temperature for 20 minutes. After ethyl acetate was removed, the residue was further washed with ethyl acetate twice to yield Example 96 (0.080 g).

¹H-NMR (400 MHz, DMSO-d₆) δ 2.63 (3H, s), 3.20 (4H, m), 3.53 (4H, m), 4.02 (4H, m), 7.31 (4H, m), 7.60 (4H, m), 7.67 (2H, m), 8.11 (2H, m), 8.12 (1H, s), 8.52 (2H, m), 9.05 (4H, m), 13.87 (2H, br).

(LC-MS: [M+2H]²⁺/Rt (min)) = 266/0.36

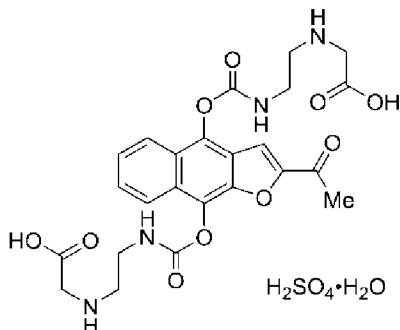
15 [0579]

Example 97

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl))diacetic acid monosulfate salt monohydrate

20 [0580]

[Chem. 93]

**Example 97**

[0581]

To a solution of Example 4A (0.21 g) in acetonitrile (3.0 mL) heated to 70°C, 1 mol/L sulfuric acid (1.0 mL) was added, and the solution was stirred at 90°C for 3 hours. The reaction solution was diluted with THF (20 mL) and then stirred at room temperature for 30 minutes. The precipitated solid was washed with THF to yield Example 97 (0.15 g).

¹H-NMR (400 MHz, D₂O) δ: 2.62 (3H, s), 3.39 (4H, m), 3.71 (4H, m), 3.85 (4H, m), 7.67 (2H, m), 7.92 (1H, s), 8.12 (2H, m).

(LC-MS: [M+2H]²⁺/Rt (min)) = 266/0.38

[0582]

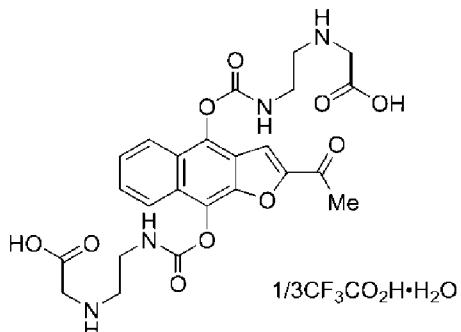
15 Example 98

2,2'-((((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)diacetic acid 1/3 trifluoroacetate salt monohydrate

20 [0583]

[Chem. 94]

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**Example 98**

[0584]

5 A solution of Example 4A (0.20 g) in trifluoroacetic acid (0.50 mL)-water (0.10 mL) heated to 70°C was stirred at 70°C for 2 hours. Trifluoroacetic acid (0.25 mL) and water (0.05 mL) were added to the reaction solution and it was further stirred at 70°C for 1.5 hours. The reaction solution was diluted with THF (20 mL) and then stirred at 10 0°C for 30 minutes. The precipitated solid was washed with THF to yield Example 98 (0.10 g).

15 ¹H-NMR (400 MHz, D₂O) δ: 2.57 (3H, s), 3.38 (4H, m), 3.68 (4H, m), 4.02 (4H, m), 7.62 (2H, m), 7.87 (1H, s), 8.07 (2H, m).

(LC-MS: [M+2H]²⁺/Rt (min)) = 266/0.36

15 [0585]

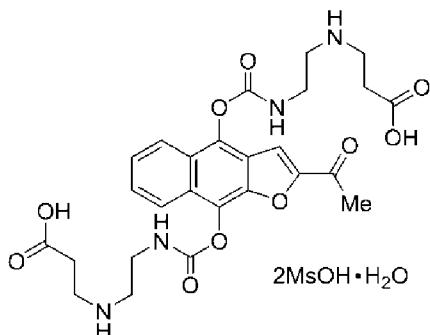
Example 99

20 3,3'-(naphtho[2,3-b]furan-4,9-diyl)bis(azanediyl)bis(ethane-2,1-diyl)bis(azanediyl)dipropionic acid dimethanesulfonate salt monohydrate

[0586]

[Chem. 95]

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Example 99

[0587]

A solution of Example 5A (0.17 g) and methanesulfonic acid (0.13 mL) in acetonitrile (3.0 mL)-water (0.1 mL) was stirred at 70°C for 2 hours. Then, the solution was diluted with ethyl acetate and stirred at room temperature for 1 hour. The precipitated solid was washed with ethyl acetate to yield Example 99 (0.13 g).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.34 (6H, s), 2.63 (3H, s), 2.71 (4H, m), 3.15-3.28 (8H, m), 3.51 (4H, m), 7.62-7.72 (2H, m), 8.11 (2H, m), 8.13 (1H, s), 8.50 (2H, m), 8.61 (4H, br), 12.74 (2H, br).

(LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.39

[0588]

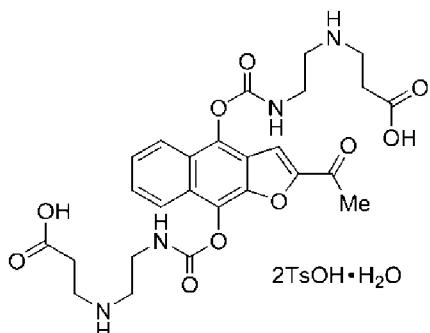
Example 100

3,3'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyil))bis(azanediyl)dipropionic acid ditoluenesulfonate salt monohydrate

[0589]

[Chem. 96]

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**Example 100**

[0590]

5 A solution of Example 5A (0.095 g) and toluenesulfonic acid (0.21 g) in THF (3.0 mL)-water (0.059 mL) was stirred at 80°C for 1 hour. The precipitated solid was washed with THF and chloroform to yield Example 100 (0.075 g).

10 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 2.28 (6H, s), 2.62 (3H, s), 2.70 (4H, m), 3.14-3.29 (8H, m), 3.47-3.53 (4H, m), 7.11 (4H, d), 7.47 (4H, d), 7.62-7.72 (2H, m), 8.10 (2H, m), 8.11 (1H, s), 8.50 (2H, m), 8.58 (4H, br), 12.76 (2H, br).

(LC-MS: $[\text{M}+2\text{H}]^{2+}/\text{Rt}$ (min)) = 280/0.45

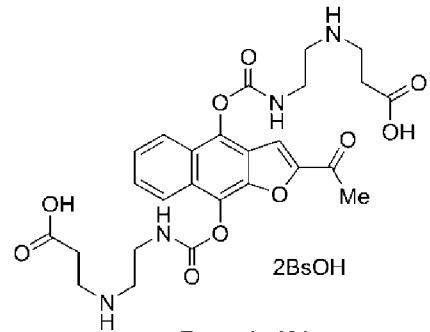
[0591]

Example 101

15 3,3'-(((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid dibenzenesulfonate salt

[0592]

[Chem. 97]

**Example 101**

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[0593]

A solution of Example 5A (0.10 g) and benzenesulfonic acid (0.18 g) in THF (3.0 mL)-water (0.062 mL) was stirred at 80°C for 1 hour and then concentrated. The residue was washed with chloroform, and then suspended in THF and stirred at room temperature for 1 minute. The precipitated solid was washed with THF to yield Example 101 (0.043 g).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.63 (3H, s), 2.67-2.81 (4H, m), 3.14-3.31 (8H, m), 3.47-3.53 (4H, m), 7.28-7.34 (6H, m), 7.58-7.61 (4H, m), 7.67 (2H, m), 8.10 (2H, m), 8.11 (1H, s), 8.50 (2H, m), 8.60 (4H, br).

(LC-MS: $[M+2H]^{2+}/R_t$ (min)) = 280/0.35

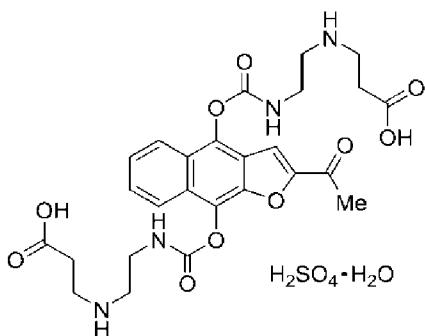
[0594]

Example 102

3,3'-(((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxo))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid monosulfate salt monohydrate

[0595]

[Chem. 98]



Example 102

[05961]

To a solution of Example 5A (0.15 g) in acetonitrile (3.0 mL) heated to 70°C, 1 mol/L sulfuric acid (0.70 mL) was added and the solution was stirred at 90°C for 2 hours. The reaction solution was diluted with ethyl acetate and then stirred at room temperature for 1 hour. The

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precipitated solid was washed with ethyl acetate to yield Example 102 (0.11 g).

¹H-NMR (400 MHz, D₂O) δ: 2.50 (3H, s), 2.75 (4H, t), 3.25-3.32 (8H, m), 3.58 (4H, t), 7.49-7.60 (2H, m), 7.79 (1H, s), 8.00 (2H, d).

(LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.48

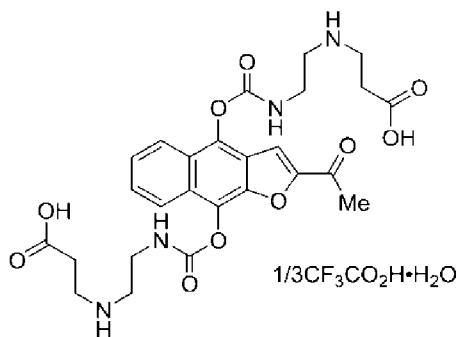
[0597]

Example 103

3,3'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(ethane-2,1-diyl))bis(azanediyl)dipropionic acid 1/3 trifluoroacetate salt monohydrate

[0598]

[Chem. 99]



Example 103

15

[0599]

A solution of Example 5A (0.15 g) in trifluoroacetic acid (0.40 mL)-water (0.080 mL) was stirred at 70°C for 50 minutes. The reaction solution was diluted with THF (XX mL) and then stirred at room temperature for 30 minutes. The precipitated solid was washed with THF to yield Example 103 (0.11 g).

¹H-NMR (400 MHz, D₂O) δ: 2.54 (3H, s), 2.70 (4H, m), 3.25-3.31 (8H, m), 3.59 (4H, t), 7.51-7.61 (2H, m), 7.85 (1H, s), 8.02 (2H, d).

(LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.39

25

[0600]

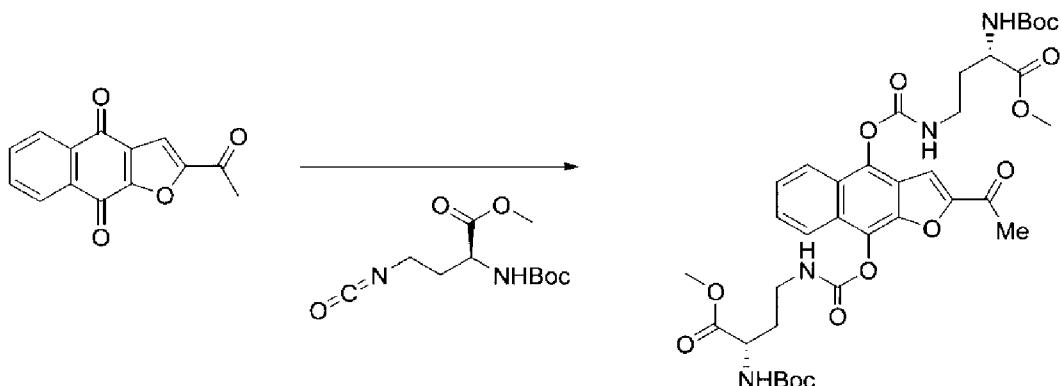
Example 104A

Dimethyl

4,4' - (((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
5 bis(carbonyl)bis(azanediyl)) (2S,2'S)-bis(2-((tert-butoxycarbonyl)amino)butanoate

[0601]

[Chem. 100]



Example 104A

10 [0602]

A suspension of 2-acetylnaphtho[2,3-b]furan-4,9-dione (200 mg), zinc (218 mg), sodium dithionite (725 mg), diisopropylethylamine (1.45 mL), and tetra-n-butylammonium bromide (27 mg) in N,N-dimethylformamide (11.9 mL) was stirred under nitrogen atmosphere at room temperature for 1 hour. Then, the suspension was cooled to 0°C, and the solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-4-isocyanatobutanoate in toluene, which was prepared from (S)-4-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (653 mg) according to the same method as in Reference example 1, was added dropwise over 15 minutes. After stirring at 0°C for 40 minutes, the reaction solution was filtered through Celite and the Celite was washed with

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ethyl acetate. Aqueous saturated ammonium chloride solution was added to the filtrate and the organic layer was separated. Then, the aqueous layer was further extracted with ethyl acetate twice. After the resulting 5 organic layer was dried over anhydrous sodium sulfate, it was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1-3:7) to yield Example 104A (256 mg).

10 (LC-MS: $[M-\text{Boc}+\text{H}]^+/\text{Rt}$ (min)) = 659/1.04
[0603]

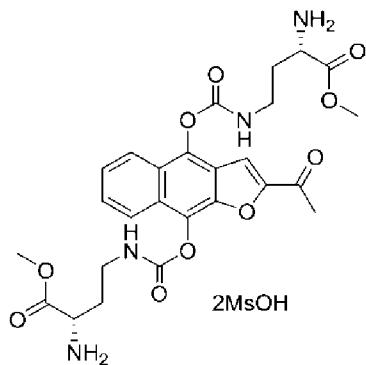
Example 104

Dimethyl

15 4,4' - (((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))
bis(carbonyl))bis(azanediyl)) (2S,2'S)-bis(2-aminobutanoate) dimethanesulfonate salt

[0604]

[Chem. 101]



Example 104

20 [0605]

A solution of Example 104A (0.052 g) and methanesulfonic acid (0.018 mL) in acetonitrile (0.50 mL) was stirred at 90°C for 1 hour. The reaction solution was diluted with ethyl acetate and stirred at room temperature for 10 minutes. 25 The precipitated solid was washed with ethyl acetate to yield

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Example 104 (0.046 g).

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.02-2.19 (4H, m), 2.31 (6H, s), 2.63 (3H, s), 3.25-3.42 (4H, m), 3.80 (3H, s), 3.81 (3H, s), 4.21 (2H, m), 7.61-7.71 (2H, m), 8.04 (2H, m), 8.07 (1H, s), 8.36-8.52 (6H, m).

5

(LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.46

[0606]

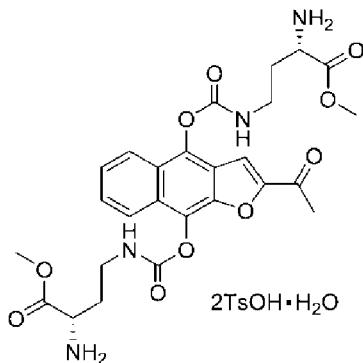
Example 105

Dimethyl

10 4,4'-((((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy)) bis(carbonyl))bis(azanediyl))(2S,2'S)-bis(2-aminobutanoate) ditoluenesulfonate salt monohydrate

[0607]

[Chem. 102]



15 **Example 105**

15

[0608]

20 A solution of Example 104A (0.10 g) and toluenesulfonic acid (0.26 g) in THF (3.0 mL)-water (0.073 mL) was stirred at 80°C for 1.5 hours and then stirred at room temperature overnight. The precipitated solid was washed with THF and chloroform to yield Example 105 (0.10 g).

20

¹H-NMR (400 MHz, DMSO-d₆) δ: 2.00-2.21 (4H, m), 2.28 (6H, s), 2.62 (3H, s), 3.27-3.41 (4H, m), 3.80 (3H, s), 3.81 (3H, s), 4.22 (2H, m), 7.11 (4H, d), 7.47 (4H, d), 7.66 (2H, m), 8.04 (2H, m), 8.06 (1H, s), 8.38-8.52 (6H, m).

25

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(LC-MS: $[M+2H]^{2+}/R_t$ (min)) = 280/0.42

[0609]

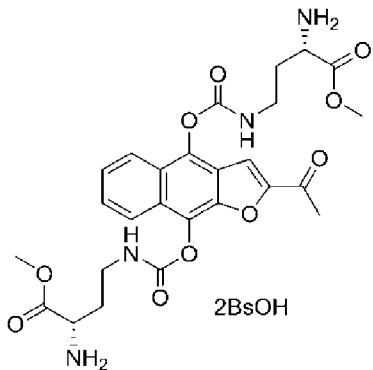
Example 106

Dimethyl

5 $4,4'$ -(((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl)) $(2S,2'S)$ -bis(2-aminobutanoate) dibenzenesulfonate salt

[0610]

[Chem. 103]



Example 106

10

[0611]

A solution of Example 104A (0.078 g) and benzenesulfonic acid (0.16 g) in THF (2.5 mL)-water (0.055 mL) was stirred at 80°C for 1 hour. The precipitated solid was washed with THF and chloroform to yield Example 106 (0.10 g).

15 1H -NMR (400 MHz, DMSO- d_6) δ : 2.01-2.20 (4H, m), 2.63 (3H, s), 3.26-3.41 (4H, m), 3.80 (3H, s), 3.81 (3H, s), 4.22 (2H, m), 7.27-7.34 (6H, m), 7.58-7.71 (6H, m), 8.04 (2H, m), 8.07 (1H, s), 8.38-8.51 (6H, m).

20 (LC-MS: $[M+2H]^{2+}/R_t$ (min)) = 280/0.48

[0612]

Example 107

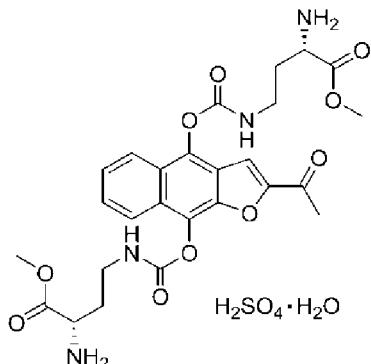
Dimethyl

25 $4,4'$ -(((2-acetylnaphtho[2,3-b]furan-4,9-diyl)bis(oxy))bis(carbonyl))bis(azanediyl)) $(2S,2'S)$ -bis(2-aminobutano

ate) monosulfate salt monohydrate

[0613]

[Chem. 104]



Example 107

5 [0614]

To a solution of Example 104A (0.070 g) in acetonitrile (3.0 mL) heated to 50°C, concentrated sulfuric acid (one drop) was added and the solution was stirred at 50°C for 30 minutes. The precipitated solid was washed with ethyl acetate to yield Example 107 (0.066 g).

10 $^1\text{H-NMR}$ (400 MHz, D_2O) δ : 2.08-2.27 (4H, m), 2.50 (3H, s), 3.37-3.43 (4H, m), 3.76 (3H, s), 3.78 (3H, s), 4.15-4.21 (2H, m), 7.48-7.59 (2H, m), 7.72-7.75 (1H, br), 7.93-7.98 (2H, m).

15 (LC-MS: $[\text{M}+2\text{H}]^{2+}/\text{Rt}$ (min)) = 280/0.48

[0615]

Example 108

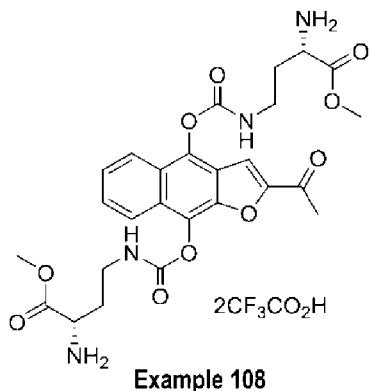
Dimethyl

4,4'-(4-acetyl-2,3-bifuran-4,9-diyl)bis(oxo) bis(carbonyl)bis(azanediyl)(2S,2'S)-bis(2-aminobutano

20 ate) ditrifluoroacetate salt

[0616]

[Chem. 105]



[0617]

A solution of Example 104A (0.11 g) in trifluoroacetic acid (1.0 mL) was stirred at room temperature for 30 minutes and then concentrated. The residue was suspended in ethyl acetate and then stirred at room temperature for 30 minutes. The precipitated solid was washed with ethyl acetate to Example 108 (0.076 g).

¹H-NMR (400 MHz, D₂O) δ: 2.11-2.28 (4H, m), 2.53 (3H, s), 3.37-3.44 (4H, m), 3.77 (3H, s), 3.78 (3H, s), 4.18 (2H, m), 7.50-7.60 (2H, m), 7.79 (1H, s), 7.96-8.00 (2H, m). (LC-MS: [M+2H]²⁺/Rt (min)) = 280/0.49

[0618]

Test examples

Hereinafter, test results of representative compounds of the present invention are shown, and the chemical characteristics and pharmacokinetics of the compounds are described. However, the present invention is not limited to these test examples.

[0619]

Test example 1. Evaluation of a conversion rate to 2-acetylnaphtho[2,3-b]furan-4,9-dione

For test compounds, the decrease rate of the test compounds and the conversion rate thereof to 2-acetylnaphtho[2,3-b]furan-4,9-dione in human plasma, CD1

mouse plasma, and pH 7.4 phosphate buffer solution were measured.

5 Test compounds were incubated at the concentration of 1 umol/L in human plasma (cat.no.12250210, COSMO BIO), CD1 mouse plasma (cat.no.AP3054, KAC), and phosphate buffer solution at 37°C, and removed at predetermined times (0, 5, 10, 30, 60, and 120 minutes). After protein-removing treatment was performed, they are analyzed with LC-MS. It should be noted that the protein-removing treatment used 10 acetonitrile containing: 10% volume of 1 mol/L hydrochloric acid; 1% volume of 46% citric acid; and phenytoin as an internal standard.

[0620]

The measurement condition of LC-MS is as described below.

15 LC-MS condition column: Kinetex 2.6u PFP 100A 50 x 2.1 mm

Column temperature: 40°C

Mobile phase: A: 0.1% formic acid-containing water
B: 0.1% formic acid-containing acetonitrile

20 A/B(min): 95/5(0) → 5/95(3) → 5/95(4) → 95/5(4.1) → 95/5(6)

Flow rate: 0.4 mL/min

Detection: ESI (positive mode)

Injection volume: 10 uL

25 [0621]

The result was shown in Table 7. The decomposition of the present compound typified by Example 6 rapidly proceeds in all conditions of the human plasma, the CD1 mouse plasma, and the pH 7.4 phosphate buffer solution. It was confirmed 30 that there is no interspecies difference.

Regarding the conversion rate, it was confirmed that the activated form, 2-acetylnaphtho[2,3-b]furan-4,9-dione (Activated form 1) was quickly produced even in the pH 7.4

5 phosphate buffer solution not containing an enzyme, which is in the same level as the human plasma and the CD1 mouse plasma. This result indicates that the test compounds are prodrugs that are converted to the activated form via a route other than an enzymatic conversion and exhibit a slight interspecies difference.

[0622]

[Table 7]

(% Measurement value)

Incubation time (min)		0	5	10	30	60	120
Human plasma	Example 6	100	0	0	0	0	0
	Activated form	0	24	31	48	64	71
CD1 mouse plasma	Example 6	100	0	0	0	0	0
	Activated form	0	23	31	63	67	76
Phosphate buffer solution (pH 7.4)	Example 6	100	0	0	0	0	0
	Activated form	0	20	29	55	61	78

10 Measurement values are calculated from the peak area ratio in LC-MS between an internal standard material, phenytoin and an active form, 2-acetylnaphtho[2,3-b]furan-4,9-dione, and are expressed in %.

15 [0623]

In the same way as Example 6, the incubation time was set as 120 minutes later, and the conversion rate of each of various test compounds to 2-acetylnaphtho[2,3-b]furan-4,9-dione in human plasma, CD1 mouse plasma, and pH 7.4 phosphate buffer solution was measured. The results are shown in Table 8. A series of the present compounds were confirmed to be converted to

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2-acetylnaphtho[2,3-b]furan-4,9-dione in pH 7.4 phosphate buffer solution in addition to human plasma and CD1 mouse plasma. Therefore, a series of the test compounds of the present invention were confirmed to be converted to the activated form via a route other than an enzymatic conversion.

5 [0624]

[Table 8-1]

(% Measurement value)

Incubation time (120 min)	Human plasma	CD1 mouse plasma	Phosphate buffer solution (pH 7.4)
Example 1	74	100	79
Example 2	87	76	59
Example 3	82	72	40
Example 4	93	79	53
Example 5	96	80	70
Example 7	69	51	41
Example 8	79	79	49
Example 9	65	81	50
Example 10	89	59	58
Example 11	100	100	58
Example 12	63	78	63
Example 13	95	50	13
Example 15	89	93	100
Example 17	80	81	80
Example 18	81	73	80
Example 20	65	73	57
Example 21	40	44	24
Example 22	37	56	22
Example 28	73	85	34
Example 32	81	74	46
Example 33	100	100	47
Example 34	41	52	24
Example 35	78	70	38
Example 36	73	66	46
Example 37	35	33	17
Example 38	85	72	39
Example 39	80	62	31
Example 40	89	86	50
Example 41	86	81	52
Example 42	69	N.T.	54

[Table 8-2]

Example 43	81	N.T.	63
Example 44	88	N.T.	48
Example 45	84	N.T.	48
Example 46	59	N.T.	54
Example 47	92	N.T.	65
Example 48	71	N.T.	59
Example 49	77	N.T.	58
Example 50	96	N.T.	61
Example 51	70	N.T.	55
Example 52	78	N.T.	55
Example 53	100	N.T.	41
Example 55	86	N.T.	63
Example 56	63	N.T.	30
Example 57	68	N.T.	34
Example 58	81	N.T.	40
Example 59	81	N.T.	66
Example 60	68	N.T.	39
Example 61	87	N.T.	55
Example 62	65	N.T.	37
Example 63	59	N.T.	51
Example 64	57	N.T.	40
Example 65	81	N.T.	73
Example 66	59	N.T.	44
Example 67	78	N.T.	60
Example 68	73	N.T.	59
Example 69	90	N.T.	71
Example 70	66	N.T.	48
Example 71	61	68	70
Example 72	53	42	38
Example 73	88	63	66
Example 74	70	62	82
Example 75	79	60	45
Example 76	68	71	57
Example 77	68	70	66
Example 78	54	66	43

[Table 8-3]

Example 79	71	N.T.	39
Example 80	54	N.T.	32
Example 81	74	N.T.	27
Example 82	74	N.T.	25
Example 83	67	67	31
Example 84	42	N.T.	31
Example 85	38	N.T.	37
Example 86	55	N.T.	38
Example 87	38	N.T.	36
Example 88	27	N.T.	26
Example 89	63	N.T.	58
Example 90	34	N.T.	26
Example 91	61	N.T.	45
Example 92	34	N.T.	26
Example 93	95	N.T.	72
Example 94	75	N.T.	53
Example 95	70	N.T.	54
Example 97	81	N.T.	61
Example 98	90	N.T.	66
Example 99	83	N.T.	60
Example 100	100	N.T.	76
Example 101	71	N.T.	56
Example 102	79	N.T.	59
Example 103	77	N.T.	53
Example 104	82	N.T.	57
Example 105	99	N.T.	65
Example 106	86	N.T.	55
Example 107	81	N.T.	50
Example 108	77	N.T.	44

Measurement values are calculated from the peak area ratio in LC-MS between an internal standard material, phenytoin and an active form, 5 2-acetylnaphtho[2,3-b]furan-4,9-dione, and are expressed in %. N.T. means that the test was not carried out.
[0625]

Test example 2. Solution stability test

For Example 6, Example 11, and Example 22, the stability in each pH was measured. Test compounds at a concentration of 25 umol/L in respective buffer solutions prepared at pH 5 2.0, 3.0, 5.0, 7.4, and 9.0 were allowed to stand at 25°C. After 0, 3, 6, 9, 12, and 24 hours, they were measured with HPLC.

[0626]

The buffer solutions used at respective pHs are as 10 described below.

pH 2.0: 50 mmol/L glycine buffer solution

pH 3.0: 50 mmol/L citrate buffer solution

pH 5.0: 50 mmol/L citrate buffer solution

pH 7.4: 50 mmol/L phosphate buffer solution

pH 9.0: 50 mmol/L glycine buffer solution

[0627]

The measurement condition of HPLC is as described below.

HPLC condition column: Acquity UPLC BEH C18, 1.7 um, 50 x 2.1 mm

20 Column temperature: 40°C

Mobile phase: A: 0.1% trifluoroacetic acid-containing water

B: acetonitrile

A/B(min): 95/5(0) → 0/100(3.5) → 0/100(4) → 95/5(4.01)

25 → 95/5(5)

Flow rate: 0.8 mL/min

Detection: Ultraviolet-visible detector, Measurement wave length 254 nm

Injection volume: 5 uL

30 [0628]

The test results are shown in Tables 9, 10, and 11.

[0629]

Example 6 and Example 11 were confirmed to be very stable

at pH 2.0, and to have sufficient stability at pH 3. In the case of pH 5.0, the residual ratio in 12 hours later was confirmed as 0%, and the residual ratios at pH 7.4 and pH 9.0 were confirmed as already 0% in 3 hours later.

5 Example 22 was confirmed to have sufficient stability although a slight decomposition was observed at pH 2.0 and pH 3.0. In the case of pH 5.0, the residual ratio in 24 hours later was confirmed as 24.5%, and the residual ratios at pH 7.4 and pH 9.0 were confirmed as already 0% in 3 hours
10 later.

15 From the above-described results, it was confirmed that the decomposition of a series of the present compounds typified by Example 6, Example 11, and Example 22 proceeds pH-dependently and chemically. From the present test result, it was shown that a series of the present compounds can become a prodrug for intravenous administration having sufficient stability by preparing an administration solution at pH 2.0 or pH 3.0 therefrom.

[0630]

20 [Table 9]

(% Residual ratio of Example 6)

Time (hr)	0	3	6	9	12	24
pH 2.0	100	100	100	100	100	99.8
pH 3.0	100	99.0	98.2	97.5	96.6	93.6
pH 5.0	100	27.3	10.8	3.6	0	0
pH 7.4	100	0	0	0	0	0
pH 9.0	100	0	0	0	0	0

[Table 10]

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(% Residual ratio of Example 11)

Time (hr)	0	3	6	9	12	24
pH 2.0	100	100	102	102	104	102
pH 3.0	100	98.6	97.3	98.8	94.5	90.7
pH 5.0	100	36.0	14.0	5.2	0	0
pH 7.4	100	0	0	0	0	0
pH 9.0	100	0	0	0	0	0

[Table 11]

(% Residual ratio of Example 22)

Time (hr)	0	3	6	9	12	24
pH 2.0	100	97.0	96.3	97.8	97.1	91.8
pH 3.0	100	98.6	97.8	96.9	96.0	92.6
pH 5.0	100	81.2	69.4	58.8	49.7	24.5
pH 7.4	100	0	0	0	0	0
pH 9.0	100	0	0	0	0	0

[0631]

5 Test example 3. Solubility test

The solubility of water-soluble prodrugs described in the EXAMPLES was measured. A water-soluble prodrug was added into 50 mmol/L glycine buffer solution (pH 2.0). After shaking at room temperature for 24 hours, the mixture 10 was filtered through a membrane filter, and then the filtrate was measured with HPLC.

[0632]

The measurement condition of HPLC is as described below. HPLC condition column: Acquity UPLC BEH C18, 1.7 um, 50 x 15 2.1 mm
Column temperature: 40°C
Mobile phase: A: 0.1% trifluoroacetic acid-containing

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water

B: acetonitrile

A/B(min): 95/5(0) → 0/100(3.5) → 0/100(4) → 95/5(4.01)
→ 95/5(9)

5 Flow rate: 0.4 mL/min

Detection: Ultraviolet-visible detector, Measurement wave length 254 nm

Injection volume: 5uL

[0633]

10 The test result is shown in Table 12. It was clarified that a series of water-soluble prodrugs relating to the present invention exhibit high water-solubility, which enables intravenous administration. It should be noted that each of 2-acetylnaphtho[2,3-b]furan-4,9-diyl bis(2,2-dimethylpropanoate), which is a prodrug for oral administration described in WO2012/119265, and 2-acetylnaphtho[2,3-b]furan-4,9-diyl dioctanoate, which is a prodrug for parenteral administration described in WO2013/120229, is completely different from a series of the 15 present compounds, and exhibits very low solubility.

20 [0634]

[Table 12-1]

Example number or Compound name	Solubility in pH 2.0 buffer solution
4	>5.0 mg/mL
5	>5.0 mg/mL
6	2.8 mg/mL
10	>5.0 mg/mL
11	>5.0 mg/mL
22	>5.0 mg/mL
23	>5.0 mg/mL
32	>5.0 mg/mL
33	>5.0 mg/mL
34	>5.0 mg/mL
35	>5.0 mg/mL
36	>5.0 mg/mL
37	>5.0 mg/mL
38	>5.0 mg/mL
39	>5.0 mg/mL
40	>5.0 mg/mL
41	>5.0 mg/mL
42	>5.0 mg/mL
43	>5.0 mg/mL
44	>5.0 mg/mL
45	>5.0 mg/mL
46	>5.0 mg/mL
47	>5.0 mg/mL
48	>5.0 mg/mL
49	>5.0 mg/mL
50	0.1 mg/mL
51	0.1 mg/mL
52	>5.0 mg/mL
53	>5.0 mg/mL
55	>5.0 mg/mL
56	3.3 mg/mL
57	>5.0 mg/mL
58	1.5 mg/mL
59	>5.0 mg/mL
60	>5.0 mg/mL
61	2.5 mg/mL
62	>5.0 mg/mL
63	>5.0 mg/mL

[Table 12-2]

64	>5.0 mg/mL
65	>5.0 mg/mL
66	>5.0 mg/mL
67	>5.0 mg/mL
68	>5.0 mg/mL
69	>5.0 mg/mL
70	>5.0 mg/mL
71	0.1 mg/mL
72	2.4 mg/mL
73	0.1 mg/mL
74	4.9 mg/mL
75	0.1 mg/mL
76	0.4 mg/mL
77	0.5 mg/mL
78	0.1 mg/mL
79	0.3 mg/mL
80	1.0 mg/mL
81	0.9 mg/mL
82	0.1 mg/mL
83	>5.0 mg/mL
84	>5.0 mg/mL
85	4.1 mg/mL
86	>5.0 mg/mL
87	4.0 mg/mL
88	3.2 mg/mL
89	>5.0 mg/mL
90	>5.0 mg/mL
91	3.6 mg/mL
92	>5.0 mg/mL
93	3.5 mg/mL
94	>5.0 mg/mL
95	>5.0 mg/mL
97	2.9 mg/mL
98	>5.0 mg/mL
99	>5.0 mg/mL
100	>5.0 mg/mL
101	>5.0 mg/mL
102	>5.0 mg/mL
103	>5.0 mg/mL
104	>5.0 mg/mL
105	>5.0 mg/mL
106	>5.0 mg/mL
107	>5.0 mg/mL

[Table 12-3]

108	>5.0 mg/mL
2-acetylnaphtho[2,3-b]furan-4,9-diyl bis(2,2-dimethylpropanoate)	<0.0001 mg/mL
2-acetylnaphtho[2,3-b]furan-4,9-diyl dioctanoate	<0.0001 mg/mL

[0635]

Test example 4. Pharmacokinetics tests

For water-soluble prodrugs described in the EXAMPLES, the concentration of 2-acetylnaphtho[2,3-b]furan-4,9-dione (Activated form 1) in plasma was measured. Animal species, an administration method, a method of making standard solutions, and a method of measuring the concentration in plasma are as described below.

[0636]

Animal: Seven-week-aged male CD1 (ICR) mice were used as an experimental animal.

Administration method: A test substance was weighed, and then dissolved in 50 mmol/L glycine buffered saline (pH 2.0) to produce an administration solution. The body weight of a mouse was measured, and the prepared administration solution was intravenously administered.

Blood collecting method: Heparin was added to a blood-collecting vessel, and blood was collected from a mouse. To the obtained blood, 46% of Citric acid was added in 1% volume. It was then centrifuged to obtain plasma. To the collected plasma, 1 mol/L HCl was added in 10% volume to produce a plasma sample. A sample obtained by adding 10% volume of 1 mol/L HCl to blank plasma was used as a blank sample.

Making of a standard solution: One mg of a test sample was weighed, and dissolved in 10 mL of acetonitrile using a measuring flask to make a standard solution of 100 ug/mL.

Measurement of the concentration in plasma: One hundred ug/mL of the standard solution was diluted in 50% acetonitrile solution to make calibration curve samples of target concentrations. Twenty uL of a blank sample was 5 added to 18 uL of the calibration curve sample to make a plasma calibration curve sample. Eighteen uL of 50% acetonitrile solution was added to 20 uL of the administered plasma sample to make a sample for plasma analysis. One hundred uL of acetonitrile (containing 1% volume of 10 mol/L 10 HCl) containing an internal standard was added to the plasma calibration curve sample and the sample for plasma analysis, respectively. It should be noted that phenytoin was used as the internal standard and its concentration was prepared in 100 nmol/L. 10 uL of each sample was analyzed with LC-MS. 15 A calibration curve was made from a value (peak ratio) of the peak area of a test substance in MS divided by the peak area of the internal standard, and the concentrations of plasma calibration curve samples. The concentration in a sample was calculated from the peak ratio of each sample 20 and the calibration curve.

[0637]

The test results are shown in Tables 13, 14, 15, 16, and 17. It was confirmed that by intravenously administering each of Examples 4, 5, 6, 11, and 23, 25 2-acetylnaphtho[2,3-b]furan-4,9-dione (Activated form 1) was rapidly produced from each of the Examples.

[0638]

In view of the result of test example 1 in addition to the result of test example 4, for a series of the present 30 compounds, the production of 2-acetylnaphtho[2,3-b]furan-4,9-dione can also be expected in human as in the case of mouse. Therefore, expansion of the use of 2-acetylnaphtho[2,3-b]furan-4,9-dione, of which

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the use in parenteral administration is limited, can be expected, and the present compounds are extremely useful.

[0639]

[Table 13]

Plasma	Example 4 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
10.0 mg/kg (i.v.)					
0.083 hr	5.87	4.62	6.37	5.62	0.90
0.5 hr	1.04	2.05	1.14	1.41	0.56
1.0 hr	0.53	0.75	1.37	0.88	0.44
2.0 hr	0.17	0.14	0.14	0.15	0.02

5

[0640]

[Table 14]

Plasma	Example 5 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
10.5 mg/kg (i.v.)					
0.083 hr	6.16	7.37	4.20	5.91	1.60
0.5 hr	1.82	2.59	2.04	2.15	0.39
1.0 hr	0.83	0.55	0.39	0.59	0.22
2.0 hr	0.20	0.67	0.12	0.33	0.30

[0641]

10

[Table 15]

Plasma	Example 6 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
9.6 mg/kg (i.v.)					
0.083 hr	4.95	5.87	5.79	5.54	0.51
0.5 hr	1.17	1.07	1.66	1.30	0.32
1.0 hr	0.53	0.28	0.38	0.40	0.12
2.0 hr	0.25	0.50	0.41	0.39	0.13

[0642]

[Table 16]

Plasma	Example 11 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
10.5 mg/kg (i.v.)					
0.083 hr	3.74	4.41	5.29	4.48	0.78
0.5 hr	0.69	1.17	1.39	1.08	0.36
1.0 hr	0.42	0.62	0.63	0.56	0.12
2.0 hr	0.36	0.28	0.08	0.24	0.15

[0643]

[Table 17]

Plasma	Example 23 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
11.0 mg/kg (i.v.)					
0.083 hr	6.87	8.20	8.49	7.85	0.87
0.5 hr	1.12	0.85	1.67	1.22	0.42
1.0 hr	0.47	0.29	0.36	0.37	0.09
2.0 hr	0.08	0.06	0.12	0.09	0.03

5 [0644]

Animal: Seven-week-aged male CD1 (ICR) mice were used as an experimental animal.

Administration method: A test substance was weighed, and then dissolved in 50 mmol/L glycine buffered solution (pH 2.0) containing 0.5% methylcellulose, to produce an administration solution. The body weight of a mouse was measured, and the prepared administration solution was orally administered.

Blood collecting method: Heparin was added to a blood-collecting vessel, and blood was collected from a mouse. To the obtained blood, 46% of Citric acid was added in 1% volume. It was then centrifuged to obtain plasma. To the collected plasma, 1 mol/L HCl was added in 10% volume to produce a plasma sample. A sample obtained by adding 10% volume of 1 mol/L HCl to blank plasma was used as a blank sample.

Making of a standard solution: One mg of a test sample was weighed, and dissolved in 10 mL of acetonitrile using a measuring flask to make a standard solution of 100 ug/mL.

Measurement of the concentration in plasma: One hundred 5 ug/mL of the standard solution was diluted in 50% acetonitrile solution to make calibration curve samples of target concentrations. Twenty uL of a blank sample was added to 18 uL of the calibration curve sample to make a plasma calibration curve sample. Eighteen uL of 50% 10 acetonitrile solution was added to 20 uL of the administered plasma sample to make a sample for plasma analysis. One hundred uL of acetonitrile (containing 1% volume of 10 mol/L HCl) containing an internal standard was added to the plasma calibration curve sample and the sample for plasma analysis, 15 respectively. It should be noted that phenytoin was used as the internal standard and its concentration was prepared in 100 nmol/L. 10 uL of each sample was analyzed with LC-MS. A calibration curve was made from a value (peak ratio) of the peak area of a test substance in MS divided by the peak 20 area of the internal standard, and the concentrations of plasma calibration curve samples. The concentration in a sample was calculated from the peak ratio of each sample and the calibration curve.

[0645]

25 The test results are shown in Tables 18, 19, and 20. It was confirmed that by orally administering each of Examples 4, 5, and 11, a high concentration of 2-acetylnaphtho[2,3-b]furan-4,9-dione (Activated form 1) was observed from each of the Example compounds.

30 [0646]

In view of the result of test example 3 in addition to the result of test example 4, a series of the present compounds are extremely useful since the improvement in oral

absorbability by increasing the water-solubility of 2-acetylnaphtho[2,3-b]furan-4,9-dione, of which the absorption in oral administration is an object due to its high crystallizability, can be expected.

5 [0647]

[Table 18]

Plasma	Example 4 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
251.2 mg/kg (p.o.)					
0.25 hr	2.74	2.17	2.88	2.60	0.37
0.5 hr	5.70	2.58	2.99	3.76	1.70
1.0 hr	10.91	3.01	3.82	5.91	4.35
2.0 hr	8.95	3.02	1.14	4.37	4.08
4.0 hr	6.00	9.28	4.70	6.66	2.36
6.0 hr	5.33	5.83	3.80	4.98	1.06
24.0 hr	0.06	0.24	0.08	0.13	0.10

[0648]

[Table 19]

Plasma	Example 5 Compound Concentration ($\mu\text{mol/L}$)				
	1	2	3	mean	S.D.
262.9 mg/kg (p.o.)					
0.25 hr	4.62	4.25	3.98	4.28	0.32
0.5 hr	4.66	3.20	2.23	3.36	1.23
1.0 hr	14.74	7.58	10.28	10.87	3.62
2.0 hr	10.37	7.99	8.70	9.02	1.22
4.0 hr	8.37	8.20	7.99	8.19	0.19
6.0 hr	1.24	1.28	0.50	1.01	0.44
24.0 hr	ND	ND	0.03	0.01	0.02

10

[0649]

[Table 20]

Plasma 232.5 mg/kg (p.o.)	Example 11 Compound Concentration (umol/L)				
	1	2	3	mean	S.D.
0.25 hr	18.86	19.65	25.31	21.27	3.52
0.5 hr	17.48	11.45	17.11	15.35	3.38
1.0 hr	10.87	18.98	15.93	15.26	4.10
2.0 hr	13.53	6.62	13.57	11.24	4.00
4.0 hr	6.12	3.73	11.49	7.11	3.98
6.0 hr	2.37	0.60	0.75	1.24	0.96
24.0 hr	ND	ND	0.04	0.01	0.02

[Industrial Applicability]

[0650]

5 Pharmaceutical compositions comprising a novel water-soluble prodrug of 2-acetylnaphtho[2,3-b]furan-4,9-dione relating to the present invention, a pharmaceutically acceptable salt, or a hydrate or solvate thereof; or solution-type formulation comprising them in an water solution exhibit excellent

10 solubility due to having a carbamate chain or carbonate chain of a certain structure containing an amine having nucleophilicity. Further, since 2-acetylnaphtho[2,3-b]furan-4,9-dione, which is an activated form, is rapidly produced through pH-dependent

15 and chemical conversion, interspecies difference and individual difference, which are clinical problems, are made small. Therefore, the present compounds are extremely useful since it is possible to expand the use of 2-acetylnaphtho[2,3-b]furan-4,9-dione, of which the absorption in oral administration is an object and of which the use in parenteral administration is also limited due

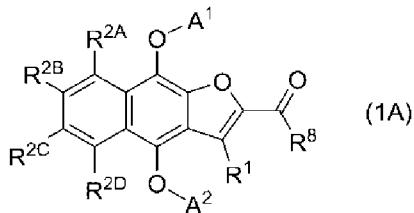
20 to its high crystallizability.

[CLAIMS]

[Claim 1]

A compound represented by formula (1A) or a pharmaceutically acceptable salt thereof:

5 [Chem. 1]



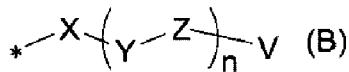
wherein

10 A^1 and A^2 are identical or different, and each independently $-C(=O)B$, $-C(=O)CR^{3A}R^{3B}B$, $-CO_2B$, $-C(=S)OB$, $-CONR^{3C}B$, $-C(=S)NR^{3C}B$, $-SO_2B$, $-SO_2CR^{3A}R^{3B}B$, $-SO_2(OB)$, $-SO_2NR^{3C}B$, $-P(=O)(B)_2$, $-P(=O)(CR^{3A}R^{3B}B)_2$, $-P(=O)(OB)_2$, $-P(=O)(NR^{3C}B)_2$, or a hydrogen atom, wherein A^1 and A^2 are not both hydrogen atoms,

wherein

15 B is an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted 3- to 12-membered cyclic amino group, or a group represented by the following formula (B):

[Chem. 2]



20 wherein

* denotes a bonding position;

25 X is a single bond, an optionally substituted C_{1-10} alkylene, an optionally substituted C_{3-10} cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or a polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C_{2-10} alkenylene, an optionally substituted

C_{2-10} alkynylene, an optionally substituted C_{6-10} arylene, or an optionally substituted C_{5-10} heteroarylene;

Y is a single bond, an oxygen atom, $-OCO-$, $-OCO_2-$, $-OCONR^{4A}-$, $-OSO_2-$, $-OSO_2NR^{4A}-$, $-CO-$, $-CO_2-$, $-CONR^{4A}-$, $-NR^{4A}-$, $-NR^{4A}CO-$, $-NR^{4A}CO_2-$, $-NR^{4A}CONR^{4B}-$, $-NR^{4A}SO_2-$, $-NR^{4A}SO_2O-$, $-NR^{4A}SO_2NR^{4B}-$, a sulfur atom, $-SO-$, $-SO_2-$, $-SO_2O-$, $-SO_2NR^{4A}-$, or an optionally substituted 3- to 12-membered cyclic aminyl linker group;

R^{4A} and R^{4B} are identical or different, and each independently a hydrogen atom, an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group;

Z is a single bond, an optionally substituted C_{1-10} alkylene, an optionally substituted C_{3-10} cycloalkylene, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, an optionally substituted 3- to 12-membered cyclic aminyl linker group, an optionally substituted C_{2-10} alkenylene, an optionally substituted C_{2-10} alkynylene, an optionally substituted C_{6-10} arylene, or an optionally substituted C_{5-10} heteroarylene;

n is 0, 1, or 2;

V is $-NHR^5$, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, or an optionally substituted 3- to 12-membered cyclic amino group, wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring; and

R^5 is a hydrogen atom, an optionally substituted

5 C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group, and
wherein

10 the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring; and

15 R^{3A} , R^{3B} , and R^{3C} are identical or different, and each independently a hydrogen atom, an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-10} alkynyl group, an optionally substituted C_{6-10} aryl group, or an optionally substituted C_{5-10} heteroaryl group;

20 R^1 is a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-10} aryl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{1-6} alkylcarbonyl group, an optionally substituted C_{3-10} cycloalkylcarbonyl group, an optionally substituted C_{6-10} arylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic carbonyl

group, a carboxyl group, an optionally substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted C_{6-10} aryloxycarbonyl group, an optionally substituted 3- to 5 12-membered monocyclic or polycyclic heterocyclyloxycarbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{3-10} cycloalkylthio group, an optionally substituted C_{6-10} arylthio group, an optionally substituted 10 3- to 12-membered monocyclic or polycyclic heterocyclylthio group, a sulfinate group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted C_{3-10} cycloalkylsulfinyl group, an optionally substituted C_{6-10} arylsulfinyl group, an optionally substituted 15 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, an optionally substituted aminosulfinyl group, an optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{3-10} cycloalkylsulfonyl group, an optionally substituted C_{6-10} arylsulfonyl group, an optionally substituted 20 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 25 12-membered cyclic aminosulfonyl group;

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, an optionally substituted amino group, an optionally substituted 3- to 12-membered cyclic amino group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally 30

substituted C_{6-10} aryl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{3-10} cycloalkoxy group, an optionally substituted C_{6-10} aryloxy group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclyloxy group, a carboxyl group, an optionally substituted C_{1-6} alkylcarbonyl group, an optionally substituted C_{3-10} cycloalkylcarbonyl group, an optionally substituted C_{6-10} arylcarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, an optionally substituted C_{1-6} alkoxycarbonyl group, an optionally substituted C_{3-10} cycloalkoxycarbonyl group, an optionally substituted C_{6-10} aryloxycarbonyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclloxycarbonyl group, an optionally substituted aminocarbonyl group, an optionally substituted 3- to 12-membered cyclic aminocarbonyl group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{3-10} cycloalkylthio group, an optionally substituted C_{6-10} arylthio group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclthio group, a sulfinate group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted C_{3-10} cycloalkylsulfinyl group, an optionally substituted C_{6-10} arylsulfinyl group, an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group, an optionally substituted aminosulfinyl group, an optionally substituted 3- to 12-membered cyclic aminosulfinyl group, a sulfonate group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{3-10} cycloalkylsulfonyl group, an optionally substituted C_{6-10} arylsulfonyl group, an optionally substituted

substituted 3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group, an optionally substituted aminosulfonyl group, or an optionally substituted 3- to 12-membered cyclic aminosulfonyl group; and

5 R⁸ is an optionally substituted C₁₋₁₀alkyl group.

[Claim 2]

The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein

10 a substituent of the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group, the optionally substituted 3- to 12-membered cyclic amino group, the optionally substituted amino group, the optionally substituted C₁₋₁₀alkyl group, the optionally substituted C₁₋₆alkyl group, the optionally substituted C₃₋₁₀cycloalkyl group, the optionally substituted C₂₋₁₀alkenyl group, the optionally substituted C₂₋₆alkenyl group, the optionally substituted C₂₋₁₀alkynyl group, the optionally substituted C₂₋₆alkynyl group, the optionally substituted C₁₋₆alkoxy group, the optionally substituted C₃₋₁₀cycloalkoxy group, the optionally substituted C₆₋₁₀aryloxy group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclxyloxy group, the optionally substituted C₆₋₁₀aryl group, the 15 optionally substituted C₁₋₆alkylcarbonyl group, the optionally substituted C₃₋₁₀cycloalkylcarbonyl group, the optionally substituted C₆₋₁₀arylcarbonyl group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclcarbonyl group, the optionally substituted C₁₋₆alkoxycarbonyl group, the optionally substituted C₃₋₁₀cycloalkoxycarbonyl group, the optionally substituted C₆₋₁₀aryloxycarbonyl group, the optionally substituted 20 3- to 12-membered monocyclic or polycyclic

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heterocyclyloxycarbonyl group, the optionally substituted aminocarbonyl group, the optionally substituted 3- to 12-membered cyclic aminocarbonyl group, the optionally substituted C₁₋₆alkylthio group, the optionally substituted C₃₋₁₀cycloalkylthio group, the optionally substituted C₆₋₁₀arylthio group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylthio group, the optionally substituted C₁₋₆alkylsulfinyl group, the optionally substituted C₃₋₁₀cycloalkylsulfinyl group, the optionally substituted C₆₋₁₀arylsulfinyl group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfinyl group, the optionally substituted aminosulfinyl group, the optionally substituted 3- to 12-membered cyclic aminosulfinyl group, the optionally substituted C₁₋₆alkylsulfonyl group, the optionally substituted C₃₋₁₀cycloalkylsulfonyl group, the optionally substituted C₆₋₁₀arylsulfonyl group, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclylsulfonyl group, the optionally substituted aminosulfonyl group, the optionally substituted 3- to 12-membered cyclic aminosulfonyl group, the optionally substituted C₅₋₁₀heteroaryl group, the optionally substituted C₁₋₁₀alkylene, the optionally substituted C₃₋₁₀cycloalkylene, the optionally substituted 3- to 12-membered monocyclic or polycyclic heterocycle, the optionally substituted 3- to 12-membered cyclic aminyl linker group, the optionally substituted C₂₋₁₀alkynylene, the optionally substituted C₆₋₁₀arylene, and the optionally substituted C₅₋₁₀heteroarylene in B, R¹, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{4A}, R^{4B}, R⁵, R⁸, X, Y, Z, and V is a group optionally substituted with one to five identical or different substituents each independently selected from the group

consisting of

- (1) a halogen atom,
- (2) a hydroxyl group,
- (3) a carboxyl group,
- 5 (4) a sulfinate group,
- (5) a sulfonate group,
- (6) a phosphate group,
- (7) an optionally substituted C_{1-6} alkyl group,
- (8) an optionally substituted C_{3-10} cycloalkyl group,
- 10 (9) an optionally substituted C_{6-10} aryl group,
- (10) an optionally substituted C_{5-10} heteroaryl group,
- (11) an optionally substituted C_{1-6} alkoxy group,
- (12) an optionally substituted C_{3-10} cycloalkoxy group,
- (13) an optionally substituted C_{1-6} alkoxycarbonyl group,
- 15 (14) an optionally substituted C_{1-6} alkylcarbonyl group,
- (15) an optionally substituted 3- to 12-membered monocyclic or polycyclic heterocyclic group,
- (16) an optionally substituted 3- to 12-membered cyclic amino group,
- 20 (17) $-NR^6R^7$,
- (18) $-CO_2R^6$,
- (19) a guanidine group,
- (20) $-CONR^6R^7$,
- (21) $-SO_2R^6$,
- 25 (22) $-SO_2NR^6R^7$,
- (23) a cyano group,
- (24) $-OCO_2R^6$,
- (25) $-OCONR^6R^7$, and
- (26) $-NR^6CO_2R^7$

30 wherein

a substituent in the (7), (8), (9), (10), (11), (12), (13), (14), (15), and (16) is a group optionally substituted with one to five identical or different substituents each

independently selected from the group consisting of

- (a) a halogen atom,
- (b) a hydroxyl group,
- (c) a C₁₋₆alkyl group,
- 5 (d) a C₁₋₆alkoxy group,
- (e) a cyano group,
- (f) a carboxyl group,
- (g) a sulfinate group,
- (h) a sulfonate group,
- 10 (i) a phosphate group,
- (j) a C₁₋₆alkoxycarbonyl group,
- (k) a C₁₋₆alkylcarbonyl group,
- (l) -NR⁶R⁷,
- (m) -CO₂R⁶,
- 15 (n) a guanidine group,
- (o) -CONR⁶R⁷,
- (p) -SO₂R⁶,
- (q) -SO₂NR⁶R⁷,
- (r) a C₆₋₁₀aryl group,
- 20 (s) C₅₋₁₀heteroaryl group,
- (t) a 3- to 12-membered cyclic amino group optionally substituted with one to three C₁₋₆alkyl groups, and
- 25 (u) a 3- to 12-membered monocyclic or polycyclic heterocyclic group optionally substituted with one to three C₁₋₆alkyl groups; and

R⁶ and R⁷ are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₁₀alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered

cyclic amino group.

[Claim 3]

The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -CONR^{3C}B, -SO₂B, -SO₂CR^{3A}R^{3B}B, -SO₂(OB), -SO₂NR^{3C}B, -P(=O)(B)₂, -P(=O)(CR^{3A}R^{3B}B)₂, -P(=O)(OB)₂, -P(=O)(NR^{3C}B)₂, or a hydrogen atom.

[Claim 4]

The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -C(=O)B, -C(=O)CR^{3A}R^{3B}B, -CO₂B, -CONR^{3C}B, or a hydrogen atom.

[Claim 5]

The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

[Claim 6]

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

R¹ is

- (1) a hydrogen atom;
- (2) a halogen atom;
- (3) a cyano group;
- (4) a hydroxyl group;

(5) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(6) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy

group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered cyclic amino group);

5 (7) a C_{1-6} alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, and a C_{3-10} cycloalkyl group);

10 (8) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

15 (9) a C_{1-6} alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered cyclic amino group);

(10) a carboxyl group;

20 (11) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

(a) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group),

25 (b) a C_{3-10} cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group), and

30 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group)); or

(12) a 3- to 12-membered cyclic aminocarbonyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups).

[Claim 7]

5 The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R¹ is a hydrogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₁₋₆alkylcarbonyl group, or a carboxyl group.

[Claim 8]

10 The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R¹ is a hydrogen atom.

[Claim 9]

15 The compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof,
wherein

R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently

(1) a hydrogen atom;

20 (2) a halogen atom;

(3) a cyano group;

(4) a hydroxyl group;

25 (5) an amino group (the amino group is optionally substituted with one or two groups selected from the group consisting of

30 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected

from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

5 (c) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

10 (d) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group));

15 (6) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three C₁₋₆alkyl groups);

20 (7) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

25 (8) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

30 (9) a C₆₋₁₀aryl group (the aryl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(10) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group

consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

5 (11) a C₁₋₆alkoxy group (the alkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

10 (12) a C₃₋₁₀cycloalkoxy group (the cycloalkoxy group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

15 (13) a C₆₋₁₀aryloxy group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

20 (14) a 3- to 12-membered monocyclic or polycyclic heterocyclyloxy group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(15) a carboxyl group;

25 (16) a C₁₋₆alkylcarbonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

30 (17) a C₃₋₁₀cycloalkylcarbonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

(18) a C₆₋₁₀arylcarbonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl

group, and a C₁₋₆alkoxy group);

5 (19) a 3- to 12-membered monocyclic or polycyclic heterocycl carbonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

10 (20) a C₁₋₆alkoxycarbonyl group (the alkoxy is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group),

15 (21) a C₃₋₁₀cycloalkoxycarbonyl group (the cycloalkoxy is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

20 (22) a C₆₋₁₀aryloxycarbonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (23) a 3- to 12-membered monocyclic or polycyclic heterocycl oxycarbonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (24) an aminocarbonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

30 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C_{3-10} cycloalkyl group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group), and

5 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group));

10 (25) a 3- to 12-membered cyclic aminocarbonyl group (the cyclic amino is optionally substituted with one to three C_{1-6} alkyl groups);

15 (26) a C_{1-6} alkylthio group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, $-NR^6R^7$, a C_{1-6} alkoxy group, a C_{3-10} cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

20 (27) a C_{3-10} cycloalkylthio group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

25 (28) a C_{6-10} arylthio group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

30 (29) a 3- to 12-membered monocyclic or polycyclic heterocyclylthio group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, and a C_{1-6} alkoxy group);

(30) a sulfinate group;

(31) a C_{1-6} alkylsulfinyl group (the alkyl is optionally substituted with one to three groups selected from the group

consisting of a halogen atom, a hydroxyl group, $-\text{NR}^6\text{R}^7$, a $\text{C}_{1-6}\text{alkoxy}$ group, a $\text{C}_{3-10}\text{cycloalkyl}$ group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

5 (32) a $\text{C}_{3-10}\text{cycloalkylsulfinyl}$ group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkyl}$ group, and a $\text{C}_{1-6}\text{alkoxy}$ group);

10 (33) a $\text{C}_{6-10}\text{arylsulfinyl}$ group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkyl}$ group, and a $\text{C}_{1-6}\text{alkoxy}$ group);

15 (34) a 3- to 12-membered monocyclic or polycyclic heterocyclsulfinyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkyl}$ group, and a $\text{C}_{1-6}\text{alkoxy}$ group);

20 (35) an aminosulfinyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

25 (a) a $\text{C}_{1-6}\text{alkyl}$ group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkoxy}$ group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three $\text{C}_{1-6}\text{alkyl}$ groups),

30 (b) a $\text{C}_{3-10}\text{cycloalkyl}$ group (the cycloalkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkyl}$ group, and a $\text{C}_{1-6}\text{alkoxy}$ group), and

(c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a $\text{C}_{1-6}\text{alkyl}$

group, and a C₁₋₆alkoxy group));

(36) a 3- to 12-membered cyclic aminosulfinyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups);

5 (37) a sulfonate group;

(38) a C₁₋₆alkylsulfonyl group (the alkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group);

10 (39) a C₃₋₁₀cycloalkylsulfonyl group (the cycloalkyl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

15 (40) a C₆₋₁₀arylsulfonyl group (the aryl is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

20 (41) a 3- to 12-membered monocyclic or polycyclic heterocyclsulfonyl group (the heterocycle is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group);

25 (42) an aminosulfonyl group (the amino is optionally substituted with one or two groups selected from the group consisting of

30 (a) a C₁₋₆alkyl group (the alkyl group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkoxy group, and a 3- to 12-membered monocyclic or polycyclic heterocyclic group, which is optionally substituted with one to three C₁₋₆alkyl groups),

(b) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is

optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group), and

5 (c) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, a C₁₋₆alkyl group, and a C₁₋₆alkoxy group)); or

10 (43) a 3- to 12-membered cyclic aminosulfonyl group (the cyclic amino is optionally substituted with one to three C₁₋₆alkyl groups).

[Claim 10]

The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are identical or different, and each independently a hydrogen atom, a halogen atom, a C₁₋₆alkyl group, a C₃₋₁₀cycloalkyl group, a C₁₋₆alkoxy group, or a carboxyl group.

[Claim 11]

20 The compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^{2A}, R^{2B}, R^{2C}, and R^{2D} are all hydrogen atoms.

[Claim 12]

25 The compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^{3A}, R^{3B}, and R^{3C} are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷.

[Claim 13]

5 The compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^{3A}, R^{3B}, and R^{3C} are identical or different, and each independently a hydrogen atom, or a C₁₋₁₀alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, -NR⁶R⁷, and -CO₂R⁶.

[Claim 14]

10 The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^{3A}, R^{3B}, and R^{3C} are all hydrogen atoms.

[Claim 15]

15 The compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R⁸ is a C₁₋₁₀alkyl group optionally substituted with one to three groups selected from the group consisting of a halogen atom, a hydroxyl group, -NR⁶R⁷, a C₁₋₆alkoxy group, a C₃₋₁₀cycloalkyl group, a C₆₋₁₀aryl group, and a 3- to 12-membered monocyclic 20 or polycyclic heterocyclic group.

[Claim 16]

The compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R⁸ is a methyl group.

25 [Claim 17]

The compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein

B is

30 (1) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group,

a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷);

5 (2) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷); or

10 (3) a group represented by the formula (B),
wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms
15 in the ring.

[Claim 18]

The compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof,
wherein

20 B is a 3- to 6-membered monocyclic heterocyclic group, a 3- to 6-membered cyclic amino group, or a group represented by the formula (B),

25 wherein the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

[Claim 19]

The compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof,
wherein

30 X is

(1) a single bond;
(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group

consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷);

5 (3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷);

10 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷); or

15 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

20 25 [Claim 20]

The compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein

X is

30 (1) a single bond;

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate

group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$); or

(3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$).

[Claim 21]

The compound according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Y is a single bond, an oxygen atom, $-\text{OCO}_2-$, $-\text{OCONR}^{4A}-$, $-\text{CONR}^{4A}-$, $-\text{NR}^{4A}-$, $-\text{NR}^{4A}\text{CO}-$, $-\text{NR}^{4A}\text{CO}_2-$, $-\text{NR}^{4A}\text{CONR}^{4B}-$, $-\text{NR}^{4A}\text{SO}_2-$, $-\text{NR}^{4A}\text{SO}_2\text{NR}^{4B}-$, a sulfur atom, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{4A}-$, or an optionally substituted 3- to 12-membered cyclic aminyl linker group.

[Claim 22]

The compound according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein Y is a single bond, an oxygen atom, or $-\text{NR}^{4A}-$.

[Claim 23]

The compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are identical or different, and each independently a hydrogen atom, or a C_{1-10} alkyl group optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$.

[Claim 24]

The compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are hydrogen atoms.

[Claim 25]

The compound according to any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein

5 Z is

(1) a single bond;

10 (2) a C_{1-10} alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

15 (3) C_{3-10} cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

20 (4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

25 (5) a 3- to 12-membered cyclic aminyl linker group (the cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-NR^6R^7$, $-CO_2R^6$, $-CONR^6R^7$, $-SO_2R^6$, and $-SO_2NR^6R^7$);

30 (6) C_{6-10} arylene (the arylene is optionally substituted

with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷); or

(7) C₅₋₁₀heteroarylene (the heteroarylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

[Claim 26]

The compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein

Z is

(1) a single bond;

(2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶);

(3) C₃₋₁₀cycloalkylene (the cycloalkylene is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶);

(4) a 3- to 12-membered monocyclic or polycyclic heterocycle (the heterocycle is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, -NR⁶R⁷, and -CO₂R⁶); or

(5) a 3- to 12-membered cyclic aminyl linker group (the

cyclic aminyl linker group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, $-\text{NR}^6\text{R}^7$, and $-\text{CO}_2\text{R}^6$).

5 [Claim 27]

The compound according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Z is a single bond, or C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting 10 of a carboxyl group and $-\text{CO}_2\text{R}^6$.

[Claim 28]

The compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein

15 V is

(1) $-\text{NHR}^5$;

(2) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$); or

(3) a 3- to 12-membered cyclic amino group (the cyclic amino group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, and $-\text{SO}_2\text{NR}^6\text{R}^7$), and

25 wherein the 3- to 12-membered monocyclic or polycyclic heterocyclic group and the 3- to 12-membered cyclic amino group have at least one or more secondary nitrogen atoms

in the ring.

[Claim 29]

The compound according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein V 5 is -NHR⁵, a 3- to 6-membered monocyclic heterocyclic group, or a 3- to 6-membered cyclic amino group, wherein the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring.

10 [Claim 30]

The compound according to any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein

R⁵ is

15 (1) a hydrogen atom;

(2) a C₁₋₁₀alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₆₋₁₀aryl group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, -SO₂NR⁶R⁷, -OCO₂R⁶, -OCONR⁶R⁷, and -NR⁶CO₂R⁷);

25 (3) a C₃₋₁₀cycloalkyl group (the cycloalkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷);

30 (4) a 3- to 12-membered monocyclic or polycyclic heterocyclic group (the heterocyclic group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group,

a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷);

5 (5) a C₆₋₁₀aryl group (the aryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷); or

10 (6) a C₅₋₁₀heteroaryl group (the heteroaryl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, and -SO₂NR⁶R⁷).

15 [Claim 31]

The compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, wherein

20 R⁵ is

(1) a hydrogen atom; or

25 (2) a C₁₋₁₀alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a sulfonate group, a phosphate group, a C₆₋₁₀aryl group, a C₁₋₆alkoxy group, a C₃₋₈cycloalkoxy group, -NR⁶R⁷, -CO₂R⁶, -CONR⁶R⁷, -SO₂R⁶, -SO₂NR⁶R⁷, -OCO₂R⁶, -OCONR⁶R⁷, and -NR⁶CO₂R⁷).

30 [Claim 32]

The compound according to any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷ are identical or different, and each independently

5 a hydrogen atom, or a C₁₋₆alkyl group optionally substituted with one to two groups selected from the group consisting of a halogen atom and a carboxyl group, wherein R⁶ and R⁷, when both are optionally substituted C₁₋₆alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered cyclic amino group.

[Claim 33]

The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

10 wherein

A¹ and A² are identical or different, and each independently -C(=O)B, -CO₂B, -CONR^{3C}B, or a hydrogen atom, wherein A¹ and A² are not both hydrogen atoms,

wherein

15 B is

(1) a 3- to 6-membered monocyclic or polycyclic heterocyclic group,

(2) a 3- to 6-membered cyclic amino group, or

(3) a group represented by the formula (B),

20 wherein

X is

(1) a single bond,

25 (2) C₁₋₆alkylene (the alkylene is optionally substituted with one to three substituents selected from the group consisting of a carboxyl group and -CO₂R⁶), or

(3) C₃₋₁₀cycloalkylene;

Y is a single bond, an oxygen atom, or -NR^{4A}-;

R^{4A} is a hydrogen atom;

Z is

30 (1) a single bond, or

(2) C₁₋₆alkylene;

n is 0 or 1;

V is

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(1) $-\text{NHR}^5$,

(2) a 3- to 6-membered monocyclic or polycyclic heterocyclic group, or

5 (3) a 3- to 6-membered cyclic amino group, wherein the 3- to 6-membered monocyclic or polycyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring;

R^5 is

10 (1) a hydrogen atom, or

(2) a C_{1-6} alkyl group (the alkyl group is optionally substituted with one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, a carboxyl group, a sulfinate group, a 15 sulfonate group, a phosphate group, a C_{6-10} aryl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, $-\text{NR}^6\text{R}^7$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{SO}_2\text{R}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $-\text{OCO}_2\text{R}^6$, $-\text{OCONR}^6\text{R}^7$, and $-\text{NR}^6\text{CO}_2\text{R}^7$), and

20 R^6 and R^7 are identical or different, and each independently a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two carboxyl groups, wherein R^6 and R^7 , when both are optionally substituted C_{1-6} alkyl groups, may be taken together with the nitrogen atom to which they are attached to form a 3- to 12-membered 25 cyclic amino group, and

wherein

the 3- to 6-membered monocyclic heterocyclic group and the 3- to 6-membered cyclic amino group have at least one or more secondary nitrogen atoms in the ring, and

30 R^{3c} is a hydrogen atom;

R^1 is a hydrogen atom;

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms; and

R^8 is a methyl group.

[Claim 34]

5 The compound according to any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein X is a single bond, or C₁₋₆alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶.

[Claim 35]

10 The compound according to any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein V is -NHR⁵.

[Claim 36]

15 The compound according to any one of claims 1 to 35, or a pharmaceutically acceptable salt thereof, wherein R⁵ is a hydrogen atom, or C₁₋₆alkyl optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and -CO₂R⁶.

[Claim 37]

20 The compound according to any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷ are C₁₋₆alkyl groups optionally substituted with one to two carboxyl groups.

[Claim 38]

25 The compound according to any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein A¹ and A² are identical or different, and each independently -CONR^{3C}B, or a hydrogen atom.

[Claim 39]

30 The compound according to any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein n is 1.

[Claim 40]

The compound according to any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein n

is 0.

[Claim 41]

The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

5 wherein

A^1 and A^2 are -CONHB,

wherein

B is a 3- to 6-membered monocyclic heterocyclic group or a group represented by the formula (B),

10 wherein

X is C_{1-6} alkylene optionally substituted with one to two substituents selected from the group consisting of a carboxyl group and $-CO_2R^6$,

n is 0,

15 V is $-NHR^5$ or a 3- to 6-membered monocyclic heterocyclic group, wherein the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring,

20 R^5 is a hydrogen atom, or a C_{1-6} alkyl group optionally substituted with one to two carboxyl groups, and

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

wherein

25 the 3- to 6-membered monocyclic heterocyclic group has at least one or more secondary nitrogen atoms in the ring;

R^1 is a hydrogen atom; and

R^{2A} , R^{2B} , R^{2C} , and R^{2D} are all hydrogen atoms.

[Claim 42]

30 A pharmaceutical composition comprising a compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof.

[Claim 43]

A therapeutic agent and/or prophylactic agent for cancer,

comprising a compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 44]

5 The therapeutic agent and/or prophylactic agent according to claim 43, wherein the cancer is at least one type of cancer selected from the group consisting of acute leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, polycythemia vera, malignant lymphoma, brain tumor, head and neck cancer, esophageal cancer, thyroid cancer, small cell lung cancer, non-small-cell lung cancer, 10 breast cancer, gastric cancer, gallbladder•bile duct cancer, hepatoma, pancreatic cancer, colon cancer, rectal cancer, chorioepithelioma, chorioblastoma, choriocarcinoma, 15 endometrial cancer, cervical cancer, urothelial cancer, renal cell cancer, testicular tumor, Wilms' tumor, skin cancer, malignant melanoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma.

[Claim 45]

20 A method for treating and/or preventing a cancer, characterized by administering to a patient in need thereof a therapeutically and/or prophylactically effective amount of a compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof.

25 [Claim 46]

The use of a compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutic agent and/or prophylactic agent for cancer.

30 [Claim 47]

The compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051706

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/14 C07D405/12 C07D307/92 A61K31/343 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/119265 A1 (ZHOUSHAN HAIZHONGZHOU XINSHENG PHARMACEUTICALS CO LTD [CN]; JIANG ZHIW) 13 September 2012 (2012-09-13) claims 1, 24 page 10 pages 13, 14 -----	1-47
A	VIG BALVINDER S ET AL: "Amino acids as promotoieties in prodrug design and development", ADVANCED DRUG DELIVERY REVIEWS, vol. 65, no. 10, 22 August 2012 (2012-08-22), pages 1370-1385, XP028737354, ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2012.10.001 figures 9, 15, 17, 20 page 1374, left column ----- -/-	1-47

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

3 May 2016

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Information on patent family members

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