

DESCRIPTION

[TITLE OF THE INVENTION]

URACIL DERIVATIVE HAVING VIRAL GROWTH INHIBITORY ACTIVITY AND PHARMACEUTICAL COMPOSITION CONTAINING SAME

[TECHNICAL FIELD]

[0001]

The present invention relates to a compound exhibiting coronavirus 3CL protease inhibitory activity and a pharmaceutical composition comprising a compound exhibiting coronavirus 3CL protease inhibitory activity.

[BACKGROUND ART]

[0002]

Coronaviruses, which belong to the order Nidovirales, family Coronaviridae, and the subfamily Coronavirinae, are positive-sense single-stranded RNA viruses that have a genome size of about 30 kilobases and are the largest among the known RNA viruses. Coronaviruses are classified into four genera, namely, the genus Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, and a total of seven types of coronaviruses, including two kinds in the genus Alphacoronavirus (HCoV-229E and HCoV-NL63) and five kinds in the genus Betacoronavirus (HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and SARS-CoV-2), are known as coronaviruses that infect humans. Among these, four kinds (HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43) are pathogens of common cold, while the other three kinds are severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), and a novel coronavirus (SARS-CoV-2), all of which cause severe pneumonia.

[0003]

Novel coronavirus infections (COVID-19) that occurred in December 2019, rapidly spread to the international community, and the pandemic was announced by the WHO on March 11, 2020. The number of infected people confirmed as of March 10, 2023, was more than 670 million, and the number of deaths reached more than 6.88 million (Non-patent Document 1). Droplet infection, contact infection, and aerosol infection have been reported as main routes of infection of SARS-CoV-2, and it has been confirmed that SARS-CoV-2 continues to drift in air together with aerosols and maintains infectivity for about 3 hours (Non-patent Document 2). The incubation period is about 2 to 14 days, and cold-like symptoms such as fever (87.9%), dry cough (67.7%), malaise (38.1%), and phlegm (33.4%) are typical (Non-patent Document 3). In severe cases, respiratory failure due to acute respiratory distress syndrome, acute lung injury, interstitial pneumonia, and the like occurs. Furthermore, multiple organ failure such as renal failure and hepatic failure has also been reported.

[0004]

In Japan, as a result of drug repositioning of existing drugs, remdesivir, which is an antiviral drug, dexamethasone, which is an anti-inflammatory drug, and baricitinib, which is an antirheumatic drug, have been approved as therapeutic agents against COVID-19, and in January 2022, tocilizumab, which is an anti-IL-6 receptor antibody, have been received additional approval. Furthermore, in July

2021, ronapreve(casirivimab/imdevimab), which is an antibody cocktail therapy, was approved as special case approval, in September 2021, sotrovimab was approved as special case approval, and in December 2021, molnupiravir was approved as special case approval. Sufficient evidence has not been obtained on the efficacy and safety of these drugs. Accordingly, it is imperative to create therapeutic agents against COVID-19.

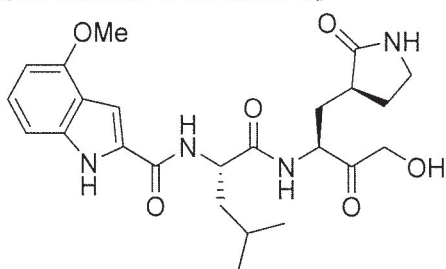
[0005]

Upon infection of cells, coronaviruses synthesize two polyproteins. In these two polyproteins, replication complexes producing viral genomes, and two proteases are included. Proteases play an indispensable role for cleaving the polyproteins synthesized by viruses and causing each of the proteins to function. Between these two proteases, 3CL protease (main protease) bears most of the cleavage of the polyproteins (Non-patent Document 4).

Regarding COVID-19 therapeutic agents targeting 3CL proteases, it was published in ClinicalTrials.gov that Phase 1b trials for Lufotrelvir (PF-07304814), which is a prodrug of PF-00835231, have completed by Pfizer Inc (NCT04535167). Furthermore, in March 2021, Pfizer Inc. announced that Phase 1 trials for PF-07321332, a therapeutic agent against novel coronavirus infections, will be initiated. The structural formulae of PF-00835231, Lufotrelvir and PF-07321332 are as shown below, and these agents are different from the compound of the present invention in chemical structure (Non-patent Documents 5, 9 and 10 and Patent Documents 1 and 2).

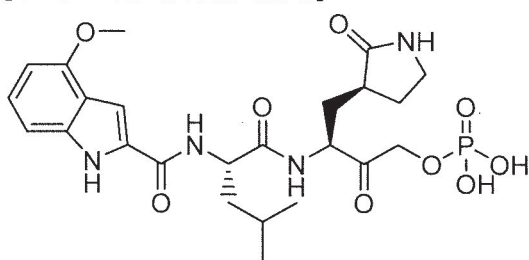
PF-00835231:

[Chemical Formula 1]



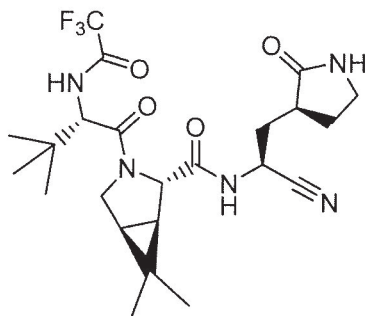
Lufotrelvir (PF-07304814):

[Chemical Formula 2]



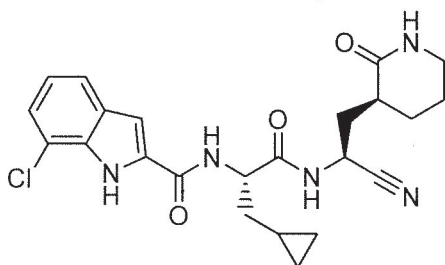
PF-07321332:

[Chemical Formula 3]



In December 2021, PAXLOVID (trademark) was approved for emergency use in the United States, and on February 10, 2022, the Paxlovid (registered trademark) PACK was approved as special case approval in Japan.
[0006]

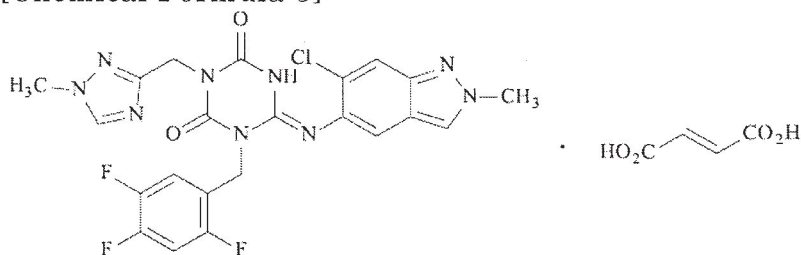
Furthermore, regarding COVID-19 therapeutic agents targeting 3CL proteases, the start of Phase 1 trials for PBI-0451 by Pardes Biosciences was reported in ClinicalTrials.gov on August 2021 (NCT05011812). The structural formula of PBI-0451 is as shown below, and these agents are different from the compound of the present invention in chemical structure (Non-patent Document 13).
[Chemical Formula 4]



[0007]

Furthermore, Xocova (registered trademark) was emergently approved in Japan on November 22, 2022 as a COVID-19 therapeutic agent targeting 3CL protease (Non-Patent Document 18).

The active ingredient of Xocova is ensitrelvir fumaric acid, and the structural formula thereof is as shown below and is different in chemical structure from the compound of the present invention (Patent Documents 10 and 11).
[Chemical Formula 5]



[0008].

No sufficient evidence has been obtained for mutations resistant to COVID-19 therapeutic agents targeting 3CL proteases.

[0009]

Compounds having 3CL protease inhibitory activity are disclosed in Non-patent Documents 5 to 8 and 14 to 17; however, the compounds related to the present invention are neither described nor suggested in any of the documents.

Compounds having P2X₃ and/or P2X_{2/3} receptor inhibitory activity have been disclosed in Patent Documents 3 to 9; however, the 3CL protease inhibitory activity

and the antiviral effect are neither described nor suggested in any of the documents.

Although compounds having an inhibitory action on HIV-1 reverse transcriptase are disclosed in Non-patent Document 12, 3CL protease inhibitory activity and anti-coronavirus effect have neither been described nor suggested.

[PRIOR ART REFERENCES]

[Patent Document]

[0010]

[Patent Document 1] International Publication WO 2021/205298A

[Patent Document 2] International Publication WO 2021/250648A

[Patent Document 3] International Publication WO 2012/020742A

[Patent Document 4] International Publication WO 2013/118855A

[Patent Document 5] China Patent Application Publication CN 113620888A

[Patent Document 6] China Patent Application Publication CN 113666914A

[Patent Document 7] China Patent Application Publication CN 113735838A

[Patent Document 8] Chinese Patent Application Publication CN 113773300A

[Patent Document 9] Chinese Patent Application Publication CN 113801097A

[Patent Document 10] International Publication WO 2022/138987A

[Patent Document 11] International Publication WO 2022/138988A

[Non-patent Document]

[0011]

[Non-patent Document 1] "COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University", [online], Johns Hopkins University, [retrieved on March 16, 2023], Internet <URL: <https://coronavirus.jhu.edu/map.html>>.

[Non-patent Document 2] The NEW ENGLAND JOURNAL of MEDICINE (2020), Vol. 382, pp. 1564-1567.

[Non-patent Document 3] "Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)", [online], February 28, 2020, WHO, [retrieved on March 16, 2023], Internet <URL: <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>>.

[Non-patent Document 4] Science (2003), Vol. 300, pp. 1763-1767.

[Non-patent Document 5] "A comparative analysis of SARS-CoV-2 antivirals characterizes 3CLpro inhibitor PF-00835231 as a potential new treatment for COVID-19", Journal of Virology, 2021 Mar 10; 95(7), e01819-20

[Non-patent Document 6] Cell Research (2020), Vol. 30, pp. 678-692.

[Non-patent Document 7] Science (2020), Vol. 368, pp. 409-412.

[Non-patent Document 8] ACS Central Science (2021), Vol. 7, No. 3, pp.467-475.

[Non-patent Document 9] 261st Am Chem Soc (ACS) Natl Meet · 2021-04-05/2021-04-16 · Virtual, N/A · Abst 243

[Non-patent Document 10] Science (2021), Vol. 374, pp. 1586-1593.

[Non-patent Document 11] Pfizer's Novel COVID-19 Oral Antiviral Treatment Candidate Reduced Risk Of Hospitalization Or Death By 89% In Interim Analysis Of Phase 2/3 EPIC-HR Study, [online], November 5, 2021, Pfizer Press Release, [retrieved on March 16, 2023], Internet <URL: <https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate>>

[Non-patent Document 12] Synthetic Communications (2006), Vol. 36, No. 19,

pp.2913-2920

[Non-patent Document 13] "Discovery and Development of PBI-0451", [online], March 24, 2022, 35th International Conference on Antiviral Research (ICAR), [retrieved on March 16, 2023], Internet <URL: <https://ir.pardesbio.com/static-files/fc7c4f8c-e0bd-4b97-8c9c-eff09bafd4db>>

[Non-patent Document 14] Molecules (2020), vol. 25, p. 3193

[Non-patent Document 15] Molecules (2020), vol. 25, p. 3920

[Non-patent Document 16] European Journal of Medicinal Chemistry (2020), Vol. 206, p. 112711

[Non-patent Document 17] Journal of the American Chemical Society (2022), vol. 144, pp. 2905-2920.

[Non-patent Document 18] Shionogi & Co., Ltd. Press Release (November 22, 2022)

[SUMMARY OF THE INVENTION]

[PROBLEMS TO BE SOLVED BY THE INVENTION]

[0012]

An object of the present invention is to provide a compound having coronavirus 3CL protease inhibitory activity. Preferably, the present invention provides a compound having an antiviral activity, particularly a coronavirus replication inhibitory activity, and a medicament comprising the compound.

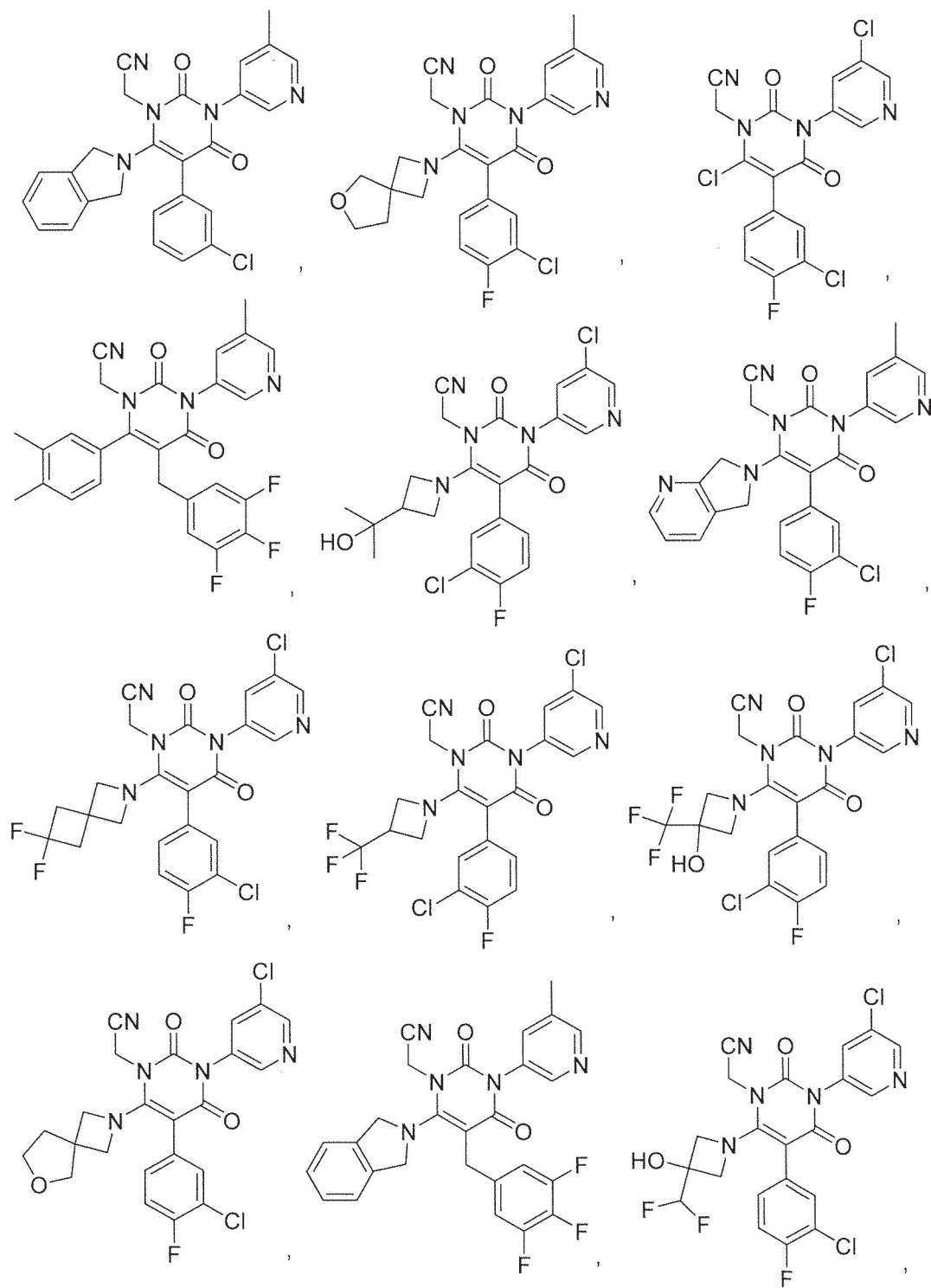
[MEANS FOR SOLVING THE PROBLEM]

[0013]

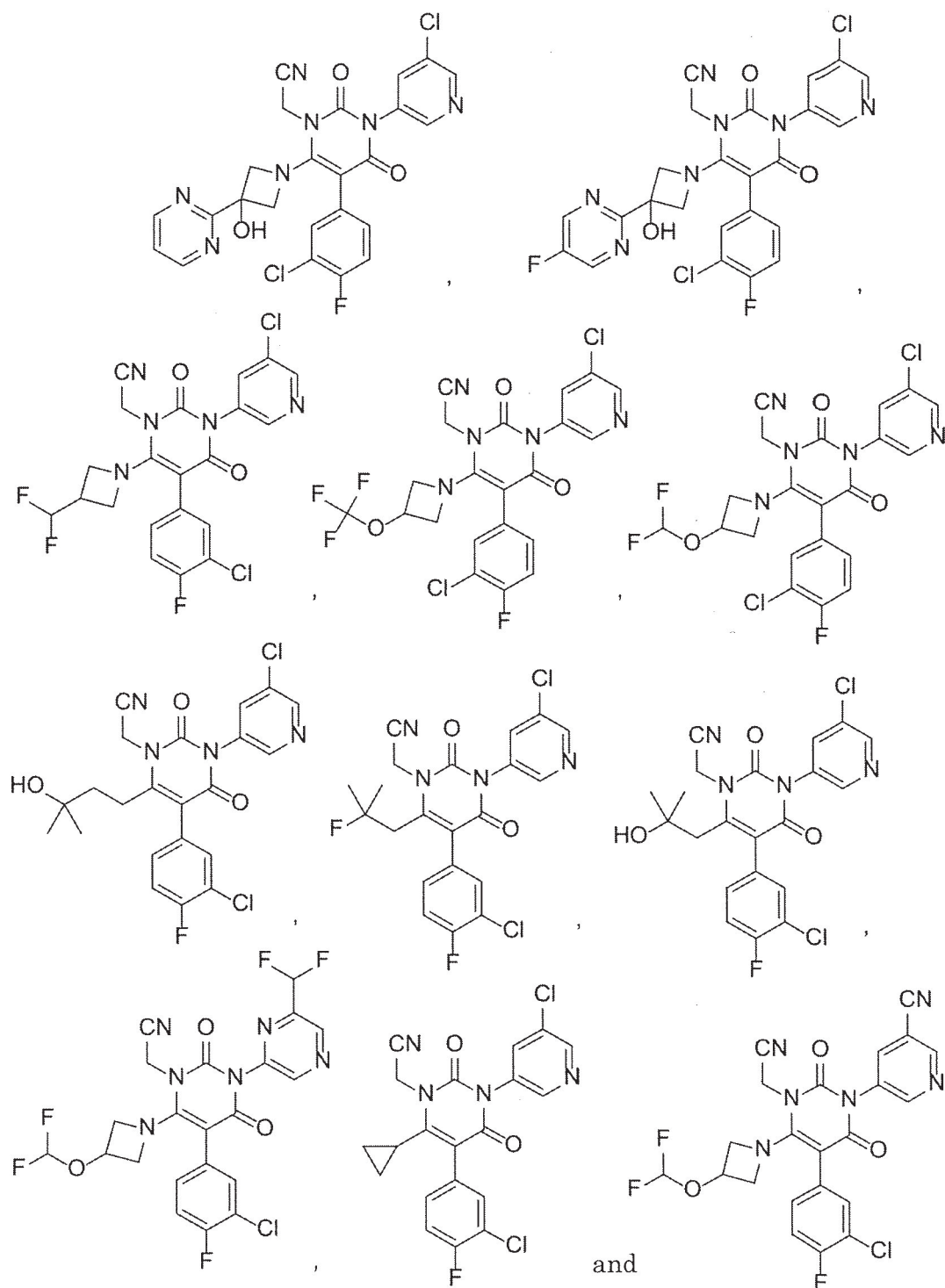
The present invention relates to the following.

(1") A compound selected from the group consisting of:

[Chemical Formula 6]

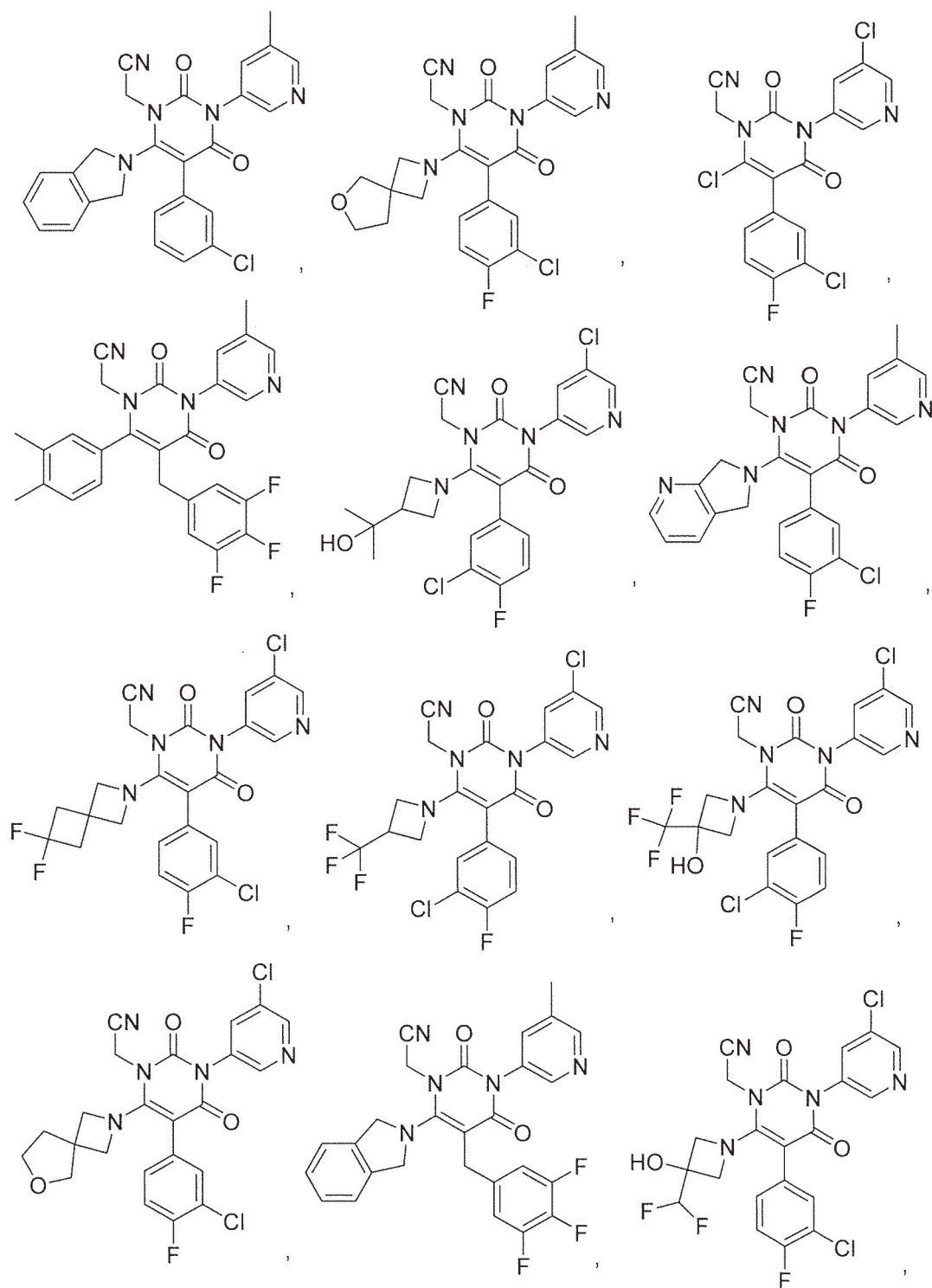


[Chemical Formula 7]



or a pharmaceutically acceptable salt thereof.

(2'') A compound is selected from the group consisting of:
[Chemical Formula 8]



[Chemical Formula 9]



(3'') A pharmaceutical composition comprising the compound according to any one of the above items (1'') or a pharmaceutically acceptable salt thereof.

(4'') A coronavirus 3CL protease inhibitor comprising the compound according to the above item (1'') or a pharmaceutically acceptable salt thereof.

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(5'') A coronavirus replication inhibitor comprising the compound according to the above item (1'') or a pharmaceutically acceptable salt thereof.

(5''') A coronavirus replication inhibitor comprising the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof.

(6'') The coronavirus replication inhibitor according to the above item (5'') or (5'''), wherein the coronavirus is an alpha coronavirus and/or beta coronavirus.

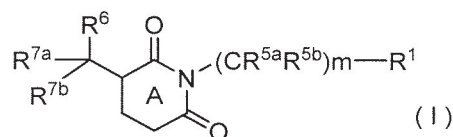
(7'') The coronavirus replication inhibitor according to the above item (6''), wherein the coronavirus is SARS-CoV-2.

[0014]

Furthermore, the present invention relates to the following.

(1') A compound represented by Formula (I):

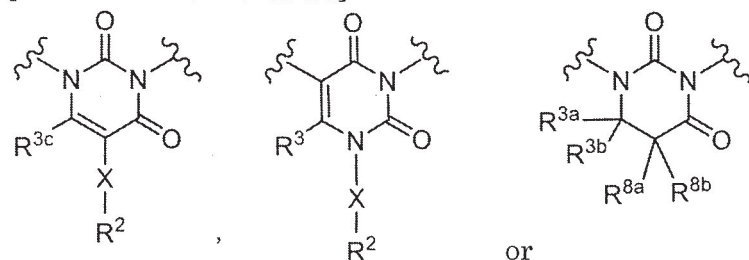
[Chemical Formula 10]



wherein

Ring A is a ring represented by:

[Chemical Formula 11]



wherein

X is a single bond, $-\text{CR}^{4a}\text{R}^{4b}-$, $-\text{C}(=\text{O})-$, $-\text{O}-$, or $-\text{S}-$;

R^{4a} and R^{4b} are each independently a hydrogen atom, or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, or substituted or unsubstituted alkyl;

R^{3c} is a hydrogen atom, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, or substituted or unsubstituted alkyloxy;

R^3 is substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or

unsubstituted non-aromatic heterocyclyloxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted carbamoyl, or substituted or unsubstituted alkyloxy;

R^{3a} is a hydrogen atom, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocyclyloxy, substituted or unsubstituted non-aromatic carbocyclyloxy, substituted or unsubstituted aromatic heterocyclyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted alkyloxy;

R^{3b} is a hydrogen atom;

R^{8a} is substituted or unsubstituted aromatic carbocyclyl or substituted or unsubstituted aromatic heterocyclyl; and

R^{8b} is a hydrogen atom, or substituted or unsubstituted alkyl;

or, R^{8a} and R^{8b} may be taken together with a carbon atom to which R^{8a} and R^{8b} are bonded to form a substituted or unsubstituted non-aromatic carbocycle or a substituted or unsubstituted non-aromatic heterocycle;

R¹ is substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino or cyano;

m is 0, 1, or 2;

R^{5a} is each independently a hydrogen atom, or substituted or unsubstituted alkyl;

R^{5b} is each independently a hydrogen atom, or substituted or unsubstituted alkyl;

R⁶ is cyano, halogen, or substituted or unsubstituted alkynyl;

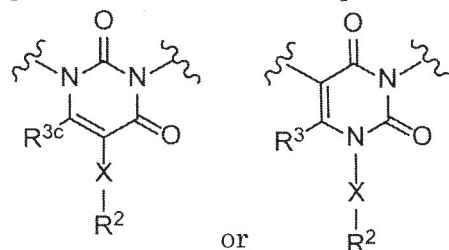
R^{7a} and R^{7b} are each independently a hydrogen atom, halogen, carboxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxycarbonyl;

or, R^{7a} and R^{7b} may be taken together with a carbon atom to which R^{7a} and R^{7b} are bonded to form a substituted or unsubstituted non-aromatic carbocycle or a substituted or unsubstituted non-aromatic heterocycle,

or a pharmaceutically acceptable salt thereof.

(2') The compound according to the above item (1'), wherein Ring A is a ring represented by:

[Chemical Formula 12]

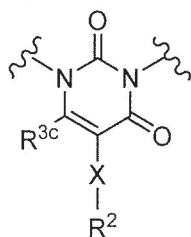


wherein R^{3c}, R³, X, and R² have the same meanings as those in the above item (1'),

or a pharmaceutically acceptable salt thereof.

(3') The compound according to the above item (1') or (2'), wherein Ring A is a ring represented by:

[Chemical Formula 13]



wherein R^{3c}, X, and R² have the same meanings as those in the above item (1'), or a pharmaceutically acceptable salt thereof.

(4') The compound according to any one of the above items (1') to (3'), wherein R¹ is substituted or unsubstituted aromatic heterocyclyl or substituted or unsubstituted non-aromatic heterocyclyl, or a pharmaceutically acceptable salt thereof.

(5') The compound according to any one of the above items (1') to (4'), wherein X is a single bond or -CH₂-, or a pharmaceutically acceptable salt thereof.

(6') The compound according to any one of the above items (1') to (5'), wherein R² is substituted or unsubstituted aromatic carbocyclyl, or a pharmaceutically acceptable salt thereof.

(7') The compound according to any one of the above items (1') to (6'), wherein R^{3c} and R³ are each independently substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkyloxy, or a pharmaceutically acceptable salt thereof.

(8') The compound according to any one of the above items (1') to (7'), wherein m is 0 or 1, or a pharmaceutically acceptable salt thereof.

(9') The compound according to any one of the above items (1') to (8'), wherein R^{5a} is each independently a hydrogen atom, and R^{5b} is each independently a hydrogen atom, or a pharmaceutically acceptable salt thereof.

(10') The compound according to any one of the above items (1') to (9'), wherein R⁶ is cyano, or a pharmaceutically acceptable salt thereof.

(11') The compound according to any one of the above items (1') to (10'), wherein R^{7a} and R^{7b} are each independently a hydrogen atom, or substituted or unsubstituted alkyl, or a pharmaceutically acceptable salt thereof.

(12') A pharmaceutical composition comprising the compound according to any one of the above items (1') to (11') or a pharmaceutically acceptable salt thereof.

(13') A coronavirus 3CL protease inhibitor comprising the compound according to any one of the above items (1') to (11') or a pharmaceutically acceptable salt thereof.

(14') A coronavirus replication inhibitor comprising the compound according to any one of the above items (1') to (11') or a pharmaceutically acceptable salt thereof.

(15') The coronavirus replication inhibitor according to the above item (14'), wherein the coronavirus is an alpha coronavirus and/or beta coronavirus.

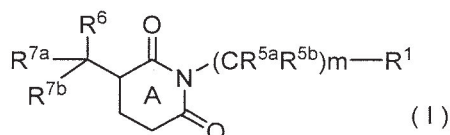
(16') The coronavirus replication inhibitor according to the above item (14'), wherein the coronavirus is SARS-CoV-2.

[0015]

Furthermore, the present invention relates to the following.

(1) A compound represented by Formula (I):

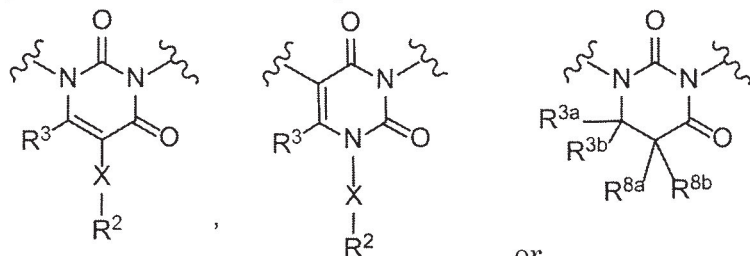
[Chemical Formula 14]



wherein

Ring A is a ring represented by:

[Chemical Formula 15]



wherein

X is a single bond, $-\text{CR}^{4a}\text{R}^{4b}-$, $-\text{C}(=\text{O})-$, $-\text{O}-$, or $-\text{S}-$;

R^{4a} and R^{4b} are each independently a hydrogen atom, or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, or substituted or unsubstituted non-aromatic heterocyclyl;

R^3 is substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, or substituted or unsubstituted alkyloxy;

R^{3a} is a hydrogen atom, substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted non-aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, substituted or unsubstituted non-aromatic carbocycloxy, substituted or unsubstituted aromatic heterocycloxy, substituted or unsubstituted non-aromatic heterocycloxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted alkyloxy;

R^{3b} is a hydrogen atom;

R^{8a} is substituted or unsubstituted aromatic carbocyclyl or substituted or unsubstituted aromatic heterocyclyl; and

R^{8b} is a hydrogen atom, or substituted or unsubstituted alkyl;

or, R^{8a} and R^{8b} may be taken together with a carbon atom to which R^{8a} and R^{8b} are bonded to form a substituted or unsubstituted non-aromatic carbocycle or a substituted or unsubstituted non-aromatic heterocycle;

R^1 is substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted carbamoyl, or substituted or unsubstituted amino;

m is 0, 1, or 2;

R^{5a} is each independently a hydrogen atom, or substituted or unsubstituted

alkyl;

R^{5b} is each independently a hydrogen atom, or substituted or unsubstituted alkyl;

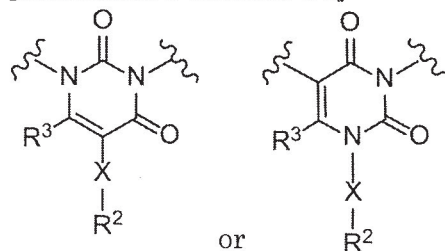
R^6 is cyano, halogen, or substituted or unsubstituted alkynyl;

R^{7a} and R^{7b} are each independently a hydrogen atom, halogen, carboxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxycarbonyl;

or, R^{7a} and R^{7b} may be taken together with a carbon atom to which R^{7a} and R^{7b} are bonded to form a substituted or unsubstituted non-aromatic carbocycle or a substituted or unsubstituted non-aromatic heterocycle,
or a pharmaceutically acceptable salt thereof.

(2) The compound according to the above item (1), wherein Ring A is a ring represented by:

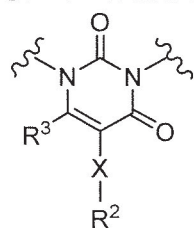
[Chemical Formula 16]



wherein R^3 , X, and R^2 have the same meanings as those in the above item (1),
or a pharmaceutically acceptable salt thereof.

(3) The compound according to the above item (1) or (2), wherein Ring A is a ring represented by:

[Chemical Formula 17]



wherein R^3 , X, and R^2 have the same meanings as those in the above item (1),
or a pharmaceutically acceptable salt thereof.

(4) The compound according to any one of the above items (1) to (3), wherein R^1 is substituted or unsubstituted aromatic heterocyclyl, or substituted or unsubstituted non-aromatic heterocyclyl, or a pharmaceutically acceptable salt thereof.

(5) The compound according to any one of the above items (1) to (4), wherein X is a single bond or $-CH_2-$, or a pharmaceutically acceptable salt thereof.

(6) The compound according to any one of the above items (1) to (5), wherein R^2 is substituted or unsubstituted aromatic carbocyclyl, or a pharmaceutically acceptable salt thereof.

(7) The compound according to any one of the above items (1) to (6), wherein R^3 is substituted or unsubstituted aromatic carbocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic carbocycloxy, halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkyloxy, or a pharmaceutically acceptable salt thereof.

(8) The compound according to any one of the above items (1) to (7), wherein m is 0 or 1, or a pharmaceutically acceptable salt thereof.

(9) The compound according to any one of the above items (1) to (8), wherein R^{5a} is each independently a hydrogen atom, and R^{5b} is each independently a hydrogen atom, or a pharmaceutically acceptable salt thereof.

(10) The compound according to any one of the above items (1) to (9), wherein R⁶ is cyano, or a pharmaceutically acceptable salt thereof.

(11) The compound according to any one of the above items (1) to (10), wherein R^{7a} and R^{7b} are each independently a hydrogen atom, or substituted or unsubstituted alkyl, or a pharmaceutically acceptable salt thereof.

(12) A pharmaceutical composition comprising the compound according to any one of the above items (1) to (11) or a pharmaceutically acceptable salt thereof.

(13) A coronavirus 3CL protease inhibitor comprising the compound according to any one of the above items (1) to (11) or a pharmaceutically acceptable salt thereof.

(14) A coronavirus replication inhibitor comprising the compound according to any one of the above items (1) to (11) or a pharmaceutically acceptable salt thereof.

(15) The coronavirus replication inhibitor according to the above item (14), wherein the coronavirus is an alpha coronavirus and/or beta coronavirus.

(16) The coronavirus replication inhibitor according to the above item (14), wherein the coronavirus is SARS-CoV-2.

[0016]

(100) A pharmaceutical composition for preventing and/or treating coronavirus infections, the pharmaceutical composition comprising the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof.

(100') A pharmaceutical composition for preventing and/or treating coronavirus infections, the pharmaceutical composition comprising the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof.

(101) The pharmaceutical composition according to the above item (100) or (100'), for preventing and/or treating novel coronavirus infections (COVID-19).

(102) The pharmaceutical composition according to the above item (100) or (100'), for preventing and/or treating infections caused by SARS-CoV-2.

(103) A method for inhibiting replication of coronavirus, the method comprising administering the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof.

(103') A method for inhibiting replication of coronavirus, the method comprising the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof.

(104) The method for inhibiting replication according to the above item (103) or (103'), wherein the coronavirus is alphacoronavirus and/or betacoronavirus.

(105) The method for inhibiting replication according to the above item (103) or (103'), wherein the coronavirus is SARS-CoV-2.

(106) A method for treating and/or preventing a disease associated with coronavirus 3CL proteases, the method comprising administering the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof.

(106') A method for treating and/or preventing a disease associated with coronavirus 3CL proteases, the method comprising administering the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof.

(107) A method for treating and/or preventing coronavirus infections, the method comprising administering the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof.

(107') A method for treating and/or preventing coronavirus infections, the method comprising administering the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof.

(108) The method for preventing and/or treating coronavirus infections according to the above item (107) or (107'), wherein the coronavirus infections are novel coronavirus infections (COVID-19).

(109) The method for treating and/or preventing coronavirus infections according to the above item (107) or (107'), wherein the coronavirus infections are infections caused by SARS-CoV-2.

(110) Use of the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for producing a therapeutic and/or prophylactic agent for a disease associated with coronavirus 3CL protease.

(110') Use of the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for producing a therapeutic and/or prophylactic agent for a disease associated with coronavirus 3CL proteases.

(111) Use of the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for producing a replication inhibitor for coronavirus.

(111') Use of the compound according to the above item (2''), a deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for producing a replication inhibitor for coronavirus.

(112) The use according to the above item (111) or (111'), wherein the coronavirus is alphacoronavirus and/or betacoronavirus.

(113) The use according to the above item (111) or (111'), wherein the coronavirus is SARS-CoV-2.

(114) Use of the compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for producing a therapeutic and/or prophylactic agent for coronavirus infections.

(114') Use of the compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for producing a therapeutic and/or prophylactic agent for coronavirus infections.

(115) The use according to the above item (114) or (114'), wherein the coronavirus infections are novel coronavirus infections (COVID-19).

(116) The use according to the above item (114) or (114'), wherein the coronavirus infections are infections caused by SARS-CoV-2.

(117) The compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a disease associated with coronavirus 3CL proteases.

(117') The compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing a disease associated with coronavirus 3CL proteases.

(118) The compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for use in the inhibition of replication of coronavirus.

(118') The compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for use in the inhibition of replication of coronavirus.

(119) The compound according to the above item (118) or (118') or a pharmaceutically acceptable salt thereof, wherein the coronavirus is alphacoronavirus and/or betacoronavirus.

(120) The compound according to the above item (118) or (118') or a pharmaceutically acceptable salt thereof, wherein the coronavirus is SARS-CoV-2.

(121) The compound according to any one of the above items (1) to (11), (1') to (11') and (1'') or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing coronavirus infections.

(121') The compound according to the above item (2'') or deuterated compound thereof, or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing coronavirus infections.

(122) The compound according to the above item (121) or (121') or a pharmaceutically acceptable salt thereof, wherein the coronavirus infections are novel coronavirus infections (COVID-19).

(123) The compound according to the above item (121) or (121') or a pharmaceutically acceptable salt thereof, wherein the coronavirus infections are infections caused by SARS-CoV-2.

[EFFECT OF THE INVENTION]

[0017]

The compound of the present invention has inhibitory activity against coronavirus 3CL proteases and is useful as a therapeutic(treating) agent and/or prophylactic(preventing) agent for coronavirus infections.

[MODE FOR CARRYING OUT THE INVENTION]

[0018]

Hereinafter, the meaning of each term used in the present specification will be described. Unless particularly stated otherwise, each term is used in the same sense, either alone or in combination with other terms.

The term "consist of" means having only the constituent elements.

The term "comprise" means that elements are not limited to the constituent elements, and elements that are not described are not excluded.

Hereinafter, the present invention will be described while showing exemplary embodiments. Throughout the present specification, it should be understood that, unless particularly stated otherwise, an expression of a singular form also includes the concept of a plural form thereof. Therefore, it should be understood that, unless particularly stated otherwise, an article for a singular form (for example, in the case of English, "a", "an", "the", or the like) also includes the concept of a plural form thereof.

Furthermore, it should be understood that, unless particularly stated otherwise, the terms used in the present specification are used in the meanings normally used in the above-described art. Accordingly, unless otherwise defined, all terminologies and scientific and technical terms used in the present specification have the same meanings as commonly understood by those having ordinary skill in the art to which the present invention belongs. In a case of contradiction, priority is given to the present specification (including definitions).

[0019]

"Halogen" includes a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom. Particularly, a fluorine atom and a chlorine atom are preferred.

[0020]

"Alkyl" includes linear or branched hydrocarbon groups each having 1 to 15 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms, and even more preferably 1 to 4 carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl, and n-decyl.

Preferred embodiments of "alkyl" include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and n-pentyl. More preferred embodiments include methyl, ethyl, n-propyl, isopropyl, and tert-butyl.

[0021]

"Alkenyl" includes linear or branched hydrocarbon groups each having one or more double bonds at any position and having 2 to 15 carbon atoms, preferably 2 to 10 carbon atoms, more preferably 2 to 6 carbon atoms, and even more preferably 2 to 4 carbon atoms. Examples include vinyl, allyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, and pentadecenyl.

Preferred embodiments of "alkenyl" include vinyl, allyl, propenyl, isopropenyl, and butenyl. More preferred embodiments include vinyl, and n-propenyl.

[0022]

"Alkynyl" includes linear or branched hydrocarbon groups each having one or more triple bonds at any position and having 2 to 10 carbon atoms, preferably 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms, and even more preferably 2 to 4 carbon atoms. Alkynyl may further have a double bond at any position. Examples include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, and decynyl.

Preferred embodiments of "alkynyl" include ethynyl, propynyl, butynyl, and pentynyl. More preferred embodiments include ethynyl and propynyl.

[0023]

"Aromatic carbocyclyl" means a cyclic aromatic hydrocarbon group having a single ring or two or more rings. Examples include phenyl, naphthyl, anthryl, and phenanthryl.

Preferred embodiments of the "aromatic carbocyclyl" include phenyl.

[0024]

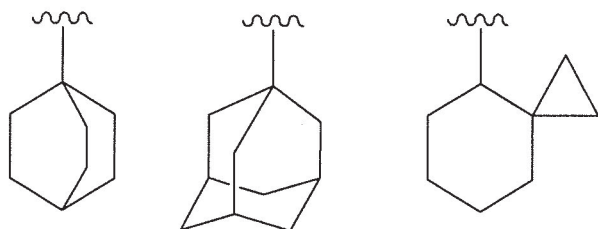
"Aromatic carbocycle" means a ring derived from the above-described "aromatic carbocyclyl".

[0025]

"Non-aromatic carbocyclyl" means a cyclic saturated hydrocarbon group or a cyclic non-aromatic unsaturated hydrocarbon group, both having a single ring or two or more rings. The "non-aromatic carbocyclyl" having two or more rings also includes a non-aromatic carbocyclyl having a single ring or two or more rings, to which the ring in the "aromatic carbocyclyl" is fused.

Furthermore, the "non-aromatic carbocyclyl" also includes a bridged group or a group forming a spiro ring, such as follows.

[Chemical Formula 18]



A non-aromatic carbocyclyl having a single ring preferably has 3 to 16 carbon atoms, more preferably 3 to 12 carbon atoms, and even more preferably 4 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclohexadienyl.

The non-aromatic carbocyclyl which is polycyclic having two or more rings preferably has 8 to 20 carbon atoms, and more preferably 8 to 16 carbon atoms. Examples include indanyl, indenyl, acenaphthyl, tetrahydronaphthyl, and fluorenyl. [0026]

“Non-aromatic carbocycle” means a ring derived from the above-described “non-aromatic carbocyclyl”. [0027]

“Aromatic heterocyclyl” means an aromatic cyclyl having a single ring or two or more rings, which has one or more identical or different heteroatoms optionally selected from O, S, and N in the ring(s).

An aromatic heterocyclyl having two or more rings also includes an aromatic heterocyclyl having a single ring or two or more rings, to which a ring in the “aromatic carbocyclyl” is fused, and the linking bond may be carried by any of the rings.

The aromatic heterocyclyl having a single ring is preferably a 5- to 8-membered ring, and more preferably a 5-membered or 6-membered ring. Examples of 5-membered aromatic heterocyclyl include pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, and thiadiazolyl. Examples of 6-membered aromatic heterocyclyl include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

The aromatic heterocyclyl having two rings is preferably an 8- to 10-membered ring, and more preferably a 9-membered or 10-membered ring. Examples include indolyl, isoindolyl, indazolyl, indoliziny, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, oxazolopyridyl, and thiazolopyridyl.

Examples of 9-membered aromatic heterocyclyl include indolyl, isoindolyl, indazolyl, indoliziny, purinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzofuryl, imidazopyridyl, triazolopyridyl, oxazolopyridyl, and thiazolopyridyl.

Examples of 10-membered aromatic heterocyclyl include quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, pteridinyl, and pyrazinopyridazinyl.

An aromatic heterocyclyl having three or more rings is preferably a 13- to 15-membered group. Examples include carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, and dibenzofuryl.

[0028]

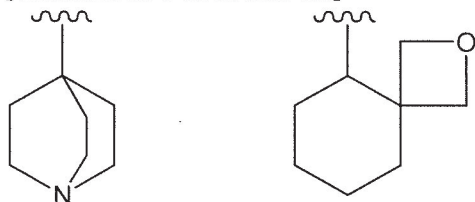
“Aromatic heterocycle” means a ring derived from the above-described “aromatic heterocyclyl”.

[0029]

“Non-aromatic heterocyclyl” means a non-aromatic cyclyl having a single ring or two or more rings, which has one or more identical or different heteroatoms optionally selected from O, S, and N in the ring(s). A non-aromatic heterocyclyl having two or more rings also includes a non-aromatic heterocyclyl having a single ring or two or more rings, to which a ring in each of the “aromatic carbocyclyl”, “non-aromatic carbocyclyl”, and/or “aromatic heterocyclyl” is fused, as well as a non-aromatic carbocyclyl having a single ring or two or more rings, to which a ring in the “aromatic heterocyclyl” is fused, and the linking bond may be carried by any of the rings.

Furthermore, the “non-aromatic heterocyclyl” also includes a bridged group or a group forming a spiro ring, such as follows.

[Chemical Formula 19]



The non-aromatic heterocyclyl having a single ring is preferably a 3- to 8-membered ring, and more preferably a 5-membered or 6-membered ring.

Examples of 3-membered non-aromatic heterocyclyl include thiiranyl, oxiranyl, and aziridinyl. Examples of 4-membered non-aromatic heterocyclyl include oxetanyl and azetidiny. Examples of 5-membered non-aromatic heterocyclyl include oxathiolanyl, thiazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, tetrahydrofuryl, dihydrothiazolyl, tetrahydroisothiazolyl, dioxolanyl, dioxolyl, and thiolanyl. Examples of 6-membered non-aromatic heterocyclyl include dioxanyl, thianyl, piperidyl, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, dihydropyridyl, tetrahydropyridyl, tetrahydropyranyl, dihydroxazinyl, tetrahydropyridazinyl, hexahydropyrimidinyl, dioxazinyl, thiinyl, and thiazinyl. Examples of the 7-membered non-aromatic heterocyclyl include hexahydroazepinyl, tetrahydrodiazepinyl, and oxepanyl.

The non-aromatic heterocyclyl having two or more rings is preferably an 8- to 20-membered ring, more preferably an 8- to 13-membered ring, and even more preferably an 8- to 10-membered ring. Examples include indolinyl, isoindolinyl, chromanyl, and isochromanyl.

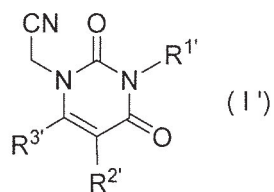
[0030]

“Non-aromatic heterocycle” means a ring derived from the above-described “non-aromatic heterocyclyl”.

[0031]

Furthermore, examples of the compound represented by Formula (I) include a compound represented by the following Formula (I'):

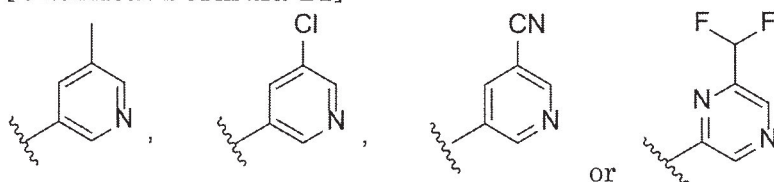
[Chemical Formula 20]



wherein

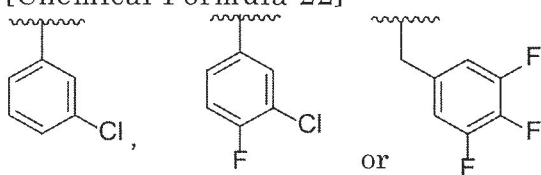
R¹ is a group represented by:

[Chemical Formula 21]



R² is a group represented by:

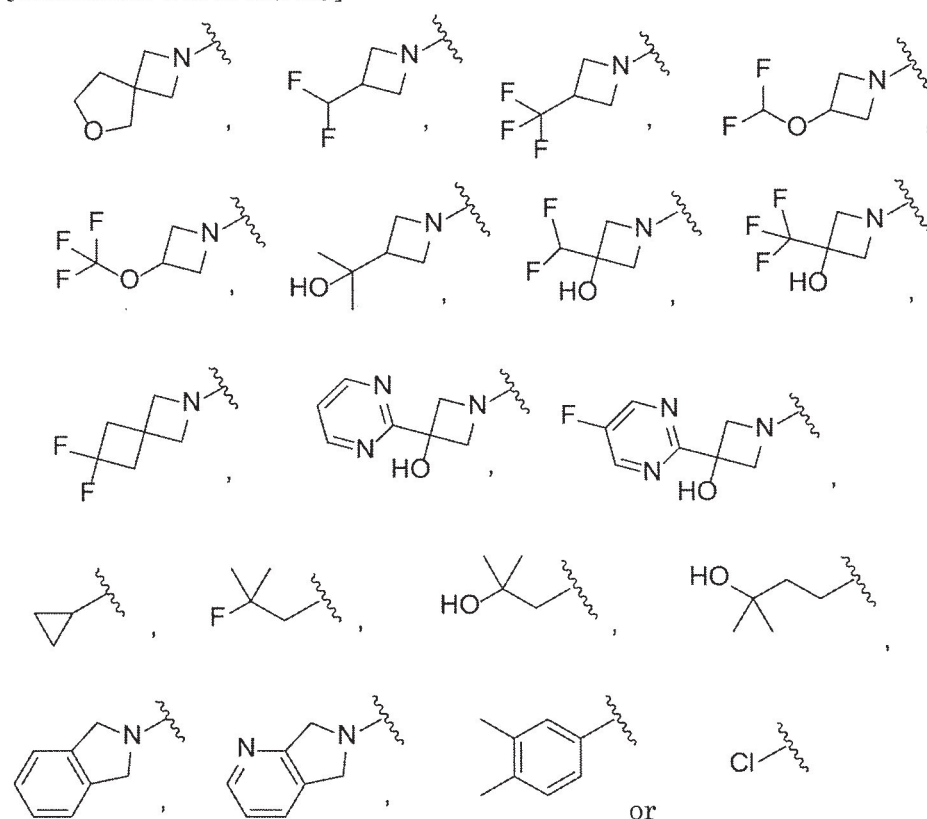
[Chemical Formula 22]



and

R³ is a group represented by:

[Chemical Formula 23]



[0032]

The compounds represented by Formula (I) are not limited to specific isomers but include all possible isomers (e.g., keto-enol isomers, imine-enamine isomers, diastereoisomers, enantiomers, rotamers or the like), racemates or mixtures thereof.

[0033]

One or more hydrogen, carbon and/or other atoms in the compounds represented by Formula (I) may be replaced with isotopes of hydrogen, carbon and/or other atoms respectively. Examples of such isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, as in the cases of ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , and ^{36}Cl , respectively. The compounds represented by Formula (I) include the compounds replaced with these isotopes. The compounds replaced with the isotopes are also useful as pharmaceutical products. The compounds represented by Formula (I) encompass all of radiolabeled forms replaced with radioactive isotopes included in the above isotopes. Furthermore, a "radiolabeling method" for producing the "radiolabeled forms" is also included in the present invention, and the "radiolabeled forms" are useful as tools for metabolic pharmacokinetics studies, studies on binding assay, and/or diagnostics.

[0034]

The radiolabeled form of the compound represented by Formula (I) can be prepared using well-known methods in the art. For example, a tritium-labeled compound represented by Formula (I) can be prepared by introducing tritium into a specific compound represented by Formula (I) by catalytic dehalogenation reaction using tritium. This method includes reacting an appropriately halogenated precursor of the compound represented by Formula (I) with tritium gas in the presence of an appropriate catalyst, such as Pd/C, and in the presence or absence of a base. Regarding other appropriate methods for preparing tritium-labeled compounds, "Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987)" can be referred to. A ^{14}C -labeled compound can be prepared by using a raw material having ^{14}C carbon.

[0035]

Examples of the pharmaceutically acceptable salt of the compound represented by Formula (I) include salts of the compound represented by Formula (I) with alkali metals (e.g., lithium, sodium, potassium, and the like), alkaline earth metals (e.g., calcium, barium, and the like), magnesium, transition metals (e.g., zinc, iron, and the like), ammonia, organic bases (e.g., trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, pyridine, picoline, quinoline, and the like), and amino acids, or salts of the compound represented by Formula (I) with inorganic acids (e.g., hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid, hydroiodic acid, and the like), and organic acids (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, succinic acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, trifluoroacetic acid, and the like). These salts can be formed according to methods that are conventionally carried out.

[0036]

The compounds represented by Formula (I) or pharmaceutically acceptable salts thereof of the present invention may form solvates (e.g., hydrates), co-crystal and/or crystal polymorphs. The compounds represented by Formula (I) or pharmaceutically acceptable salts thereof of the present invention encompass those various solvates, co-crystal and crystal polymorphs. "Solvates" may be those wherein any numbers of solvent molecules (e.g., water molecules or the like) are

coordinated with the compounds represented by Formula (I). When the compound represented by Formula (I) or a pharmaceutically acceptable salt thereof is allowed to stand in the atmosphere, the compound may absorb water, resulting in attachment of adsorbed water or formation of a hydrate. Furthermore, crystalline polymorphs may be formed by recrystallizing the compounds represented by Formula (I) or pharmaceutically acceptable salts thereof. The term "co-crystal" means that the compound represented by Formula (I) or a salt thereof and a counter molecule are present in the same crystal lattice, and may contain any number of counter molecules.

[0037]

The compounds represented by Formula (I) or pharmaceutically acceptable salts thereof of the present invention may form prodrugs, and the present invention also encompasses such various prodrugs. A prodrug is a derivative of a compound of the present invention having a group that can be chemically or metabolically degraded, and is a compound which becomes a pharmaceutically active compound of the present invention in vivo as a result of solvolysis or under physiological conditions. Prodrugs encompass compounds that are converted to the compounds represented by Formula (I) through enzymatic oxidation, reduction, hydrolysis or the like under physiological conditions and in vivo, compounds that are converted to the compounds represented by Formula (I) through hydrolysis by gastric acid etc., and the like. Methods for selecting and producing an appropriate prodrug derivative are described in, for example, "Design of Prodrugs, Elsevier, Amsterdam, 1985". A prodrug may have activity per se.

[0038]

When the compounds represented by Formula (I) or pharmaceutically acceptable salts thereof have hydroxy group(s), examples of the prodrug include acyloxy derivatives and sulfonyloxy derivatives that are prepared by, for example, reacting compounds having hydroxy group(s) with suitable acyl halide, suitable acid anhydride, suitable sulfonyl chloride, suitable sulfonyl anhydride and mixed anhydride, or with a condensing agent. Examples include CH_3COO^- , $\text{C}_2\text{H}_5\text{COO}^-$, tert-BuCOO^- , $\text{C}_{15}\text{H}_{31}\text{COO}^-$, PhCOO^- , $(\text{m-NaOOCPh})\text{COO}^-$, $\text{NaOOCCH}_2\text{CH}_2\text{COO}^-$, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COO}^-$, $\text{CH}_2\text{N}(\text{CH}_3)_2\text{COO}^-$, CH_3SO_3^- , $\text{CH}_3\text{CH}_2\text{SO}_3^-$, CF_3SO_3^- , $\text{CH}_2\text{FSO}_3^-$, $\text{CF}_3\text{CH}_2\text{SO}_3^-$, $\text{p-CH}_3\text{O-PhSO}_3^-$, PhSO_3^- , and $\text{p-CH}_3\text{PhSO}_3^-$.

[0039]

Since the compound according to the present invention has coronavirus 3CL protease inhibitory activity, the compound is useful as a therapeutic and/or prophylactic agent for a disease associated with coronavirus 3CL proteases. When the term "therapeutic agent and/or prophylactic agent" is used in the present invention, this also includes a symptom ameliorating agent. The disease associated with coronavirus 3CL proteases may be viral infections, and preferably coronavirus infections.

According to an aspect, the coronavirus may be a coronavirus that infects human beings. The coronavirus that infects human beings may be HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and/or SARS-CoV-2.

As an embodiment, as the coronavirus, alphacoronavirus and/or betacoronavirus, more preferably betacoronavirus, and further preferably sarbecovirus are exemplified.

According to an aspect, the alphacoronavirus may be HCoV-229E and HCoV-NL63. The alphacoronavirus may be particularly preferably HCoV-229E.

According to an aspect, the betacoronavirus may be HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and/or SARS-CoV-2. The betacoronavirus may be HCoV-OC43 or SARS-CoV-2, and particularly preferably SARS-CoV-2.

According to an aspect, the betacoronavirus may be betacoronavirus lineage A (β -coronavirus lineage A), betacoronavirus lineage B (β -coronavirus lineage B), and betacoronavirus lineage C (β -coronavirus lineage C). The betacoronavirus may be more preferably betacoronavirus lineage A (β -coronavirus lineage A) and betacoronavirus lineage B (β -coronavirus lineage B) and particularly preferably betacoronavirus lineage B (β -coronavirus lineage B).

Examples of the betacoronavirus lineage A (β -coronavirus lineage A) include HCoV-HKU1 and HCoV-OC43, and preferably HCoV-OC43. Examples of the betacoronavirus lineage B (β -coronavirus lineage B) include SARS-CoV and SARS-CoV-2, and preferably SARS-CoV-2. The betacoronavirus lineage C (β -coronavirus lineage C) may be MERS-CoV.

According to an aspect, the coronavirus may be HCoV-229E, HCoV-OC43, and/or SARS-CoV-2, and particularly preferably SARS-CoV-2.

The coronavirus infections may be infections caused by HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and/or SARS-CoV-2. Preferably, the coronavirus infections may be infections caused by HCoV-229E, HCoV-OC43, and/or SARS-CoV-2, and particularly preferably infection caused by SARS-CoV-2.

The coronavirus infections may be particularly preferably novel coronavirus infections (COVID-19).

[0040]

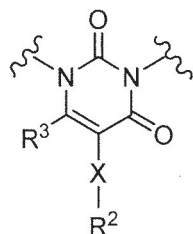
(Method for producing compound of present invention)

For example, the compound represented by Formula (I) according to the present invention can be prepared by the general procedure described below. Regarding extraction, purification, and the like, the treatments carried out in ordinary experiments of organic chemistry may be carried out.

The compounds of the present invention can be produced with reference to techniques known in the art. The compound can be produced, for example, with reference to WO 2012/020742 A, WO 2013/118855 A, and the like.

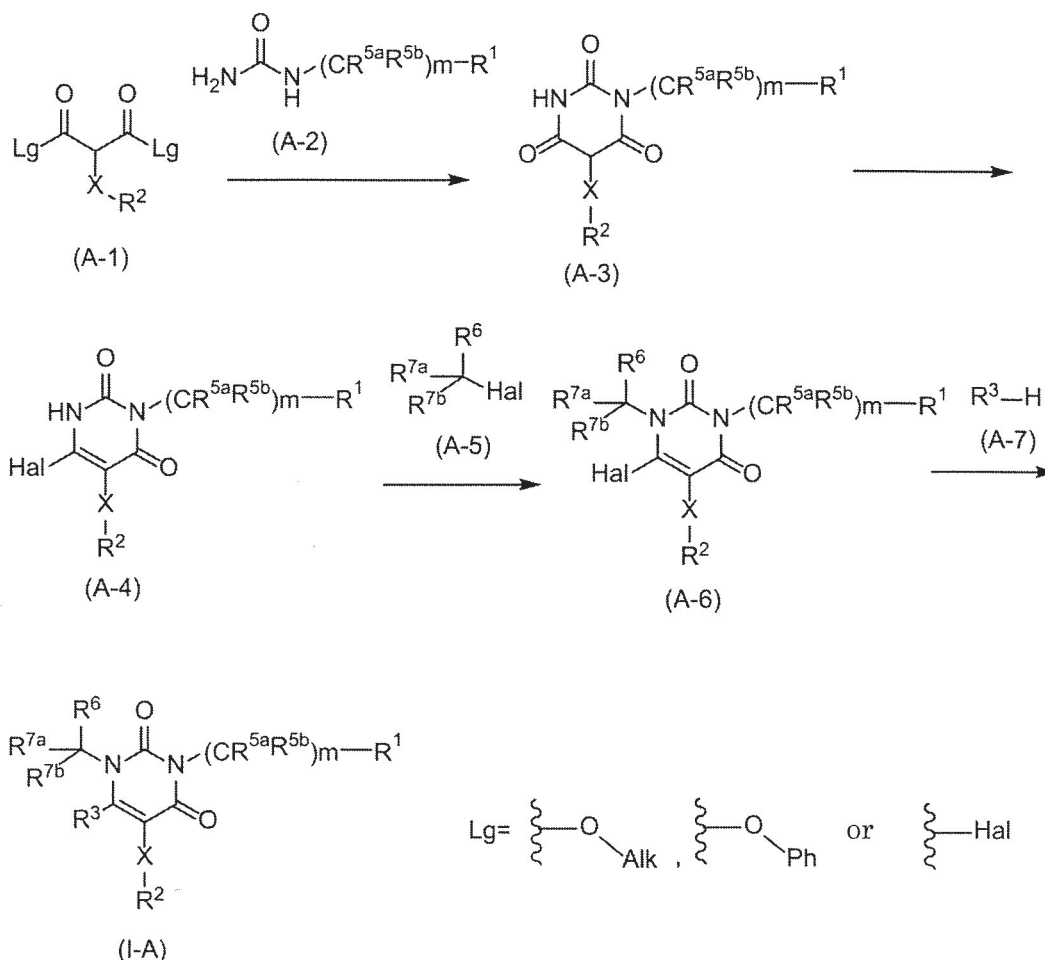
[0041]

(Method A) When Ring A in the formula is a ring represented by Formula: [Chemical Formula 24]



wherein the reference symbols have the same meanings as described above, X is a single bond, -CR^{4a}R^{4b}- or -O-, and R³ is non-aromatic heterocyclyl, aromatic carbocycloxy, non-aromatic carbocycloxy, aromatic heterocycloxy, non-aromatic heterocycloxy, amino or alkyloxy.

[Chemical Formula 25]



wherein Hal is halogen (a chlorine atom, a bromine atom, an iodine atom, or the like), Alk is C1-C3 alkyl, Lg is a leaving group, and other reference symbols have the same meanings as described above.

(First step)

Compound (A-3) can be produced by reacting Compound (A-1) with Compound (A-2) in the presence of methanol, ethanol, toluene, tetrahydrofuran, 1,4-dioxane, DMF, or the like, or in a mixed solvent thereof, in the presence or absence of a base such as sodium methoxide or sodium ethoxide, at 0°C to 140°C, preferably at 60°C to 100°C, for 0.1 hours to 48 hours, and preferably for 0.5 hours to 18 hours.

(Second step)

A compound represented by Compound (A-4) can be produced by reacting Compound (A-3) with phosphorus oxychloride or phosphorous oxybromide at 60°C to 150°C, and preferably at 80°C to 120°C in the presence of water.

(Third step)

Compound (A-6) can be produced by adding Compound (A-5) to Compound (A-4), in a solvent such as acetonitrile, acetone, DMF, DMSO, NMP, tetrahydrofuran, or 1,4-dioxane, in the presence of a base such as potassium carbonate, sodium carbonate, cesium carbonate, DBU, triethylamine, N,N-diisopropylethylamine, or pyridine, at 0°C to 100°C, and preferably at 20°C to 60°C, for 0.1 hours to 24 hours, and preferably 0.5 hours to 12 hours.

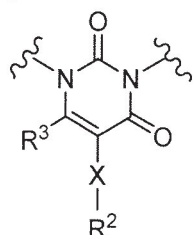
(Fourth step)

Compound (I-A) can be produced by adding Compound (A-7) to Compound (A-6), in acetonitrile, acetone, DMF, DMSO, NMP, tetrahydrofuran, 1,4-dioxane, or the like, or in a mixed solvent thereof, in the presence of a base such as triethylamine, N,N-

diisopropylethylamine, pyridine, or DBU, at 0°C to 100°C, and preferably at 20°C to 60°C, for 0.1 hours to 24 hours, and preferably 0.5 hours to 12 hours.

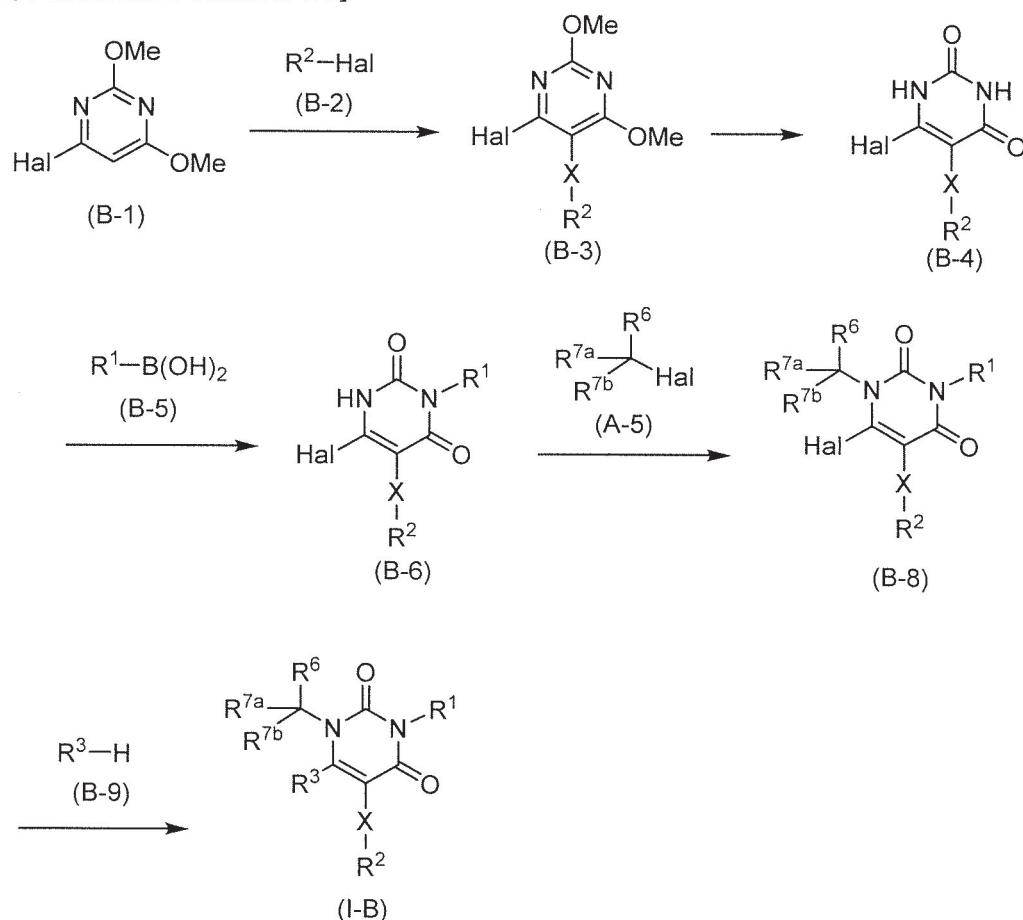
[0042]

(Method B) When Ring A in the formula is a ring represented by Formula:
[Chemical Formula 26]



wherein the reference symbols have the same meanings as described above,
X is a single bond, and m=0.

[Chemical Formula 27]



wherein the reference symbols have the same meanings as described above.
(First step)

Compound (B-3) can be produced by organic zincation of Compound (B-1), followed by the Negishi Reaction using Compound (B-2).

To Compound (B-1), n-butyllithium solution is added, in an organic solvent such as tetrahydrofuran or diethyl ether or a mixed solvent thereof, and the mixture is reacted at -78°C to -30°C, and preferably at -78°C to -60°C, for 0.1 hours to 6 hours, and preferably 0.5 hours to 1 hour. Next, zinc chloride is added, and the mixture is reacted at -78°C to 25°C, and preferably at -20°C to 25°C, for 0.1 hours to 6 hours, and preferably 0.5 hours to 1 hour. Subsequently, a palladium catalyst, a phosphine ligand, and Compound (B-2) are reacted at 25°C to 100°C, and preferably at 45°C to 60°C, for 0.1 hours to 24 hours, and preferably 10 hours to 16 hours, whereby

Compound (B-3) can be produced.

As the palladium catalyst, $\text{Pd}_2(\text{dba})_3$, $\text{PdCl}_2(\text{dppf})$, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_4$, Pd/C , PdCl_2 , Pd-PEPPSI-IPr , Bis[cinnamyl palladium Cl], $\text{PdCl}_2(\text{Xantphos})$, or $\text{Pd}(\text{OH})_2$ can be used.

As the phosphine ligand, Xantphos, $\text{P}(2\text{-furyl})_3$, PPh_3 , $\text{P}(o\text{-tol})_3$, $\text{P}(\text{OPh})_3$, $\text{P}(\text{OMe})_3$, dppp, dppb, dppf, BINAP, X-Phos, $\text{P}(t\text{-Bu})_3$, $\text{P}(\text{Oi-Pr})_3$, $\text{P}(p\text{-MeOPh})_3$, DPEPhos, or the like can be used.

(Second step)

Compound (B-4) can be produced by heat-treating compound (B-3) with a strong acid such as hydrochloric acid in an organic solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, acetone, DMF, DMSO or NMP, or a mixed solvent thereof.

(Third step)

Compound (B-6) can be produced by the Chan-Lam coupling reaction using Compound (B-4) and Compound (B-5).

Regarding the solvent, acetonitrile, DMF, NMP, dioxane, DMSO, or the like can be used.

Regarding the copper catalyst, for example, commercially available copper catalysts such as copper acetate, copper iodide, copper cyanide, or copper bromide, can be used.

As the base, triethylamine, N,N-diisopropylethylamine, pyridine, and DBU can be used.

Regarding the reaction temperature, the reaction may be carried out at from room temperature to a temperature at which the solvent refluxes, and preferably, the reaction may be carried out at room temperature to 50°C.

(Fourth step)

Compound (B-8) can be produced by reacting Compound (B-6) with Compound (A-5) in the same manner as in the third step of the above-described method A.

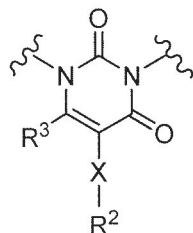
(Fifth step)

Compound (I-B) can be produced by reacting Compound (B-8) with Compound (B-9) in the same manner as in the fourth step of the above-described method A.

[0043]

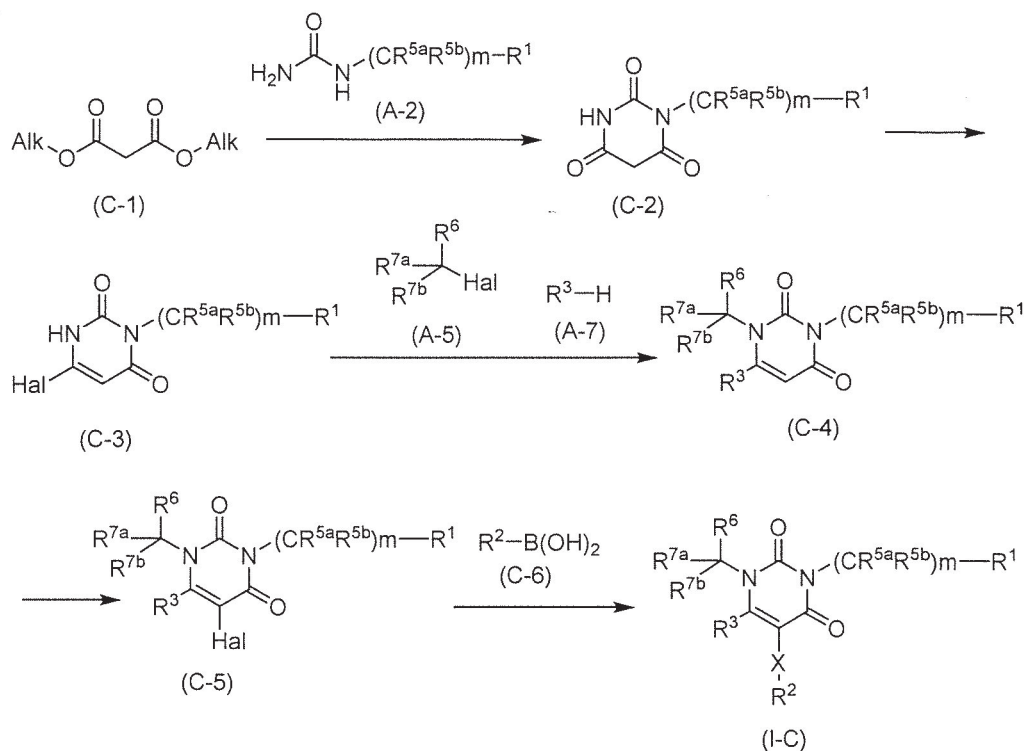
(Method C) When Ring A in the formula is represented by Formula:

[Chemical Formula 28]



wherein the reference symbols have the same meanings as described above, and X is a single bond.

[Chemical Formula 29]



wherein the reference symbols have the same meanings as described above.

(First step)

Compound (C-2) can be produced by reacting Compound (C-1) with Compound (A-2) in the same manner as in the first step of the above-described method A.

(Second step)

Compound (C-3) can be produced by reacting Compound (C-2) in the same manner as in the second step of the above-described method A.

(Third step)

Compound (C-4) can be produced by performing the third step and the fourth step of the above-described Method A in one pot.

(Fourth step)

Compound (C-5) can be produced by halogenating Compound (C-4).

Regarding the solvent, acetonitrile, DMF, NMP, dioxane, DMSO, or the like can be used.

As the halogenation reagent, for example, commercially available halogenation reagents such as NIS, NBS, and NIS can be used.

Regarding the reaction temperature, the reaction may be carried out at from room temperature to a temperature at which the solvent refluxes, and preferably, the reaction may be carried out at room temperature to 50°C.

(Fifth step)

Compound (I-C) can be produced by the Suzuki-Miyaura reaction using Compound (C-5) and Compound (C-6).

As the palladium catalyst, $\text{Pd}_2(\text{dba})_3$, $\text{PdCl}_2(\text{dppf})$, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_4$, Pd/C , PdCl_2 , Pd-PEPPSI-IPr , Bis[cinnamyl palladium Cl], $\text{PdCl}_2(\text{Xantphos})$, or $\text{Pd}(\text{OH})_2$ can be used.

As the phosphine ligand, Xantphos, $\text{P}(2\text{-furyl})_3$, PPh_3 , $\text{P}(o\text{-tol})_3$, $\text{P}(\text{OPh})_3$, $\text{P}(\text{OMe})_3$, dppp, dppb, dppf, BINAP, X-Phos, $\text{P}(t\text{-Bu})_3$, $\text{P}(\text{Oi-Pr})_3$, $\text{P}(p\text{-MeOPh})_3$, DPEPhos, or the like can be used.

As the solvent, 1,4-dioxane, tetrahydrofuran, water, or the like can be used.

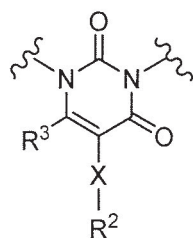
Regarding the reaction temperature, the reaction may be carried out at from

room temperature to a temperature at which the solvent refluxes, and preferably, the reaction may be carried out by heating under reflux.

[0044]

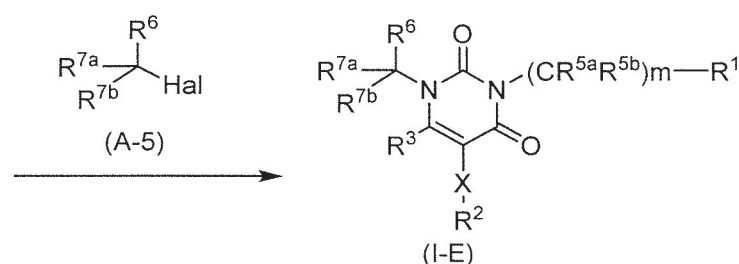
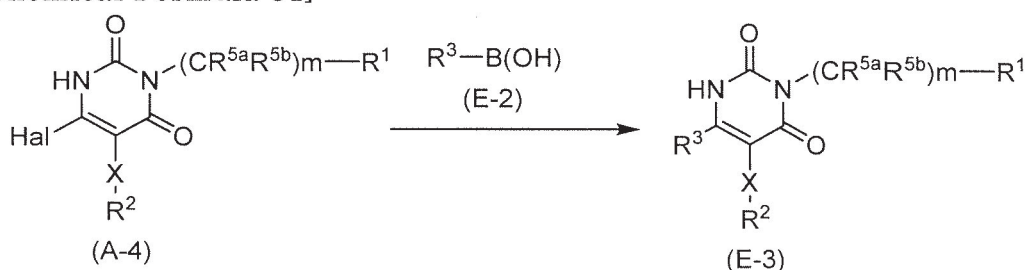
(Method E) When Ring A in the formula is represented by Formula:

[Chemical Formula 30]



wherein the reference symbols have the same meanings as described above, X is a single bond, CR^{4a}R^{4b}-, -O-, or -S-, and R³ is aromatic carbocyclyl or aromatic heterocyclyl.

[Chemical Formula 31]



wherein the reference symbols have the same meanings as described above.
(First step)

Compound (E-3) can be produced by the Suzuki-Miyaura reaction using Compound (A-4) and Compound (E-2).

As the palladium catalyst, Pd₂(dba)₃, PdCl₂(dppf), PdCl₂(PPh₃)₂, Pd(OAc)₂, Pd(PPh₃)₄, Pd/C, PdCl₂, Pd-PEPPSI (trademark)-IPr, Bis[cinnamyl palladium Cl], PdCl₂ (Xantphos), Pd(OH)₂, or the like can be used.

As the phosphine ligand, Xantphos, P(2-furyl)₃, PPh₃, P(o-tol)₃, P(OPh)₃, P(OMe)₃, dppp, dppb, dppf, dtbpf, BINAP, X-Phos, P(t-Bu)₃, P(Oi-Pr)₃, P(p-MeOPh)₃, DPEPhos, or the like can be used.

As the solvent, 1,4-dioxane, tetrahydrofuran, water, or the like can be used.

Regarding the reaction temperature, the reaction may be carried out at from room temperature to a temperature at which the solvent refluxes, and preferably, the reaction may be carried out by heating under reflux.

(Second step)

Compound (I-E) can be produced by reacting Compound (E-3) with Compound (A-5) in the same manner as in the third step of the above-described method A.

[0045]

Since the compound of the present invention has coronavirus 3CL protease inhibitory activity, the compound is useful as a therapeutic and/or prophylactic agent for coronavirus infections.

Furthermore, the compound of the present invention has utility as a medicine, and preferably, the compound of the present invention has any one or a plurality of the following excellent features.

- a) Inhibitory activity against CYP enzymes (for example, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) is weak.
- b) Satisfactory pharmacokinetics such as high bioavailability or adequate clearance are exhibited.
- c) Metabolic stability is high.
- d) Irreversible inhibitory activity is not exhibited against CYP enzymes (for example, CYP3A4) within the concentration range of the measurement conditions described in the present specification.
- e) Mutagenicity is not exhibited.
- f) The cardiovascular risk is low.
- g) High solubility is exhibited.
- h) The protein unbinding rate (f_u value) is high.
- i) High coronavirus 3CL protease selectivity is exhibited.
- j) High coronavirus replication inhibitory activity is exhibited. For example, high coronavirus replication inhibitory activity is exhibited when human blood serum (HS) or human serum albumin (HSA) is added.
- k) High proliferation inhibitory activity is exhibited against 3CL protease inhibitor-resistant viruses.

Regarding the coronavirus replication inhibitor, for example, an aspect in which in the CPE effect (SARS-CoV-2) that will be described below, for example, EC_{50} is 10 μ M or less, preferably 1 μ M or less, and more preferably 100 nM or less, may be mentioned.

[0046]

The pharmaceutical composition of the present invention can be administered by either an oral method or a parenteral method. Examples of a parenteral administration method include percutaneous, subcutaneous, intravenous, intra-arterial, intramuscular, intraperitoneal, transmucosal, inhalation, transnasal, ocular instillation, ear instillation, and intravaginal administration.

[0047]

In the case of oral administration, the pharmaceutical composition may be prepared into any dosage form that is commonly used, such as a solid preparation for internal use (for example, a tablet, a powder preparation, a granular preparation, a capsule, a pill, or a film preparation), or a liquid preparation for internal use (for example, a suspension, an emulsion, an elixir, a syrup, a limonade, a spirit preparation, an aromatic water preparation, an extraction, a decoction, or a tincture) and administered. The tablet may be a dragee, a film-coated tablet, an enteric-coated tablet, a sustained release tablet, a troche, a sublingual tablet, a buccal tablet, a chewable tablet, or an orally disintegrating tablet; the powder preparation and granular preparation may be dry syrups; and the capsule may be a soft capsule, a microcapsule, or a sustained release capsule.

[0048]

In the case of parenteral administration, the pharmaceutical composition can be suitably administered in any dosage form that is commonly used, such as an

injectable preparation, an infusion, or a preparation for external use (for example, an eye drop, a nasal drop, an ear drop, an aerosol, an inhalant, a lotion, an impregnating agent, a liniment, a gargling agent, an enema, an ointment, a plaster, a jelly, a cream, a patch, a poultice, a powder preparation for external use, or a suppository). The injectable preparation may be an O/W, W/O, O/W/O, or W/O/W type emulsion, or the like.

[0049]

A pharmaceutical composition can be obtained by mixing an effective amount of the compound of the present invention with various pharmaceutical additives appropriate for the dosage form, such as an excipient, a binder, a disintegrating agent, and a lubricating agent, as necessary. Furthermore, the pharmaceutical composition can be prepared into a pharmaceutical composition for use for a child, an elderly, a patient with a serious case, or a surgical operation, by appropriately changing the effective amount of the compound of the present invention, the dosage form, and/or various pharmaceutical additives. For example, pediatric pharmaceutical compositions may be administered to patients who are neonates (younger than 4 weeks old after the birth), infants (4 weeks old to younger than 1 year old after the birth), infant children (1 year old or older and younger than 7 years old), children (7 years old or older and younger than 15 years old), or 15 to 18 years old. For example, a pharmaceutical composition for an elderly may be administered to a patient 65 years of age or older.

[0050]

It is desirable to set the amount of administration of the pharmaceutical composition of the present invention, after considering the age and body weight of the patient, the type and degree of the disease, the route of administration, and the like; however, in the case of oral administration, the amount of administration is usually 0.01 to 100 mg/kg/day and is preferably in the range of 0.05 to 50 mg/kg/day. In the case of parenteral administration, the amount of administration may vary greatly depending on the route of administration; however, the amount of administration is usually 0.005 to 200 mg/kg/day and is preferably in the range of 0.01 to 100 mg/kg/day. This may be administered once a day or several times a day.

[0051]

The compound of the present invention may be used in combination with, for example, another therapeutic agent for novel coronavirus infections (COVID-19) (the therapeutic agent includes an approved drug and a drug that is under development or to be developed in the future) (hereinafter, referred to as concomitant drug), for the purpose of enhancing the action of the compound, reducing the amount of administration of the compound, or the like. At this time, the timing of administration for the compound of the present invention and the concomitant drug is not limited, and these may be administered simultaneously to the target of administration or may be administered with a time difference. Furthermore, the compound of the present invention and the concomitant drug may be administered as two or more kinds of preparations each including active ingredients, or may be administered as a single preparation including those active ingredients.

[0052]

The amount of administration of the concomitant drug can be appropriately selected based on the clinically used dosage. Furthermore, the blending ratio of the compound of the present invention and the concomitant drug can be appropriately selected according to the target of administration, the route of administration, the

target disease, symptoms, combination, and the like. For example, when the target of administration is a human being, 0.01 to 100 parts by weight of the concomitant drug may be used with respect to 1 part by weight of the compound of the present invention.

[EXAMPLES]

[0053]

Hereinafter, the present invention will be described in more detail by way of Examples, Reference Examples, and Test Examples; however, the present invention is not intended to be limited by these.

[0054]

Furthermore, abbreviations used in the present specification denote the following meanings.

DBU: 1,8-Diazabicyclo[5.4.0]-7-undecene

DMA: N,N-dimethylacetamide

DMF: N,N-dimethylformamide

DMSO: Dimethyl sulfoxide

DPEphos: bis[2-(diphenylphosphino)phenyl]ether

ESI: Electrospray ionization

FBS: Fetal bovine serum

LDA: Lithium diisopropylamide

LHMDS: Lithium hexamethyldisilazide

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

NIS: N-iodosuccinimide

NMP: N-methylpyrrolidone

P(2-furyl)₃: Tri(2-furyl)phosphine

P(o-tol)₃: Tris(2-methylphenyl)phosphine

Pd(OAc)₂: Palladium acetate

Pd(PPh₃)₄: Tetrakis(triphenylphosphine)palladium

Pd₂(dba)₃: Tris(dibenzylideneacetone)bispalladium

PdCl₂(PPh₃)₂: Bis(triphenylphosphine)palladium (II) dichloride

PdCl₂(dppf): [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride
dichloromethane adduct

PdCl₂(dtbpf): [1,1'-bis(di-tert-butylphosphino)ferrocene]palladium (II) dichloride

Ph: Phenyl

X-Phos: 2,4,6-triisopropyl-2'-(dicyclohexylphosphino)biphenyl

Xantphos: 4,5'-Bis(diphenylphosphine)-9,9'-dimethylxanthene

dppb: 1,4-bis(diphenylphosphino)butane

dppf: 1,1'-bis(diphenylphosphino)ferrocene

dppp: 1,3-bis(diphenylphosphino)propane

i-Pr: Isopropyl

t-Bu: tert-butyl

mM: mmol/L

nM: nmol/L

μM: μmol/L

[0055]

(Method for identifying compound)

The NMR analysis obtained in each Example was performed at 400 MHz, and

measurement was made using DMSO- d_6 or $CDCl_3$. Furthermore, when NMR data are shown, there are occasions in which all the measured peaks are not described.

The term RT in the specification indicates retention time in an LC/MS: liquid chromatography/mass analysis, and the retention time was measured under the following conditions.

(Measurement conditions A)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m i.d. 2.1 $\times$ 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution.

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Measurement conditions B)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m i.d. 2.1 $\times$ 50 mm) (Waters)

Flow rate: 0.8 mL/min

UV detection wavelength: 254 nm

Mobile phase: [A] is 10mM ammonium carbonate in aqueous solution, and [B] is acetonitrile.

Gradient: A linear gradient of 5% to 100% solvent [B] was carried out for 3.5 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

(Measurement conditions D)

Column: Shim-pack XR-ODS (2.2 μ m, i.d. 3.0 $\times$ 50 mm) (Shimadzu)

Flow rate: 1.6 mL/min

UV detection wavelength: 254 nm

Mobile phase: [A] was 0.1% formic acid-containing aqueous solution, and [B] was 0.1% formic acid-containing acetonitrile solution.

Gradient: A linear gradient of 10% to 100% solvent [B] was carried out for 3 minutes, and then 100% solvent [B] was maintained for 0.5 minutes.

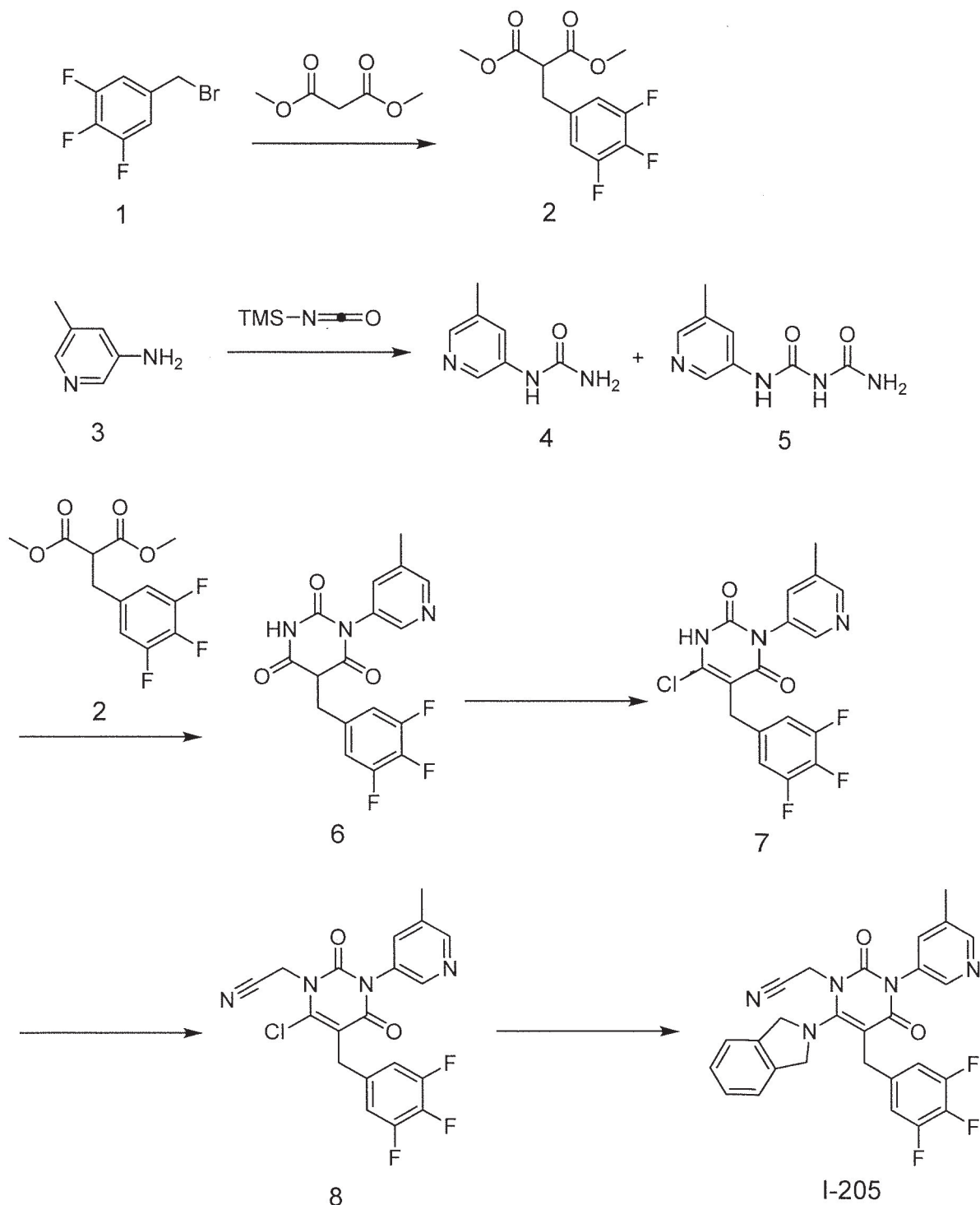
Incidentally, in the specification, the description of MS(m/z) indicates a value observed by mass analysis.

[EXAMPLE 1]

[0056]

Synthesis of Compound (I-205)

[Chemical Formula 32]



Step 1 Synthesis of Compound 2

Compound 1 (5.9 mL, 44.4 mmol), acetone (40 mL), potassium carbonate (9.2 g, 66.7 mmol), and dimethyl malonate (8.4 mL, 66.7 mmol) were mixed, and the solution thus obtained was stirred at 45°C for 1 hour and 30 minutes, and then, it was allowed to stand at room temperature for 15 hours 30 minutes. The precipitate was filtered off and washed with acetone. The filtrate was concentrated, the residue thus obtained was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 0 to 9 : 1), the solvent was distilled off under reduced pressure, and Compound 2 (6.0 g, 21.5 mmol, yield 49%) was obtained.

LC/MS (ESI): m/z = 277, RT = 2.20 min, LC/MS measurement conditions A [0057]

Step 2 Synthesis of Compound 4

A solution obtained by mixing dichloromethane (42 mL) to Compound 3 (11.3 g, 104 mmol) was ice-cooled, trimethylsilyl isocyanate (6.9 mL, 52.1 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. The reaction solution was allowed to stand at room temperature for 66 hours, then methanol (12 mL) was added thereto, and the mixture was stirred for 5 minutes. The solution was concentrated, dichloromethane (15 mL) and diisopropyl ether (45 mL) were added thereto, and the obtained precipitate was collected by filtration and washed with a mixed solution of dichloromethane and diisopropyl ether (1 : 3). The residue thus obtained was dried under reduced pressure, and a mixture of Compounds 4 and 5 (6.8 g, 5 : 1) was obtained. Compound 4 (purity 80%, 36.2 mmol, yield 70%)

LC/MS (ESI): m/z = 152, RT = 0.58 min, LC/MS measurement conditions B
[0058]

Step 3 Synthesis of Compound 6

Compound 2 (2.4 g, 8.73 mmol), a 5 : 1 mixture of Compounds 4 and 5 (1.2 g, Compound 4: 6.35 mmol), and a 20% sodium ethoxide solution (9.2 mL) were mixed, and the obtained solution was stirred at 90°C for 4 hours. The reaction solution was cooled in an ice bath, and was neutralized with 2 mol/L hydrochloric acid (7.9 mL). A saturated aqueous sodium bicarbonate solution (1 mL) was added, then water (14 mL) was added, and the obtained precipitate was collected by filtration and washed with water and diisopropyl ether. The residue thus obtained was dried under reduced pressure, and Compound 6 (1.2 g, 3.30 mmol, yield 52%) was obtained.

LC/MS (ESI): m/z = 364, RT = 1.28 min, LC/MS measurement conditions B
[0059]

Step 4 Synthesis of Compound 7

Phosphorus oxychloride (6.6 mL, 70.5 mmol) was slowly added dropwise to Compound 6 (1.3 g, 3.52 mmol), and water (0.3 mL, 17.6 mmol) was slowly added thereto dropwise. The obtained solution was stirred at room temperature for 5 minutes, and then stirred at 100 °C for 6 hours. The reaction solution was slowly added dropwise to water (10 mL) cooled in an ice bath, and then a 4 mol/L aqueous lithium hydroxide solution (53 mL) was added little by little. The obtained precipitate was collected by filtration and washed with water. The residue thus obtained was dried under reduced pressure, and Compound 7 (1.2 g, 3.14 mmol, yield 89%) was obtained.

LC/MS (ESI): m/z = 382, RT = 1.80 min, LC/MS measurement conditions A
[0060]

Step 5 Synthesis of Compound 8

To a solution obtained by mixing Compound 7 (700 mg, 1.83 mmol), potassium carbonate (760 mg, 5.50 mmol), and DMF (7.0 mL), 2-bromoacetonitrile (367 μ L, 5.50 mmol) was added. The obtained solution was stirred at room temperature for 3 hours, then the reaction solution was cooled in an ice bath, water (14 mL) was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated, and ethyl acetate (3.5 mL) and hexane (7.0 mL) were added thereto. The obtained precipitate was collected by filtration and washed with a mixed solution of hexane and ethyl acetate (1 : 2). The residue thus obtained was dried under reduced pressure, and Compound 8 (469 mg, 1.12 mmol, yield 61%) was obtained.

LC/MS (ESI): m/z = 421, RT = 2.11 min, LC/MS measurement conditions A

[00061]

Step 6 Synthesis of Compound (I-205)

A solution obtained by mixing Compound 8 (51.5 mg, 0.122 mmol), isoindoline (41.3 μ L, 0.367 mmol), and ethanol (1.0 mL) was stirred at 100°C for 2 hours. The reaction solution was cooled to room temperature, water (2 mL) was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and filtered. The filtrate was concentrated, the residue thus obtained was purified by silica gel column chromatography (chloroform : methanol = 10 : 0 to 9.5 : 0.5), the solvent was distilled off under reduced pressure, and Compound (I-205) (6.1 mg, 0.012 mmol, yield 10%) was obtained.

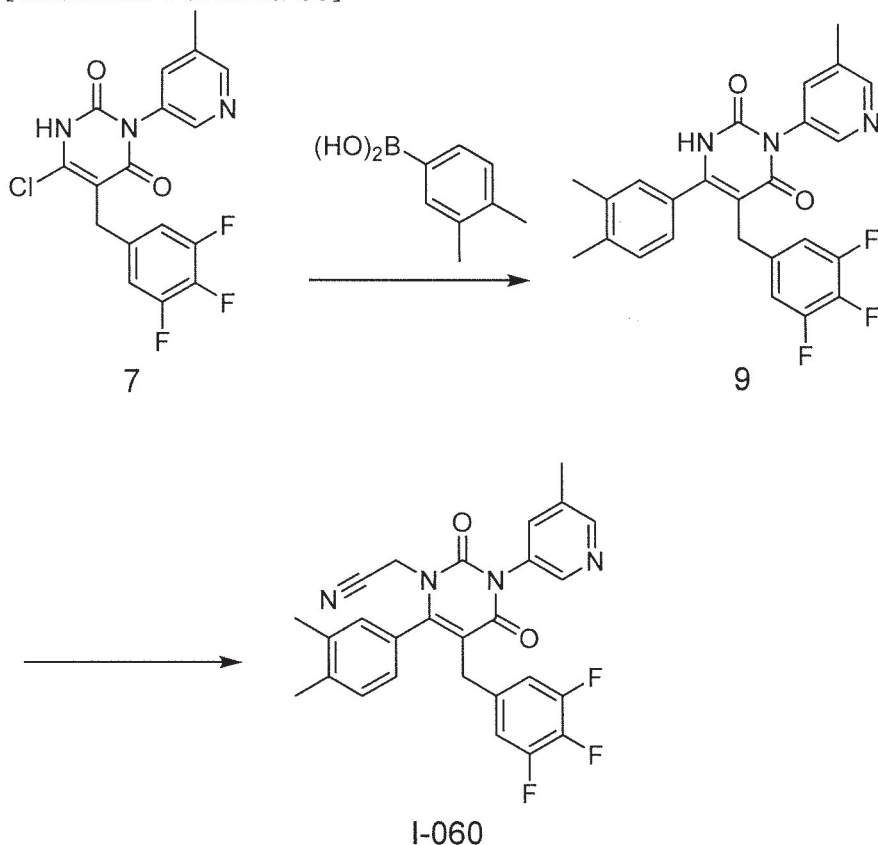
$^1\text{H-NMR}$ (CDCl_3) δ : 2.42 (s, 3H), 3.57 (s, 2H), 4.64 (s, 4H), 4.95 (s, 2H), 6.64 (dd, J = 6.7, 8.0 Hz, 2H), 7.30 (dd, J = 3.2, 5.6 Hz, 2H), 7.40 (dd, J = 3.2, 5.6 Hz, 2H), 7.45 (dd, J = 1.3, 2.3 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.51 (d, J = 1.3 Hz, 1H)

LC/MS (ESI): m/z = 504, RT = 2.41 min, LC/MS measurement conditions A

[EXAMPLE 2]

[0062]

[Chemical Formula 33]



[0063]

Step 1 Synthesis of Compound 9

A solution obtained by mixing Compound 7 (20.0 mg, 0.052 mmol), (3,4-dimethylphenyl)boronic acid (9.4 mg, 0.063 mmol), sodium carbonate (16.7 mg, 0.157 mmol), PdCl_2 (dtbpf) (3.4 mg, 5.2 μ mol), 1,4-dioxane (0.2 mL), and water (40 μ L) was stirred at 120°C for 1 hour and 30 minutes, and then the reaction solution was concentrated. The residue thus obtained was purified by silicagel column chromatography (chloroform : methanol = 10 : 0 to 9.7 : 0.3), and the solvent was distilled off under reduced pressure. Ethyl acetate (0.2 mL) and hexane (0.4 mL)

were added to the obtained residue, and the obtained precipitate was collected by filtration and washed with a mixed solution of hexane and ethyl acetate (1 : 2). The residue thus obtained was dried under reduced pressure, and Compound 9 (8.3 mg, 0.018 mmol, yield 35%) was obtained.

LC/MS (ESI): m/z = 452, RT = 2.35 min, LC/MS measurement conditions A [0064]

Step 8 Synthesis of Compound (I-060)

To a solution obtained by mixing Compound 9 (59 mg, 0.131 mmol), potassium carbonate (21.7 mg, 0.157 mmol), and DMF (0.6 mL), 2-bromoacetonitrile (9.6 μ L, 0.144 mmol) was added. The obtained solution was stirred at room temperature for 30 minutes, then water (2 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated, and ethyl acetate (0.6 mL) and hexane (0.6 mL) were added thereto. The obtained precipitate was collected by filtration and washed with a mixed solution of hexane and ethyl acetate (1 : 1). The residue thus obtained was dried under reduced pressure, and Compound (I-060) (29.6 mg, 0.060 mmol, yield 46%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.36 (s, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 3.39 (d, J = 14.8 Hz, 1H), 3.49 (d, J = 14.7 Hz, 1H), 4.43 (s, 2H), 6.56 (dd, J = 6.8, 8.5 Hz, 2H), 7.06 (d, J = 1.6 Hz, 1H), 7.07 (dd, J = 1.6, 7.8 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.48 (dd, J = 1.1, 2.3 Hz, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.53 (d, J = 1.1 Hz, 1H)

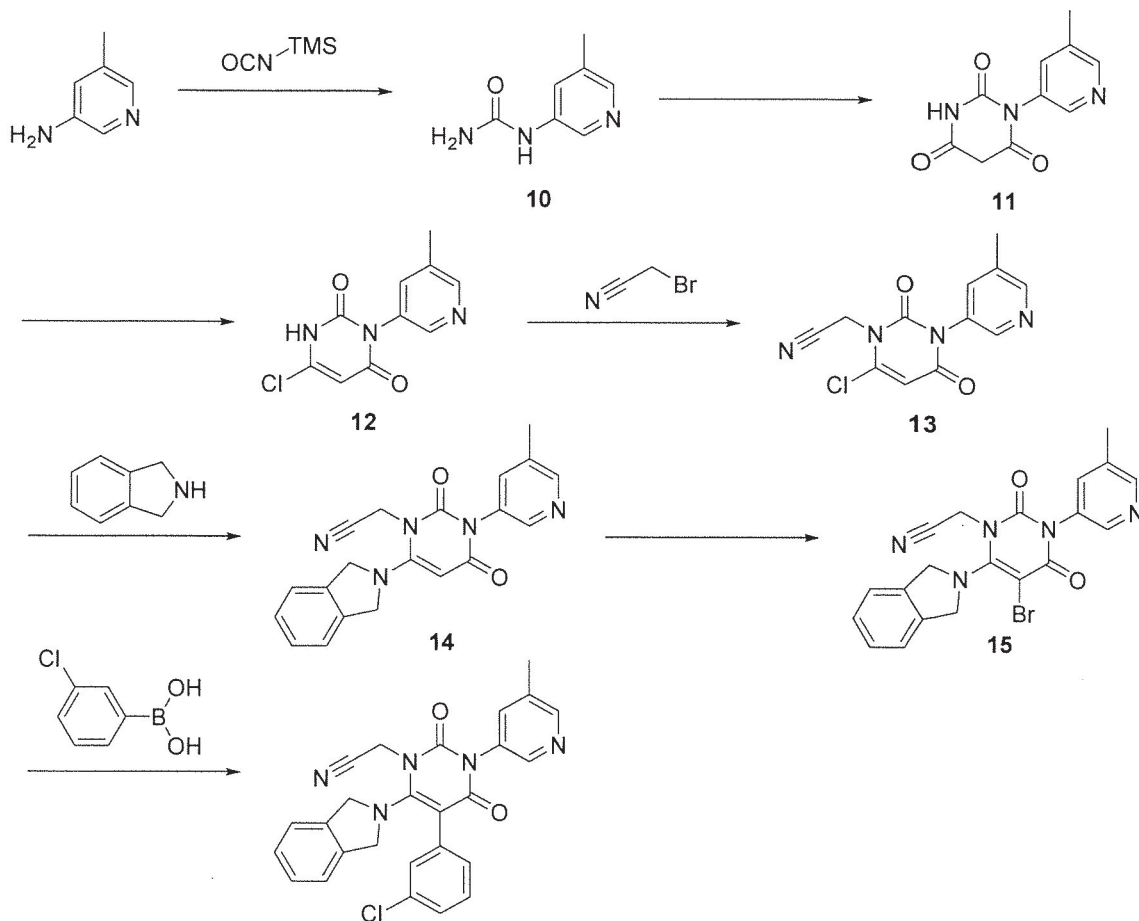
LC/MS (ESI): m/z = 491, RT = 2.58 min, LC/MS measurement conditions A

[EXAMPLE 3]

[0065]

Synthesis of Compound (I-042)

[Chemical Formula 34]



I-042

Step 1 Synthesis of Compound 10

In dichloromethane (75 mL), 2-amino-4-methylpyridine (20.1 g, 186 mmol) was dissolved under ice cooling, and trimethylsilyl isocyanate (12.6 mL, 93 mmol) was added dropwise thereto. The reaction solution was heated to room temperature and stirred for 17 hours. Methanol (18.8 mL) and diisopropyl ether (240 mL) were added into the reaction solution, and the obtained solid was separated by filtration, washed with a mixed solution (60 mL) of dichloromethane : diisopropyl ether = 1 : 3, and dried under reduced pressure to obtain Compound 10 (7.05 g, 44.6 mmol, yield 50%). The obtained Compound 10 was used in the next step without further purification. ¹H-NMR (DMSO-d₆) δ: 8.66 (1H, s), 8.30 (1H, d, J = 2.3 Hz), 7.95 (1H, d, J = 1.1 Hz), 7, 75 (1H, s), 5.99 (2H, s), 2.24 (3H, s).

[0066]

Step 2 Synthesis of Compound 11

Compound 10 (3 g, 19.9 mmol) was dissolved in ethanol (21 mL), and diethyl malonate (3.33 mL, 21.8 mmol) and a sodium ethoxide ethanol solution (20 wt%, 9.21 mL, 23.8 mmol) were sequentially added thereto, then the mixture was refluxed for 20 hours. The reaction solution was air-cooled, then 2 mol/l hydrochloric acid (11.9 mL, 23.8 mmol) was added thereto, and the mixture was concentrated and dried. The obtained solid was purified by silicagel column chromatography (chloroform/methanol = 99 : 1 to 95 : 5) to give Compound 11 (4.4 g, 20.07 mmol, yield 101 %).

LC/MS (ESI): m/z = 220 [M+H]⁺, RT = 0.75 min, LC/MS measurement conditions A

[0067]

Step 3 Synthesis of Compound 12

Phosphorus oxychloride (4.24 mL, 45.6 mmol) and water (205 μ L, 11.4 mmol) were sequentially added to Compound 11 (1 g, 4.56 mmol) at room temperature, and the mixture was stirred for 10 minutes, then stirred at 100°C for 1 hour. The reaction solution was cooled with ice, and water (2.46 mL, 137 mmol) and an aqueous potassium carbonate solution (9.1 mol/L, 15 mL, 137 mmol) were gradually added dropwise thereto. A 2 mol/L aqueous sodium hydroxide solution was added so that the pH of the reaction solution was 5 to 6, and the obtained solid was separated by filtration and washed with water. The obtained solid was suspended in water (5 mL) and finely crushed, then separated by filtration and washed with water to obtain compound 12 (523 mg, 2.20 mmol, yield 48%). The obtained Compound 12 was used in the next step without further purification.

LC/MS (ESI): m/z = 238 $[M+H]^+$, RT = 0.85 min, LC/MS measurement conditions A
 $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 8.43 (1H, d, J = 1.3 Hz), 8.28 (1H, d, J = 2.1 Hz), 7.58 (1H, s), 6.05 (1H, s), 2.34 (3H, s).

[0068]

Step 4 Synthesis of Compound 13

Compound 12 (523 mg, 2.20 mmol) was suspended in DMF (5.2 mL), and potassium carbonate (912 mg, 6.60 mmol) and 2-bromoacetonitrile (440 μ L, 6.60 mmol) were added, then the mixture was stirred at room temperature for 20 hours. The reaction solution was diluted with ethyl acetate, the organic layer was washed with water, and then dried over sodium sulfate. The solid was separated by filtration and dried under reduced pressure, then purified by silicagel column chromatography (ethyl acetate 100%) to give Compound 13 (89 mg, 0.321 mmol, yield 14.6 %).

LC/MS (ESI): m/z = 277 $[M+H]^+$, RT = 1.05 min, LC/MS measurement conditions A
 $^1\text{H-NMR}$ (CDCl_3) δ : 8.47 (1H, s), 8.25 (1H, d, J = 2.3 Hz), 7.34 (1H, s), 6.13 (1H, s), 4.96 (2H, s), 2.35 (3H, s).

[0069]

Step 5 Synthesis of Compound 14

Compound 13 (89 mg, 0.322 mmol) was dissolved in ethanol (1.8 mL), isoindoline (73 μ L, 0.643 mmol) was added thereto, and the mixture was stirred at 100°C for 30 minutes. The reaction solution was air-cooled, diluted with ethyl acetate, and washed with water. After the solid thus obtained was separated by filtration and washed with ethyl acetate, the solid together with an organic layer were dried under reduced pressure, and then purified by silicagel column chromatography (ethyl acetate 100%) to give Compound 14 (63 mg, 175 μ mol, yield 54 %).

LC/MS (ESI): m/z = 360 $[M+H]^+$, RT = 1.57 min, LC/MS measurement conditions A
 $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 8.44 (1H, d, J = 1.3 Hz), 8.26 (1H, d, J = 2.1 Hz), 7.55 (1H, s), 7.42-7.34 (4H, m), 5.50 (1H, s), 4.95 (2H, s), 4.78 (4H, s), 2.36 (3H, s).

[0070]

Step 6 Synthesis of Compound 15

Compound 14 (63 mg, 0.175 mmol) and N-bromosuccinimide (34.3 mg, 0.193 mmol) were dissolved in chloroform (1.3 mL), and the mixture was stirred at room temperature for 2.5 hours. The reaction solution was purified by silicagel column chromatography (hexane : ethyl acetate = 50 : 50 to 30 : 70), and Compound 15 (59 mg, 0.135 mmol, yield 77%) was obtained.

LC/MS (ESI): m/z = 438 $[M+H]^+$, RT = 1.98 min, LC/MS measurement conditions A
 $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 8.39 (1H, s), 8.24 (1H, d, J = 2.3 Hz), 7.54 (1H, s), 7.33 (2H, dd),

J = 5.4, 3.4 Hz), 7.25 (2H, dd, J = 5.4, 3.1 Hz), 5.00 (2H, s), 4.66 (4H, s), 2.28 (3H, s).
[0071]

Step 7 Synthesis of Compound (I-042)

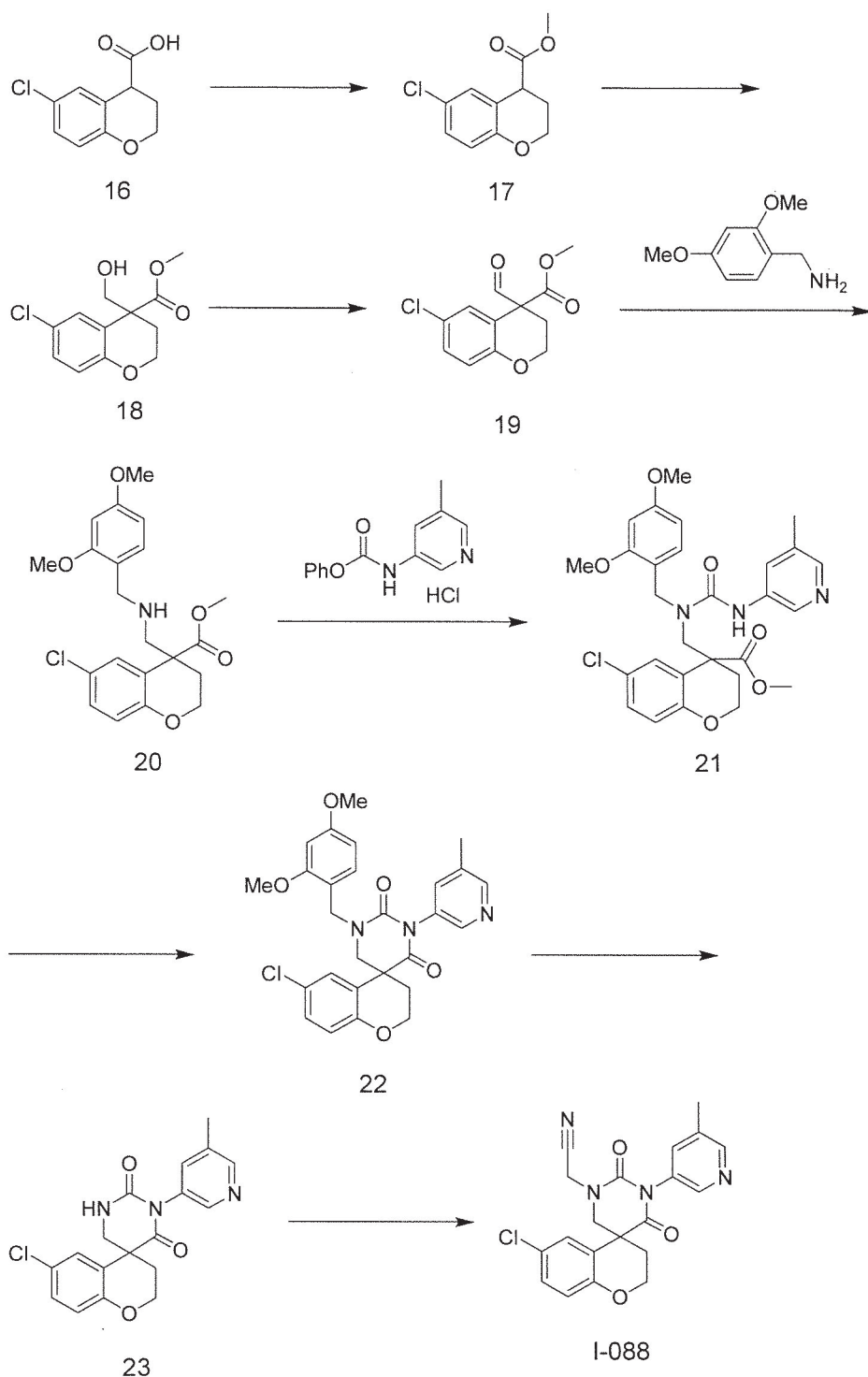
Compound 15 (59 mg, 0.135 mmol) was dissolved in 1,4 dioxane (1.2 mL), and (3-chlorophenyl) boronic acid (31.6 mg, 0.202 mmol), an aqueous potassium carbonate solution (2 mmol/L, 135 μ L, 0.269 mmol) and PdCl₂ (dppf) CH₂Cl₂ (11 mg, 0.013 mmol) were sequentially added. Nitrogen purge was carried out, and then, the mixture was stirred at 100 °C for 1 hour and allowed to stand for 16 hours. The reaction solution was diluted with ethyl acetate, and washed sequentially with water and brine. The organic layer was dried under reduced pressure and purified by HPLC (acetonitrile: water = 30 : 70 to 80 : 20) to give Compound (I-042) (23.4 mg, 0.05 mmol, yield 37%). LCMS (ESI): m/z = 470 [M+H]⁺, RT = 2.23 min, LC/MS measurement conditions A ¹H-NMR (DMSO-d₆) δ : 8.47 (1H, s), 8.32 (1H, s), 7.60 (1H, s), 7.25-7.11 (8H, m), 5.08 (2H, s), 4.44 (4H, s), 2.36 (3H, s).

[EXAMPLE 4]

[0072]

Synthesis of Compound (I-088)

[Chemical Formula 35]



Step 1 Synthesis of Compound 17

Compound 16 (300 mg, 1.41 mmol) and potassium carbonate (299 mg, 2.12 mmol) were suspended in dimethylformamide (3 mL), and methyl iodide (0.14 mL, 2.1 mmol) was added under ice cooling. The reaction solution was heated to room temperature and stirred for 1 hour. A 10% aqueous citric acid solution was added to the reaction solution, followed by the extraction with ethyl acetate. The obtained organic layer was washed with water and dried under reduced pressure to obtain Compound 17 (298 mg, 1.32 mmol, yield 94%). The obtained Compound 17 was used in the next step without further purification.

$^1\text{H-NMR}$ (CDCl_3) δ : 7.23 (1H, dd, $J = 2.5, 0.6$ Hz), 7.11 (1H, dd, $J = 8.8, 2.5$ Hz), 6.77 (1H, d, $J = 8.8$ Hz), 4.29-4.21 (2H, m), 3.76 (3H, s), 3.75 (1H, dd, $J = 9.6, 5.6$ Hz), 2.32 (1H, dq, $J = 14.1, 3.7$ Hz), 2.14-2.03 (1H, m).

[0073]

Step 2 Synthesis of Compound 18

N, N-diisopropylamine (0.41 mL, 2.9 mmol) was dissolved in tetrahydrofuran (3.8 mL), and a n-butyllithium hexane solution (1.6 M, 1.8 mL, 2.9 mmol) was added dropwise thereto at -78 °C. The reaction solution was heated to the level of ice cooling and stirred for 20 minutes, and then a tetrahydrofuran solution (4 mL) of the compound 17 (279 mg, 1.23 mmol) was added thereto at -78 °C. The reaction solution was stirred at -78 °C for 1 hour, and paraformaldehyde (343 mg, 11.4 mmol) was added thereto. The reaction solution was heated to the level of ice cooling and stirred for 1 hour. A 10% aqueous citric acid solution was added to the reaction solution, followed by the extraction with ethyl acetate. The obtained organic layer was washed with a 10% citric acid aqueous solution and water, and dried under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane : ethyl acetate = 90 : 10 to 60 : 40), and Compound 18 (251 mg, 0.978 mmol, yield 79%) was obtained.

¹H-NMR (CDCl₃) δ: 7.15 (1H, d, J = 2.5 Hz), 7.13 (1H, dd, J = 8.7, 2.5 Hz), 6.81 (1H, d, J = 8.8 Hz), 4.28 (1H, ddd, J = 11.4, 7.0, 3.5 Hz), 4.22-4.15 (2H, m), 3.75 (3H, s), 3.68 (1H, dd, J = 11.6, 8.6 Hz), 2.48-2.39 (2H, m), 2.28 (1H, ddd, J = 14.3, 7.0, 3.3 Hz).

[0074]

Step 3 Synthesis of Compound 19

Compound 18 (91wt%, 1.49 g, 5.25 mmol) was dissolved in dichloromethane (22 mL), and Dess-Martin periodinane (2.67 g, 6.86 mmol) was added thereto. The reaction solution was stirred at room temperature for 1.5 hours, and an aqueous sodium carbonate solution and an aqueous sodium thiosulfate solution were sequentially added thereto under ice cooling. The mixture was extracted with hexane : ethyl acetate = 2 : 1, and the organic layer was washed with an aqueous sodium carbonate solution and water and dried under reduced pressure to obtain Compound 19 (1.46 g, 5.54 mmol, yield 106%). The obtained Compound 19 was used in the next step without further purification.

¹H-NMR (CDCl₃) δ: 9.67 (1H, d, J = 10.9 Hz), 7.29 (1H, d, J = 2.6 Hz), 7.21 (1H, dd, J = 8.8, 2.6 Hz), 6.86 (1H, d, J = 8.6 Hz), 4.21 (1H, ddd, J = 11.4, 7.0, 3.5 Hz), 4.09 (1H, ddd, J = 11.4, 7.6, 3.1 Hz), 4.06 (1H, d, J = 3.1 Hz), 3.83 (3H, s), 2.51 (1H, ddd, J = 14.1, 7.6, 3.4 Hz), 2.42 (1H, ddd, J = 14.1, 7.3, 3.5 Hz).

[0075]

Step 4 Synthesis of Compound 20

Compound 19 (102 mg, 0.401 mmol) was dissolved in methanol (1.5 mL), and acetic acid (0.12 mL, 2.0 mmol), 2,4-dimethoxyphenylmethylamine (0.30 mL, 2.0 mmol), and sodium cyanoborohydride (76 mg, 1.2 mmol) were sequentially added. The reaction solution was stirred at room temperature for 1 hour, and an aqueous sodium carbonate solution was added thereto. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and dried under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane : ethyl acetate = 60 : 40 to 20 : 80), and Compound 20 (94.1mg, 0.232 mmol, yield 58%) was obtained.

LC/MS (ESI): m/z = 406 [M+H]⁺, RT = 1.83 min, LC/MS measurement conditions A
¹H-NMR (CDCl₃) δ: 7.26 (1H, d, J = 2.4 Hz), 7.08 (1H, d, J = 8.8 Hz), 7.08 (1H, dd, J = 8.4, 2.4 Hz), 6.75 (1H, d, J = 8.8 Hz), 6.45 (1H, d, J = 2.3 Hz), 6.42 (1H, dd, J = 8.4, 2.3 Hz), 4.21-4.12 (2H, m), 3.80 (3H, s), 3.77 (3H, s), 3.76 (2H, d, J = 13.6 Hz), 3.69 (3H, s), 3.64 (1H, d, J = 13.6 Hz), 3.16 (1H, d, J = 12.0 Hz), 2.78 (1H, d, J = 12.0 Hz),

2.45 (1H, ddd, J = 14.1, 5.2, 3.2 Hz), 2.22 (1H, ddd, J = 14.1, 8.9, 4.7 Hz).

[0076]

Step 5 Synthesis of Compound 21

Compound 20 (94.1mg, 0.232mmol) was dissolved in toluene (1.8 mL), phenyl(5-methylpyridin-3-yl)carbonate (123 mg, 0.464 mmol) and triethylamine (0.16 mL, 1.2 mmol) were added, and the mixture was stirred at 70 °C. for 4 hours. The reaction solution was purified by silicagel column chromatography (hexane/ethyl acetate = 60 : 40 to 0 : 100), and Compound 21 (110 mg, 0.204 mmol, yield 88%) was obtained.

LC/MS (ESI): m/z = 540 [M+H]⁺, RT = 2.06 min, LC/MS measurement conditions A
¹H-NMR (CDCl₃) δ: 8.08-8.05 (2H, m), 7.80-7.77 (1H, m), 7.42 (1H, d, J = 2.5 Hz), 7.37 (1H, brs), 7.14 (1H, d, J = 8.3 Hz), 7.11 (1H, dd, J = 8.7, 2.6 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.51 (1H, dd, J = 8.3, 2.4 Hz), 6.48 (1H, d, J = 2.4 Hz), 4.43-4.30 (3H, m), 4.27-4.16 (2H, m), 3.99 (1H, d, J = 14.7 Hz), 3.87 (3H, s), 3.81 (4H, s), 3.80 (1H, d, J = 14.2 Hz), 3.71 (3H, s), 2.57 (1H, ddd, J = 14.2, 6.6, 2.7 Hz), 2.30 (3H, s), 2.17 (1H, ddd, J = 14.2, 8.5, 3.1 Hz).

[0077]

Step 6 Synthesis of Compound 22

Compound 21 (110 mg, 0.204 mmol) and diazabicycloundecene (0.092 mL, 0.61 mmol) were dissolved in toluene (1.7 mL) and stirred at 60°C for 1 hour. The reaction solution was concentrated under reduced pressure and purified by silica gel column chromatography (hexane : ethyl acetate = 50 : 50 to 0 : 100), and Compound 22 (81.5 mg, 0.160 mmol, yield 79%) was obtained.

LC/MS (ESI): m/z = 508 [M+H]⁺, RT = 2.28 min, LC/MS measurement conditions A
¹H-NMR (CDCl₃) δ: 8.44 (1H, d, J = 1.3 Hz), 8.27 (1H, d, J = 2.3 Hz), 7.38-7.36 (1H, m), 7.12 (1H, dd, J = 8.8, 2.3 Hz), 6.98 (1H, d, J = 2.3 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.48 (2H, dd, J = 8.3, 2.3 Hz), 6.44 (2H, d, J = 2.3 Hz), 4.86 (1H, d, J = 14.0 Hz), 4.40 (1H, d, J = 14.0 Hz), 4.13 (1H, dd, J = 15.2, 5.6 Hz), 3.84 (1H, d, J = 13.5 Hz), 3.82-3.74 (2H, m), 3.82 (3H, s), 3.78 (3H, s), 3.48 (1H, d, J = 13.5 Hz), 2.39 (3H, s), 2.24 (1H, ddd, J = 13.9, 9.6, 3.6 Hz), 1.96 (1H, ddd, J = 14.0, 5.7, 2.6 Hz).

[0078]

Step 7 Synthesis of Compound 23

Compound 22 (76 mg, 0.15 mmol) was dissolved in anisole (1.1 mL) and trifluoroacetic acid (1.6 mL), and the mixture was sealed and stirred at 115°C for 5 hours. The reaction solution was dried under reduced pressure, and was purified by silicagel column chromatography (chloroform/methanol = 100 : 0 to 85 : 15) to give Compound 23 (50 mg, 0.134 mmol, yield 89 %).

LC/MS (ESI): m/z = 358 [M+H]⁺, RT = 1.58 min, LC/MS measurement conditions A
¹H-NMR (DMSO-d₆) δ: 8.38 (1H, d, J = 1.3 Hz), 8.30 (1H, d, J = 4.1 Hz), 8.26 (1H, d, J = 2.1 Hz), 7.55 (1H, brs), 7.42 (1H, d, J = 2.3 Hz), 7.23 (1H, dd, J = 8.8, 2.6 Hz), 6.87 (1H, d, J = 8.6 Hz), 4.25-4.15 (2H, m), 3.97 (1H, d, J = 12.7 Hz), 3.33 (1H, d, J = 12.7 Hz), 2.34 (3H, s), 2.31-2.26 (2H, m).

[0079]

Step 8 Synthesis of Compound (I-088)

Compound 23 (42.6 mg, 0.119 mmol) and potassium carbonate (49 mg, 0.36 mmol) was suspended in DMF (0.6 mL), and 2-bromoacetonitrile (24 μL, 0.36 mmol) were added, then the mixture was stirred at room temperature for 3 hours. Potassium carbonate (49 mg, 0.36 mmol) and 2-bromoacetonitrile (24 μL, 0.36 mmol) were added, then the mixture was stirred at room temperature for 3 hours, and at

40°C for 1 hour. Water was added to the mixture under ice cooling, the thus obtained mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. The obtained solid was separated by filtration, dried under reduced pressure, and purified by silicagel column chromatography (chloroform/methanol= 100 : 0 to 93 : 7) to give Compound (I-088) (22.9 mg, 0.055 mmol, yield 47%).

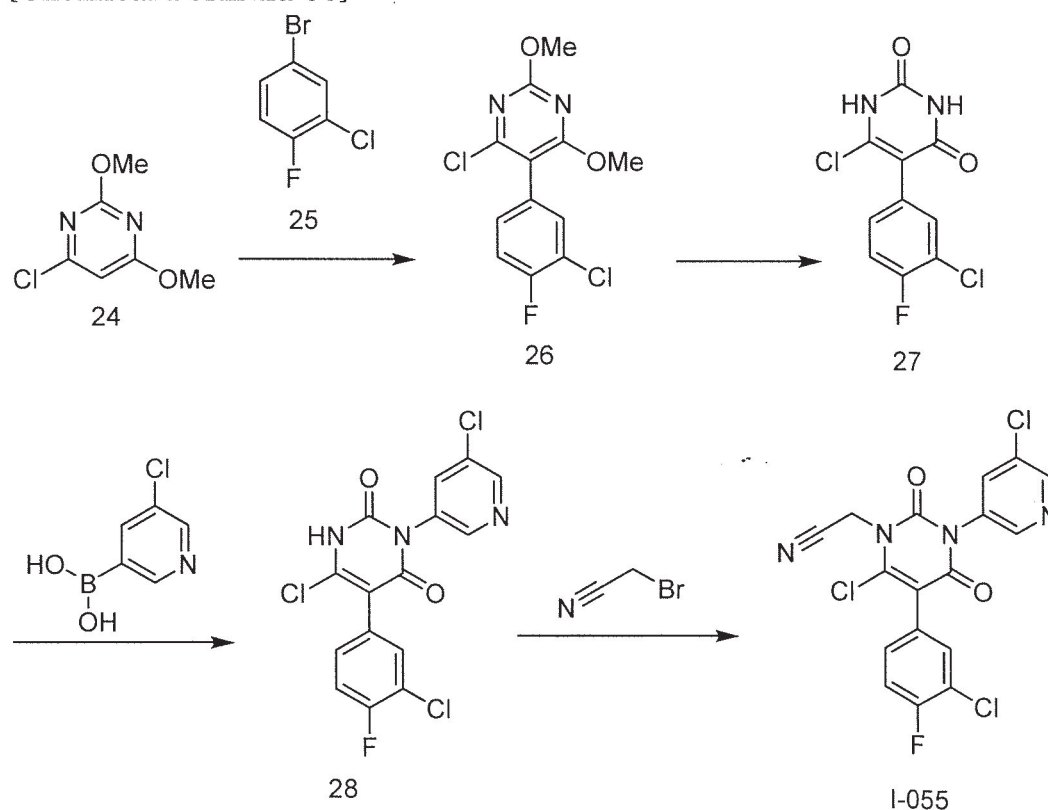
LC/MS (ESI): m/z = 397 $[M+H]^+$, RT = 1.85 min, LC/MS measurement conditions A
 1H -NMR ($CDCl_3$) δ : 8.47 (1H, brs), 8.24 (1H, d, J = 2.1 Hz), 7.34 (1H, brs), 7.20 (1H, dd, J = 8.8, 2.3 Hz), 7.05 (1H, d, J = 2.3 Hz), 6.87 (1H, d, J = 8.8 Hz), 4.77 (1H, d, J = 17.6 Hz), 4.36 (1H, ddd, J = 11.8, 6.5, 3.4 Hz), 4.29-4.23 (1H, m), 4.24 (1H, d, J = 17.6 Hz), 4.04 (1H, d, J = 12.7 Hz), 3.62 (1H, d, J = 12.7 Hz), 2.47 (1H, ddd, J = 14.1, 8.6, 3.6 Hz), 2.39 (3H, s), 2.30 (1H, ddd, J = 14.3, 6.7, 3.2 Hz).

[EXAMPLE 5]

[0080]

Synthesis of Compound (I-055)

[Chemical Formula 36]



Step 1 Synthesis of Compound 26

To a mixed solution of a 2.64 mol/L *n*-butyllithium solution in hexane (31 mL, 82.4 mmol) and tetrahydrofuran (20 mL), a tetrahydrofuran (70 mL) solution of Compound 24 (12 g, 68.7 mmol) was added dropwise at -78°C over 15 minutes. The mixture was stirred at -78°C for 1 hour. A 1.9 mol/L zinc chloride 2-methyltetrahydrofuran solution (43 mL, 82.4 mmol) was added dropwise over 5 minutes. The mixture was stirred at room temperature for 2 hours. Compound 25 (9.1 mL, 75.6 mmol) and tetrakis(triphenylphosphine)palladium (4.0 g, 3.44 mmol) were added, and the mixture was stirred at 80 °C for 1.5 hours. The reaction solution was cooled to room temperature, water (80 mL) and 2 mol/L hydrochloric acid (40 mL) were added thereto, and the mixture was extracted with ethyl acetate. The

organic layer was concentrated under reduced pressure, and isopropanol (40 mL) was added to the obtained residue. The precipitate was collected by filtration and washed with isopropanol. The mixture was air-dried to obtain Compound 26 (14.8 g, 49 mmol).

¹H-NMR (CDCl₃) δ: 3.95 (s, 3H), 4.05 (s, 3H), 7.18-7.23 (m, 2H), 7.35 (d, J = 6.8 Hz, 1H)

LC/MS (ESI): m/z = 303, RT = 2.70 min, LC/MS measurement conditions A [0081]

Step 2 Synthesis of Compound 27

Acetic acid (40 mL) and concentrated hydrochloric acid (41 mL) were added to Compound 26 (14.8 g, 48.8 mmol), and the mixture was stirred at 110 °C for 5 hours. The reaction solution was cooled to room temperature, and then water (80 mL) was added thereto. The precipitate was collected by filtration and washed with water. The mixture was air-dried to obtain Compound 27 (11.6 g, 42.2 mmol).

¹H-NMR (DMSO-d₆) δ: 7.31 (ddd, J = 8.8, 4.9, 2.1 Hz, 1H), 7.45 (t, J = 8.8 Hz, 1H), 7.53 (dd, J = 7.3, 2.1 Hz, 1H), 11.57 (s, 1H), 12.24 (brs, 1H)

LC/MS (ESI): m/z = 275, RT = 1.81 min, LC/MS measurement condition A [0082]

Step 3 Synthesis of Compound 28

Compound 27 (1.00 g, 3.64 mmol), 5-chloropyridine-3-boronic acid (1.14 g, 7.27 mmol), copper (II) acetate (0.99 g, 5.45 mmol), acetonitrile (10 mL), triethylamine (5.04 mL, 36.4 mmol) and pyridine (7.34 mL, 91.0 mmol) were mixed, and the solution was stirred at room temperature overnight. The saturated aqueous sodium hydrogen carbonate solution (5 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography (chloroform : methanol = 100 : 0 to 90 : 10), and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 28 (1.15 g, 2.97 mmol, yield 82%) was obtained.

¹H-NMR (DMSO-d₆) δ: 7.35-7.37 (1H, m), 7.49 (1H, t, J = 9.0 Hz), 7.54-7.56 (1H, m), 8.07 (1H, t, J = 2.1 Hz), 8.54 (1H, d, J = 2.0 Hz), 8.70 (1H, d, J = 2.3 Hz).

LC/MS (ESI): m/z = 386, RT = 1.98 min, LC/MS measurement condition A [0083]

Step 4 Synthesis of Compound (I-055)

To a solution obtained by mixing compound 28 (520 mg, 1.345 mmol), N,N'-diisopropylethylamine (0.705 mL, 4.04 mmol), and DMF (5.2 mL), 2-bromoacetonitrile (269 μL, 4.04 mmol) was added, and the solution was stirred at room temperature overnight. A 2 mol/L hydrochloric acid solution (2 mL) was added to the reaction solution under ice cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography (chloroform : methanol = 100 : 0 to 99 : 1), and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound (I-055) (291 mg, 0.684 mmol, yield 51%) was obtained.

¹H-NMR (CDCl₃) δ: 5.13 (2H, s), 7.23-7.24 (2H, m), 7.42 (1H, d, J = 7.3 Hz), 7.67 (1H, t, J = 2.1 Hz), 8.45 (1H, d, J = 2.3 Hz), 8.67 (1H, d, J = 2.3 Hz).

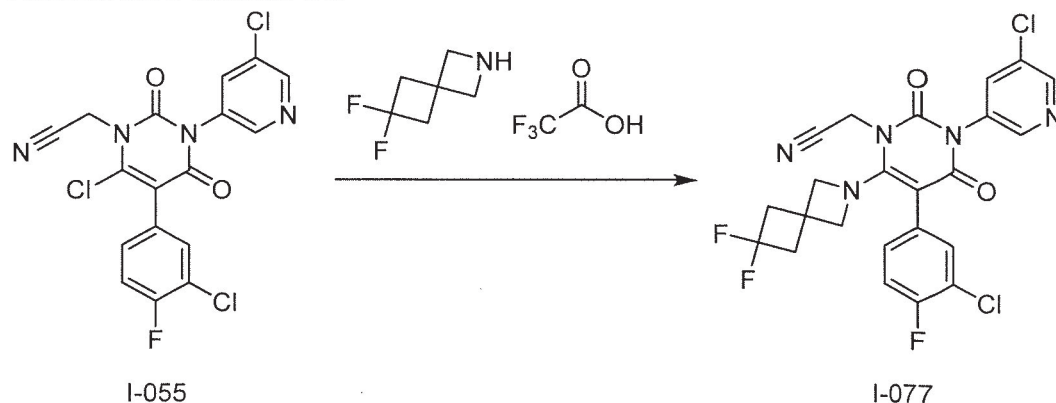
LC/MS (ESI): m/z = 425, RT = 2.17 min, LC/MS measurement condition A

[EXAMPLE 6]

[0084]

Synthesis of Compound (I-077)

[Chemical Formula 37]



Step 1 Synthesis of Compound (I-077)

Compound (I-055) (25.0 mg, 0.059 mmol), 6,6-difluoro-2-azaspiro[3.3]heptane trifluoroacetic acid salt (17.4 mg, 0.070 mmol), N, N-diisopropylethylamine (20.5 μ L, 0.117 mmol), and DMF (0.5 mL) were mixed, and the solution was stirred at 60°C for 2 hours. Water (2 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated, and ethyl acetate (0.05 mL), hexane (0.125 mL), and diisopropyl ether (0.125 mL) were added. The obtained precipitate was collected by filtration and washed with diisopropyl ether. The obtained solid was dried under reduced pressure to obtain Compound (I-077) (22.0 mg, 0.042 mmol, yield 72%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.75 (4H, t, $J = 12.0$ Hz), 4.02 (4H, s), 4.74 (2H, s), 7.16-7.18 (2H, m), 7.32-7.35 (1H, m), 7.65 (1H, t, $J = 2.1$ Hz), 8.43 (1H, d, $J = 2.3$ Hz), 8.61 (1H, d, $J = 2.3$ Hz).

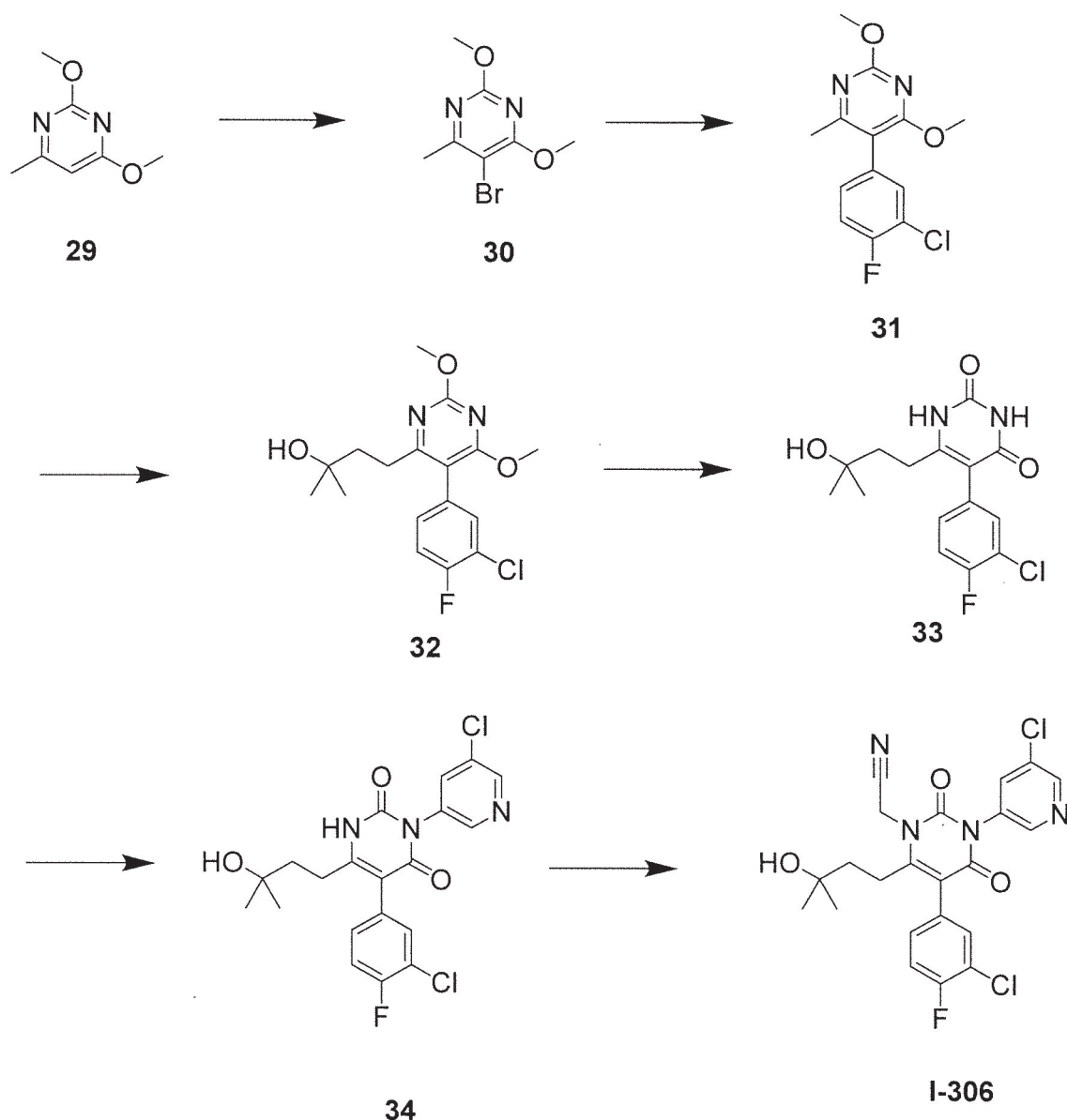
LC/MS (ESI): $m/z = 522$, $\text{RT} = 2.27$ min, LC/MS measurement condition A

[EXAMPLE 7]

[0085]

Synthesis of Compound (I-306)

[Chemical Formula 38]



Step 1 Synthesis of Compound 30

N-bromosuccinimide (6.93 g, 38.9 mmol) was added to a mixed solution of Compound 29 (5 g, 32.4 mmol) and acetic acid (50 mL) at room temperature, and then the mixture was stirred at 120°C for 3 hours. After completion of the reaction, the mixture was concentrated, an aqueous saturated sodium bicarbonate solution and an aqueous sodium thiosulfate solution were added to the reaction solution, and the mixture was extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 30 (3.11g, 13.4 mmol, yield 41%) was obtained. ¹H-NMR (CDCl₃) δ: 2.52 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H).

LC/MS (ESI): m/z = 234 [M+H]⁺, RT = 2.16 min, LC/MS measurement condition A

Step 2 Synthesis of Compound 31

To a dioxane (30 mL) solution of Compound 30 (3 g, 12.9 mmol), (3-chloro-4-fluorophenyl)boronic acid (3.37 g, 19.3 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.942 g, 1.29 mmol), and a 2 mol/l aqueous potassium carbonate solution (12.87 mL, 25.7 mmol) were added, and the mixture was stirred at 110°C for 4 hours. After completion of the reaction, a

10% aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 31 (3.23 g, 11.4 mmol, yield 89%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (s, 3H), 3.91 (s, 3H), 4.02 (s, 3H), 7.06-7.10 (m, 1H), 7.19 (t, J = 6.6 Hz, 1H), 7.25-7.28 (m, 1H).

LC/MS (ESI): m/z = 283 $[\text{M}+\text{H}]^+$, RT = 2.52 min, LC/MS measurement condition A
Step 3 Synthesis of Compound 32

A tetrahydrofuran (5 mL) solution of Compound 31 (400 mg, 1.42 mmol) was adjusted to -78°C , 2 mol/L of lithium diisopropylamide (1.42 mL, 2.83 mmol) was added thereto, and the mixture was stirred for 30 minutes. Then, 2,2-dimethyloxirane (0.26 mL, 2.83 mmol) was added, and the mixture was heated to 0°C and stirred for 1 hour. After completion of the reaction, a 10% aqueous citric acid solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 32 (258 mg, 0.73 mmol, yield 52%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.18 (s, 6H), 1.81 (t, J = 5.4 Hz, 2H), 2.60 (t, J = 5.4 Hz, 2H), 3.91 (s, 3H), 4.02 (s, 3H), 7.05-7.09 (m, 1H), 7.20 (t, J = 6.6 Hz, 1H), 7.25-7.27 (m, 1H).

LC/MS (ESI): m/z = 355 $[\text{M}+\text{H}]^+$, RT = 2.41 min, LC/MS measurement conditions A
Step 4 Synthesis of Compound 33

Acetic acid (0.497 mL) and concentrated hydrochloric acid (0.424 mL) were added to Compound 32 (180 mg, 0.509 mmol), and the mixture was stirred at 110°C for 1 hour. Then, a 2 mol/L aqueous sodium hydroxide solution was added, and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 33 (71.5 mg, 0.219 mmol, yield 43%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (s, 6H), 1.75 (t, J = 5.1 Hz, 2H), 2.49 (t, J = 5.1 Hz, 2H), 7.08-7.11 (m, 1H), 7.18 (t, J = 6.6 Hz, 1H), 7.26-7.29 (m, 1H), 9.18 (s, 1H), 10.53 (s, 1H).

LC/MS (ESI): m/z = 327 $[\text{M}+\text{H}]^+$, RT = 1.74 min, LC/MS measurement conditions A
Step 5 Synthesis of Compound 34

A solution obtained by mixing 5-chloropyridine-3-boronic acid (107 mg, 0.680 mmol), copper (II) acetate (74.1 mg, 0.408 mmol), pyridine (0.55 mL, 6.8 mmol), and triethylamine (0.377 mL, 2.72 mmol) in an acetonitrile (1 mL) solution of Compound 33 (88.9 mg, 0.272 mmol) was stirred at room temperature overnight. A saturated aqueous ammonium chloride solution (5 mL) was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound 34 (76.3 mg, 0.174 mmol, yield 64%) was obtained.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (s, 6H), 1.81 (t, J = 4.8 Hz, 2H), 2.57 (t, J = 4.8 Hz, 2H), 7.10-

7.14 (m, 1H), 7.18 (t, J = 6.6 Hz, 1H), 7.31 (dd, J = 1, 5, 6.6 Hz, 1H), 7.68 (t, J = 1.5 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 8.60 (d, J = 1.5 Hz, 1H).

LC/MS (ESI): m/z = 438 [M+H]⁺, RT = 2.13 min, LC/MS measurement conditions A
Step 6 Synthesis of Compound I-306

Potassium carbonate (33.3 mg, 0.241 mmol) and 2-bromoacetonitrile (14.8 μ L, 0.223 mmol) were added to a DMF (1 mL) solution of Compound 34 (81.3 mg, 0.185 mmol), and the mixture was stirred at room temperature overnight. After completion of the reaction, a 10% aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, the obtained residue was purified by silica gel column chromatography, and the solvent was distilled off under reduced pressure. The residue thus obtained was dried under reduced pressure, and Compound I-306 (54.4 mg, 0.114 mmol, yield 61%) was obtained.

¹H-NMR (CDCl₃) δ : 1.20 (s, 6H), 1.69 (t, J = 6.0 Hz, 2H), 2.69 (t, J = 6.0 Hz, 2H), 5.10 (s, 2H), 7.12-7.15 (m, 1H), 7.21-7.26 (m, 1H), 7.32-7.33 (m, 1H), 7.68 (t, J = 1.5 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H).

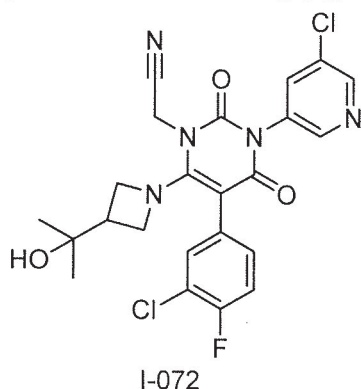
LC/MS (ESI): m/z = 477 [M+H]⁺, RT = 2.23 min, LC/MS measurement conditions A

[EXAMPLE 8]

[0086]

Synthesis of Compound (I-072)

[Chemical Formula 39]



Compound (I-072) (15 mg, 0.030 mmol, yield 63%) was obtained from Compound (I-055) (20 mg, 0.047 mmol) according to the synthesis method of Compound (I-077).

¹H-NMR (CDCl₃) δ : 1.12 (6H, s), 2.48-2.55 (1H, m), 3.89-3.97 (4H, m), 4.77 (2H, s), 7.12-7.18 (2H, m), 7.37 (1H, dd, J = 7.0, 2.0 Hz), 7.67 (1H, t, J = 2.1 Hz), 8.44 (1H, d, J = 2.3 Hz), 8.60 (1H, d, J = 2.3 Hz).

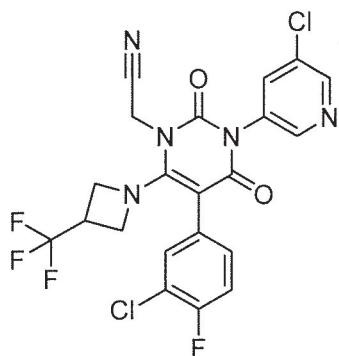
LC/MS (ESI): m/z = 504 [M+H]⁺, RT = 1.94 min, LC/MS measurement conditions A

[EXAMPLE 9]

[0087]

Synthesis of Compound (I-086)

[Chemical Formula 40]



I-086

Compound (I-086) (14 mg, 0.027 mmol, yield 58%) was obtained from Compound (I-055) (20 mg, 0.047 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.20-3.22 (1H, m), 3.91-4.19 (4H, m), 4.76 (2H, s), 7.16-7.21 (2H, m), 7.37 (1H, dd, $J = 6.9, 2.0$ Hz), 7.66 (1H, t, $J = 2.1$ Hz), 8.44 (1H, d, $J = 2.1$ Hz), 8.62 (1H, d, $J = 2.1$ Hz).

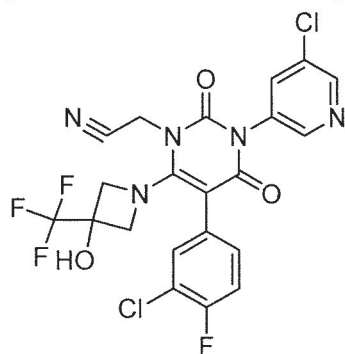
LC/MS (ESI): $m/z = 514$ $[\text{M}+\text{H}]^+$, RT = 2.25 min, LC/MS measurement conditions A

[EXAMPLE 10]

[0088]

Synthesis of Compound (I-142)

[Chemical Formula 41]



I-142

Compound (I-142) (15 mg, 0.028 mmol, yield 60%) was obtained from Compound (I-055) (20 mg, 0.047 mmol) according to the synthesis method of Compound (I-077).

NMR (CDCl_3) δ : 3.57 (1H, brs), 3.88-3.98 (2H, m), 4.12-4.21 (2H, m), 4.76 (2H, s), 7.14-7.24 (2H, m), 7.37 (1H, dd, $J = 6.8, 2.0$ Hz), 7.68 (1H, t, $J = 2.0$ Hz), 8.43 (1H, d, $J = 2.0$ Hz), 8.61 (1H, d, $J = 2.0$ Hz).

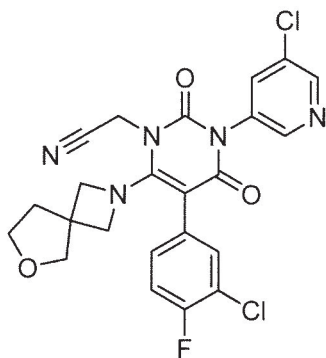
LC/MS (ESI): $m/z = 530$ $[\text{M}+\text{H}]^+$, RT = 1.89 min, LC/MS measurement conditions D

[EXAMPLE 11]

[0089]

Synthesis of Compound (I-181)

[Chemical Formula 42]



I-181

Compound (I-181) (91 mg, 0.181 mmol, yield 77%) was obtained from Compound (I-055) (100 mg, 0.235 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (2H, t, $J = 7.2$ Hz), 3.78-3.84 (4H, m), 3.92 (4H, s), 4.75 (2H, brs), 7.17 (2H, d, $J = 7.8$ Hz), 7.35 (1H, d, $J = 7.0$ Hz), 7.66 (1H, t, $J = 2.0$ Hz), 8.44 (1H, d, $J = 2.0$ Hz), 8.61 (1H, d, $J = 2.0$ Hz).

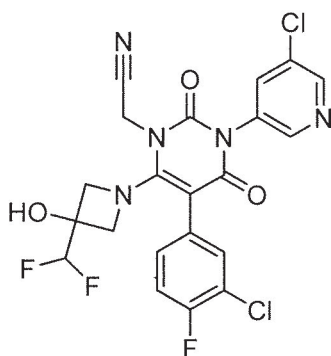
LC/MS (ESI): $m/z = 502$ $[\text{M}+\text{H}]^+$, RT = 2.04 min, LC/MS measurement conditions A

[EXAMPLE 12]

[0194]

Synthesis of Compound (I-230)

[Chemical Formula 43]



I-230

Compound (I-230) (40 mg, 0.078 mmol, yield 74%) was obtained from Compound (I-055) (45 mg, 0.106 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.73-3.84 (2H, m), 3.97-4.11 (2H, m), 4.85 (2H, s), 6.08 (1H, t, $J = 55.3$ Hz), 6.68 (1H, s), 7.21-7.26 (1H, m), 7.40-7.47 (1H, m), 8.01 (1H, t, $J = 2.1$ Hz), 8.48 (1H, d, $J = 1.9$ Hz), 8.69 (1H, d, $J = 2.3$ Hz).

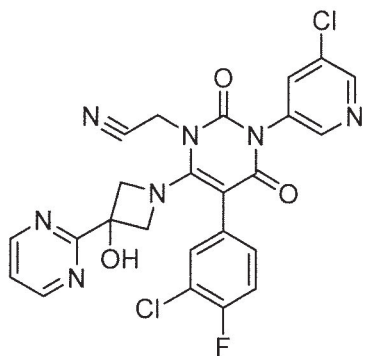
LC/MS (ESI): $m/z = 512$ $[\text{M}+\text{H}]^+$, RT = 1.75 min, LC/MS measurement conditions D

[EXAMPLE 13]

[0091]

Synthesis of Compound (I-232)

[Chemical Formula 44]



I-232

Compound (I-232) (17 mg, 0.031 mmol, yield 54%) was obtained from Compound (I-055) (25 mg, 0.059 mmol) according to the synthesis method of Compound (I-077).

¹H-NMR (CDCl₃) δ: 4.15-4.29 (2H, m), 4.34-4.48 (2H, m), 4.88 (2H, s), 5.39 (1H, s), 7.13 (1H, t, J = 8.6 Hz), 7.20-7.28 (1H, m), 7.38 (1H, t, J = 4.9 Hz), 7.44 (1H, dd, J = 7.0, 2.1 Hz), 7.70 (1H, t, J = 2.1 Hz), 8.48 (1H, d, J = 2.0 Hz), 8.61 (1H, d, J = 2.1 Hz), 8.83 (2H, d, J = 4.9 Hz).

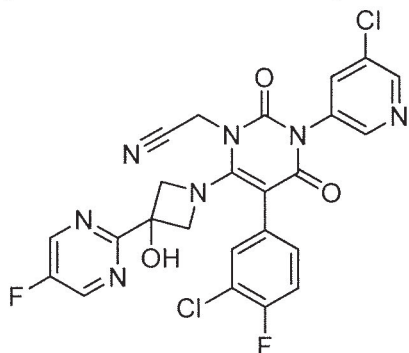
LC/MS (ESI): m/z = 540 [M+H]⁺, RT = 1.67 min, LC/MS measurement conditions D

[EXAMPLE 14]

[0092]

Synthesis of Compound (I-234)

[Chemical Formula 45]



I-234

Compound (I-234) (48 mg, 0.086 mmol, 39% yield) was obtained from Compound (I-055) (94 mg, 0.221 mmol) according to the synthesis method of Compound (I-077).

¹H-NMR (CDCl₃) δ: 4.13-4.30 (2H, m), 4.30-4.50 (2H, m), 4.86 (2H, s), 5.07 (1H, s), 7.14 (1H, t, J = 8.6 Hz), 7.19-7.28 (1H, m), 7.43 (1H, dd, J = 6.8, 1.9 Hz), 7.67-7.72 (1H, m), 8.48 (1H, d, J = 1.9 Hz), 8.69 (1H, d, J = 2.0 Hz), 8.69 (2H, s).

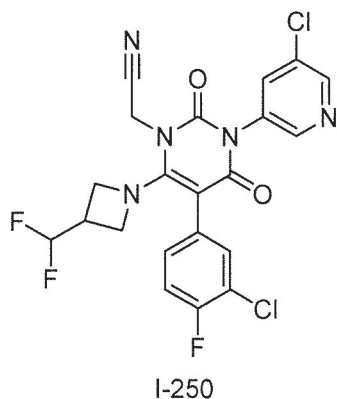
LC/MS (ESI): m/z = 558 [M+H]⁺, RT = 1.93 min, LC/MS measurement conditions A

[EXAMPLE 15]

[0093]

Synthesis of Compound (I-250)

[Chemical Formula 46]



Compound (I-250) (23 mg, 0.047 mmol, 40% yield) was obtained from Compound (I-055) (50 mg, 0.117 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.91-3.07 (1H, m), 3.91-4.09 (4H, m), 4.76 (2H, s), 5.93 (1H, td, $J = 55.7, 3.0$ Hz), 7.18 (2H, dd, $J = 6.1, 1.4$ Hz), 7.35-7.38 (1H, m), 7.67 (1H, t, $J = 2.1$ Hz), 8.44 (1H, d, $J = 2.1$ Hz), 8.61 (1H, d, $J = 2.1$ Hz).

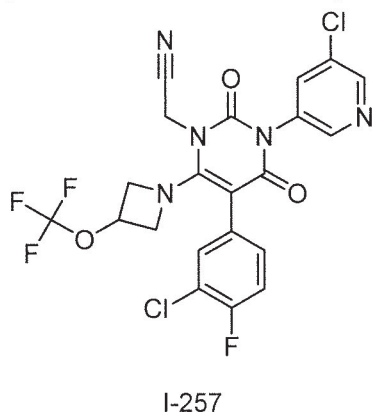
LC/MS (ESI): $m/z = 496$ $[\text{M}+\text{H}]^+$, RT = 2.20 min, LC/MS measurement conditions A

[EXAMPLE 16]

[0094]

Synthesis of Compound (I-257)

[Chemical Formula 47]



Compound (I-257) (25 mg, 0.047 mmol, yield 67%) was obtained from Compound (I-055) (30 mg, 0.070 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.97-4.10 (2H, m), 4.19-4.32 (2H, m), 4.77 (2H, s), 4.81-4.90 (1H, m), 7.17-7.22 (2H, m), 7.37 (1H, d, $J = 6.9, 1.8$ Hz), 7.66 (1H, t, $J = 2.1$ Hz), 8.44 (1H, d, $J = 2.0$ Hz), 8.62 (1H, d, $J = 2.0$ Hz).

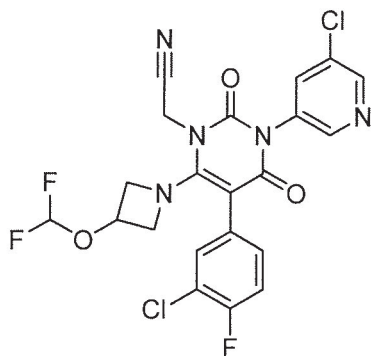
LC/MS (ESI): $m/z = 530$ $[\text{M}+\text{H}]^+$, RT = 2.33 min, LC/MS measurement conditions A

[EXAMPLE 17]

[0095]

Synthesis of Compound (I-298)

[Chemical Formula 48]



I-298

Compound (I-298) (20 mg, 0.039 mmol, yield 42%) was obtained from Compound (I-055) (40 mg, 0.094 mmol) according to the synthesis method of Compound (I-077).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.94-4.01 (2H, m), 4.19-4.27 (2H, m), 4.76 (2H, s), 4.85-4.93 (1H, m), 6.23 (1H, t, $J = 71.8$ Hz), 7.16-7.21 (2H, m), 7.34-7.38 (1H, m), 7.66 (1H, t, $J = 2.3$ Hz), 8.44 (1H, d, $J = 2.0$ Hz), 8.61 (1H, d, $J = 2.0$ Hz).

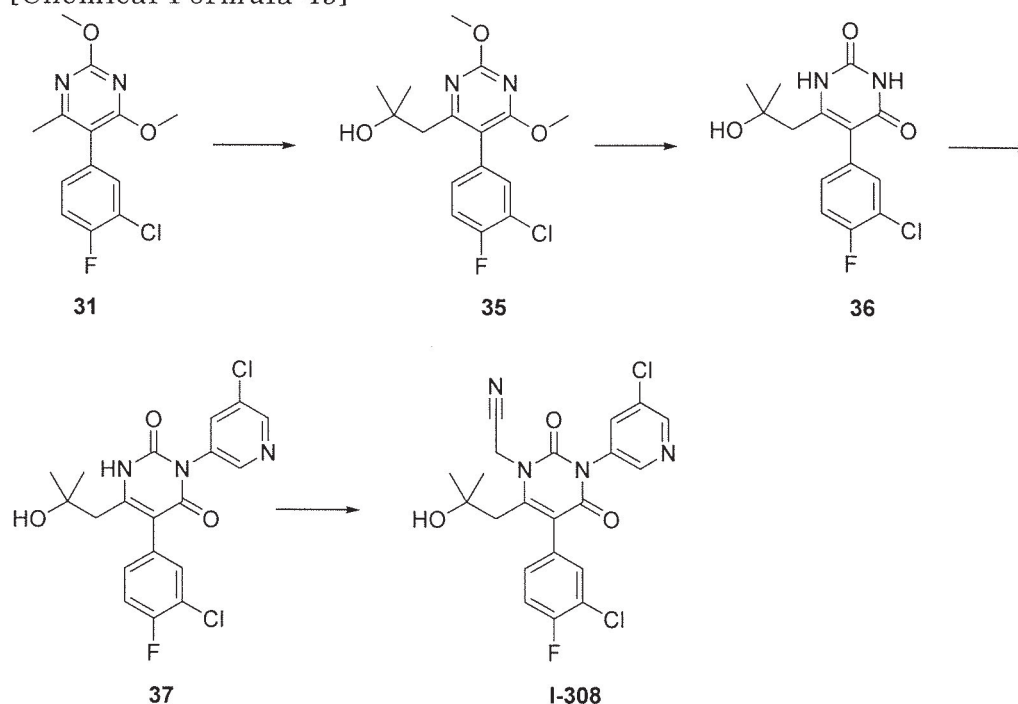
LC/MS (ESI): $m/z = 512$ $[\text{M}+\text{H}]^+$, RT = 2.17 min, LC/MS measurement conditions A

[EXAMPLE 18]

[0096]

Synthesis of Compound (I-308)

[Chemical Formula 49]



Step 1 Synthesis of Compound 35

LDA (2 mol/L, 0.796 mL, 1.59 mmol) was added to a THF (2 mL) solution of Compound 31 (300 mg, 1.06 mmol) at -78°C , and the mixture was stirred for 35 minutes at the same temperature. Acetone (0.094 mL, 1.27 mmol) was added to the reaction solution, and the mixture was stirred at -78°C for 1 hour. After completion of the reaction, a 10% aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography to obtain Compound 35 (362 mg,

1.06 mmol, yield 100%).

LC/MS (ESI): $m/z = 341$ $[M+H]^+$, RT = 2.56 min, LC/MS measurement conditions A [0097]

Step 2 Synthesis of Compound 36

Concentrated hydrochloric acid (0.885 μ L, 10.6 mmol) was added to an acetic acid (1.0 mL) solution of Compound 35 (362 mg, 1.06 mmol), and the mixture was stirred at 110°C. After completion of the reaction, the mixture was allowed to cool, water was added thereto, and the mixture was stirred at room temperature for 1 hour. The reaction solution was filtered to obtain Compound 36 (265 mg, 0.847 mmol, yield 80%).

LC/MS (ESI): $m/z = 313$ $[M+H]^+$, RT = 1.87 min, LC/MS measurement conditions A [0098]

Step 3 Synthesis of Compound 37

(5-Chloropyridin-3-yl)boronic acid (333 mg, 2.12 mmol), copper (II) acetate (231 mg, 1.27 mmol), pyridine (1.71 mL, 21.2 mmol) and triethylamine (1.17 mL, 8.47 mmol) were added to an acetonitrile (2.5 mL) solution of Compound 36 (265 mg, 0.847 mmol), and the mixture was stirred at room temperature overnight. After completion of the reaction, a saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography to obtain Compound 37 (276 mg, 0.649 mmol, yield 77%).

LC/MS (ESI): $m/z = 424$ $[M+H]^+$, RT = 2.21 min, LC/MS measurement conditions A [0099]

Step 4 Synthesis of Compound (I-308)

Potassium carbonate (42.3 mg, 0.306 mmol) and 2-bromoacetonitrile (19 μ L, 0.283 mmol) were added to a DMF (1 mL) solution of Compound 37 (100 mg, 0.236 mmol), and the mixture was stirred at room temperature for 1.5 hours. To the reaction solution, 2-bromoacetonitrile (19 μ L, 0.283 mmol) was added, and the mixture was stirred at room temperature overnight. Furthermore, 2-bromoacetonitrile (38 μ L, 0.566 mmol) was added, and the mixture was stirred at room temperature for 2 hours. After completion of the reaction, a 10% aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography to obtain Compound (I-308) (81 mg, 0.175 mmol, yield 74%).

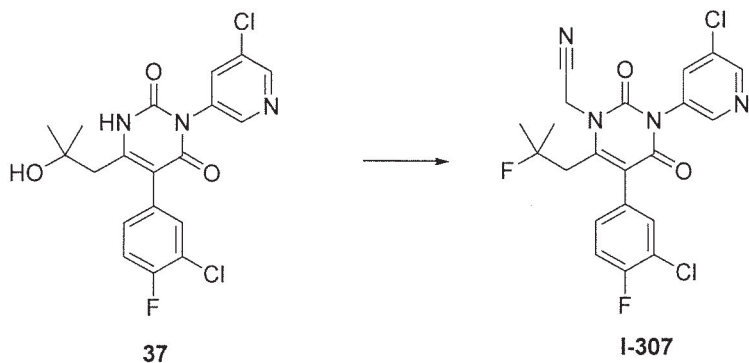
$^1\text{H-NMR}$ (CDCl_3) δ : 1.04-1.38 (6H, m), 3.04 (2H, brs), 5.41 (2H, brs), 7.10-7.40 (3H, m), 7.70 (1H, t, $J = 2.1$ Hz), 8.47 (1H, d, $J = 2.0$ Hz), 8.63 (1H, d, $J = 2.0$ Hz).

LC/MS (ESI): $m/z = 463$ $[M+H]^+$, RT = 2.26 min, LC/MS measurement conditions A [Example 19]

[0100]

Synthesis of Compound (I-307)

[Chemical Formula 50]

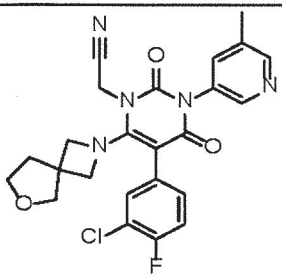
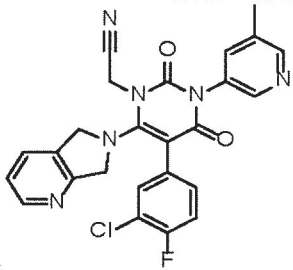
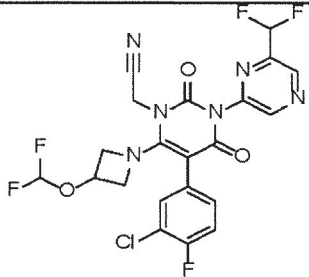
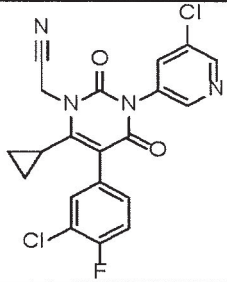
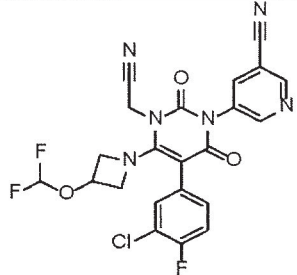


Step 1 Synthesis of Compound (I-307)

DAST (3.1 μL , 0.024 mmol) was added to a CH_2Cl_2 (0.5 mL) solution of Compound 37 (10 mg, 0.024 mmol), and the mixture was stirred at room temperature for 15 minutes. After completion of the reaction, a saturated aqueous sodium bicarbonate solution was added. DAST (6.2 μL , 0.047 mmol) was added to a CH_2Cl_2 (0.5 mL) solution of Compound 37 (20 mg, 0.047 mmol) prepared in another flask, and the mixture was stirred at room temperature for 15 minutes. After completion of the reaction, a saturated aqueous sodium bicarbonate solution was added. The reaction mixtures were mixed, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product. Potassium carbonate (12.7 mg, 0.091 mmol) and 2-bromoacetonitrile (5.6 μL , 0.084 mmol) were added to a DMF (0.5 mL) solution of the obtained crude product, and the mixture was stirred at room temperature overnight. After completion of the reaction, a 10% aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was concentrated, and the obtained residue was purified by silica gel column chromatography to obtain Compound (I-307) (8.5 mg, 0.018 mmol, yield 26%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.23-1.44 (6H, m), 3.15 (2H, brs), 5.12 (2H, brs), 7.08-7.39 (3H, m), 7.70 (1H, t, $J = 1.9$ Hz), 8.47 (1H, d, $J = 1.9$ Hz), 8.65 (1H, d, $J = 1.9$ Hz). LC/MS (ESI): $m/z = 465$ $[\text{M}+\text{H}]^+$, RT = 2.42 min, LC/MS measurement conditions A [0101]

The following compounds were synthesized according to the above general synthesis method and the method described in Examples. The structure and physical properties (LC/MS data, NMR spectrum) are shown in the tables below. [0102]

[Table 1]

Structure	Compound No.	LC/MS measurement condition	Retention time(min)	m/z
	I-045	A	1.51	482
	I-075	A	1.69	489
	I-358	D	1.97	529
	I-388	A	2.49	431
	I-437	A	2.19	503

[0103]

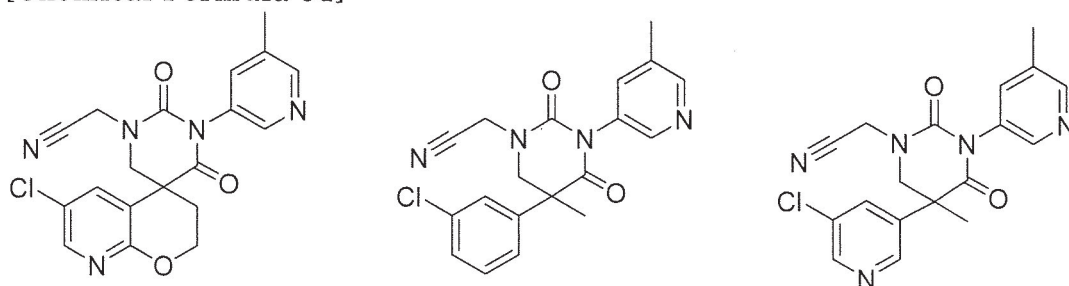
[Table 2]

	NMR
I-045	¹ H-NMR (CDCl ₃) δ: 2.11 (2H, t, J = 7.0 Hz), 2.38 (3H, s), 3.76-3.85 (4H, m), 3.91 (4H, s), 4.76 (2H, brs), 7.14-7.18 (2H, m), 7.34-7.37 (1H, m), 7.44 (1H, s), 8.34 (1H, s), 8.47 (1H, s).
I-075	¹ H-NMR (CDCl ₃) δ: 2.41 (3H, s), 4.52 (4H, brs), 5.02 (2H, s), 6.93-7.04 (2H, m), 7.16 (1H, dd, J = 6.9, 2.1 Hz), 7.22 (1H, dd, J = 7.7, 4.9 Hz), 7.45-7.48 (2H, m), 8.38 (1H, dd, J = 2.0 Hz), 8.47-8.53 (2H, m).
I-358	¹ H-NMR (CDCl ₃) δ: 3.91-4.04 (2H, m), 4.16-4.32 (2H, m), 4.76 (2H, s), 4.82-4.94 (1H, m), 6.23 (1H, t, J = 71.8 Hz), 6.72 (1H, t, J = 54.5 Hz), 7.18 (2H, t, J = 6.8 Hz), 7.37 (1H, d, J = 7.0 Hz), 8.77 (1H, s), 8.99 (1H, s).
I-388	¹ H-NMR (CDCl ₃) δ: 0.58-0.62 (2H, m), 1.05-1.09 (2H, m), 1.87-1.95 (1H, m), 5.18 (2H, s), 7.20 (2H, d, J = 6.5 Hz), 7.39 (1H, d, J = 7.4 Hz), 7.67 (1H, t, J = 2.1 Hz), 8.44 (1H, d, J = 1.9 Hz), 8.64 (1H, d, J = 2.0 Hz).
I-437	¹ H-NMR (CDCl ₃) δ: 3.96-4.03 (2H, m), 4.21-4.28 (2H, m), 4.76 (2H, s), 4.86-4.93 (1H, m), 6.23 (1H, t, J = 71.8 Hz), 7.17-7.21 (2H, m), 7.34-7.38 (1H, m), 7.93 (1H, t, J = 2.1 Hz), 8.75 (1H, d, J = 2.4 Hz), 8.90 (1H, d, J = 1.9 Hz).

[0104]

The following compounds can also be synthesized in the same manner as described above.

[Chemical Formula 51]



[0105]

Biological Test Examples for the compounds of the present invention will be described below.

The compound represented by Formula (I) according to the present invention may have coronavirus 3CL protease inhibitory action and may inhibit coronavirus 3CL protease.

Specifically, in the evaluation method described below, the IC₅₀ is preferably 50 μM or less, more preferably 1 μM or less, and even more preferably 100 nM or less. EC₅₀ is preferably 10 μM or less, more preferably 1 μM or less, and even more preferably 100 nM or less.

[0106]

Test Example 1: Cytopathic effect (CPE) suppression effect confirmation test using HEK293T cells expressing human TMPRSS2, ACE2 (HEK293T/ACE2-TMPRSS2 cells)

<Operational procedure>

· Dilution and dispensing of sample to be tested

The sample to be tested is diluted in advance to an appropriate concentration with DMSO, and a 2- to 5-fold series of serial dilutions is prepared and then dispensed into a 384-well plate.

· Dilution and dispensing of cells and SARS-CoV-2

HEK293T/ACE2-TMPRSS2 cells (GCP-SL222, 5×10³ cells/well) and SARS-CoV-2 (200-600 TCID₅₀/well) are mixed in a medium (MEM, 2% FBS, penicillin-streptomycin), the mixture is dispensed into the wells in which the sample to be tested has been introduced, and then the cells are cultured for 3 days in a CO₂ incubator.

· Dispensing of CellTiter-Glo (registered trademark) 2.0 and measurement of luminescence signals

The plate that has been cultured for 3 days is returned to room temperature, subsequently CellTiter-Glo (registered trademark) 2.0 is dispensed into each well, and the plate is mixed using a plate mixer. The plate is left to stand for a certain time, and then the luminescence signals (Lum) is measured with a plate reader.

<Calculation of each measurement item value>

· Calculation of 50% SARS-CoV-2 infected cell death inhibitory concentration (EC₅₀)

When x denotes the logarithmic value of the compound concentration and y denotes %Efficacy, the inhibition curve is approximated by the following Logistic regression equation, and the value of x when y = 50 (%) is inputted is calculated as EC₅₀.

$$y = \min + (\max - \min) / \{1 + (X50/x)^{\text{Hill}}\}$$

$$\% \text{Efficacy} = \{(\text{Sample} - \text{virus control}) / (\text{cell control} - \text{virus control})\} * 100\%$$

cell control: the average of Lum of cell control wells

virus control: the average of Lum of virus control wells

min: lower limit value of y-axis, max: upper limit value of y-axis, X50: x-coordinates of inflection point, Hill: slope of curve at midpoint between min and max

[0107]

The compounds of the present invention were tested essentially as described above. Results are shown below.

The EC₅₀ value was determined as "A" for less than 100 nM, "B" for 100 nM or more and less than 1000 nM, and "C" for 1000 nM or more and less than 5000 nM.

[0108]

(Result)

[Table 3]

Compound No.	EC50 [nM]	Compound No.	EC50 [nM]
I-060	19	I-230	5.36
I-072	5.21	I-232	6.46
I-077	1.66	I-234	6.6
I-086	3.31	I-250	3.31
I-142	3.35	I-257	2.98
I-205	5		

[0109]

[Table 4]

Compound No.	EC50
I-042	A
I-045	A
I-055	B
I-075	A
I-181	A
I-298	A
I-306	A
I-307	A
I-308	A
I-358	A
I-388	A
I-437	A

[0110]

Test Example 2: Inhibitory activity test against SARS-CoV-2 3CL proteases

<Materials>

- Commercially available Recombinant SARS-CoV-2 3CL Protease
- Commercially available substrate peptide

Dabcyl-Lys-Thr-Ser-Ala-Val-Leu-Gln-Ser-Gly-Phe-Arg-Lys-Met-Glu(Edans)-NH₂(SEQ ID NO: 1)

- Internal Standard peptide

Dabcyl-Lys-Thr-Ser-Ala-Val-Leu(13C₆,15N)-Gln (SEQ ID NO: 2)

Dabcyl-Lys-Thr-Ser-Ala-Val-Leu(13C₆,15N)-Gln can be synthesized with reference to documents (Atherton, E.; Sheppard, R. C., "In Solid Phase Peptide Synthesis, A Practical Approach", IRL Press at Oxford University Press, 1989.; Bioorg. Med. Chem., Vol. 5, No. 9, 1997, pp. 1883-1891; and the like). An example will be shown below.

H-Lys-Thr-Ser-Ala-Val-Leu(13C₆,15N)-Glu(resin)-O_tBu (the Lys-side chain is Boc-protected, the Thr-side chain is protected with a tert-butyl group, the Ser-side chain is protected with a tert-butyl group, the C-terminal OH of Glu is protected with a tert-butyl group, and the carboxylic acid of the Glu-side chain is condensed into the resin) is synthesized by Fmoc solid-phase synthesis using a Rink amide resin. Regarding the modification of the N-terminal Dabcyl group, 4-dimethylaminoazobenzene-4'-carboxylic acid (Dabcyl-OH) is condensed on the resin using EDC/HOBT. Final deprotection and cleavage from the resin are carried out by treatment with TFA/EDT = 95 : 5. Thereafter, purification is performed by reverse phase HPLC.

- RapidFire Cartridge C4 typeA

<Operational procedure>

- Preparation of assay buffer

In this test, an assay buffer consisting of 20 mM Tris-HCl, 1 mM EDTA, 10 mM DTT, and 0.01% BSA is used.

- Dilution and dispensing of sample to be tested

The sample to be tested is diluted in advance to an appropriate concentration with DMSO, and a 2- to 5-fold series of serial dilutions is prepared and then dispensed into a 384-well plate.

- Addition of enzyme and substrate, and enzymatic reaction

To a prepared compound plate, 8 μM substrate, and a 6 or 0.6 nM enzyme solution are added, and incubation is carried out for 3 to 5 hours at room temperature. Thereafter, a reaction stopping solution (0.067 μM Internal Standard, 0.1% formic acid, and 10% or 25% acetonitrile) is added to stop the enzymatic reaction.

- Measurement of reaction product

The plate in which the reaction has been completed is measured using RapidFire System 360 and a mass analyzer (Agilent, 6550 iFunnel Q-TOF), or RapidFire System 365 and a mass analyzer (Agilent, 6495C Triple Quadrupole). Solution A (75% isopropanol, 15% acetonitrile, 5 mM ammonium formate) and solution B (0.01% trifluoroacetic acid, 0.09% formic acid) are used as a mobile phase at the measurement.

The reaction product detected by the mass analyzer is calculated using RapidFire Integrator or an equivalent program capable of analysis and is taken as Product area value. Furthermore, the Internal Standard that has been detected at the same time is also calculated and is designated as Internal Standard area value.

<Calculation of each measurement item value>

· Calculation of P/IS

The area values obtained in the previous items are calculated by the following formula, and P/IS is calculated.

P/IS = Product area value/Internal Standard area value

· Calculation of 50% SARS-CoV-2 3CL protease inhibitory concentration (IC₅₀)

When x denotes the logarithmic value of the compound concentration and y denotes %Inhibition, the inhibition curve is approximated by the following Logistic regression equation, and the value of x obtainable when y = 50 (%) is inputted is calculated as IC₅₀.

$$y = \min + (\max - \min) / \{1 + (X50/x)^{\text{Hill}}\}$$

$$\% \text{Inhibition} = \{1 - (\text{Sample} - \text{Control}(-)) / (\text{Control}(+) - \text{Control}(-))\} * 100$$

Control(-): the average of P/IS of enzyme inhibited condition wells

Control(+): the average of P/IS of DMSO control wells

min: lower limit value of y-axis, max: upper limit value of y-axis, X50: x-coordinates of inflection point, Hill: slope of curve at midpoint between min and max

[0111]

The compounds of the present invention were tested essentially as described above. Results are shown below.

Incidentally, regarding the IC₅₀ value, a value of less than 0.01 μM is denoted by "A", a value of 0.01 μM or more and less than 0.1 μM is denoted by "B", and a value of 0.1 μM or more is denoted by "C".

[0112]

(Result)

[Table 5]

Compound No.	IC50 [μM]	Compound No.	IC50 [μM]
I-060	0.0047	I-230	0.00042
I-072	0.00066	I-232	0.00086
I-077	0.00036	I-234	0.0012
I-086	0.00070	I-250	0.00054
I-142	0.00046	I-257	0.00035
I-205	0.00076		

[00113]

[Table 6]

Compound No.	IC50
I-042	A
I-045	A
I-055	B
I-075	A
I-181	A
I-298	A
I-306	A
I-307	A
I-308	A
I-358	A
I-388	A
I-437	A

[0114]

The preparation examples shown below are only for illustrative purposes and are by no means intended to limit the scope of the invention.

The compound of the present invention can be administered as a pharmaceutical composition by any conventional route, particularly enterally, for example, orally, for example, in the form of a tablet or a capsule; parenterally, for example, in the form of an injectable preparation or a suspension; and topically, for example, in the form of a lotion, a gel, an ointment or a cream, or as a pharmaceutical composition in a transnasal form or a suppository form. A pharmaceutical composition comprising the compound of the present invention in a free form or in the form of a pharmaceutically acceptable salt together with at least one pharmaceutically acceptable carrier or diluent can be produced by a mixing, granulating, or coating method in a conventional manner. For example, the oral composition can be a tablet, a granular preparation, or a capsule, each containing an excipient, a disintegrating agent, a binder, a lubricating agent, and the like, as well as an active ingredient and the like. Furthermore, the composition for injection can be prepared as a solution or a suspension, may be sterilized, and may contain a preservative, a stabilizer, a buffering agent, and the like.

[INDUSTRIAL APPLICABILITY]

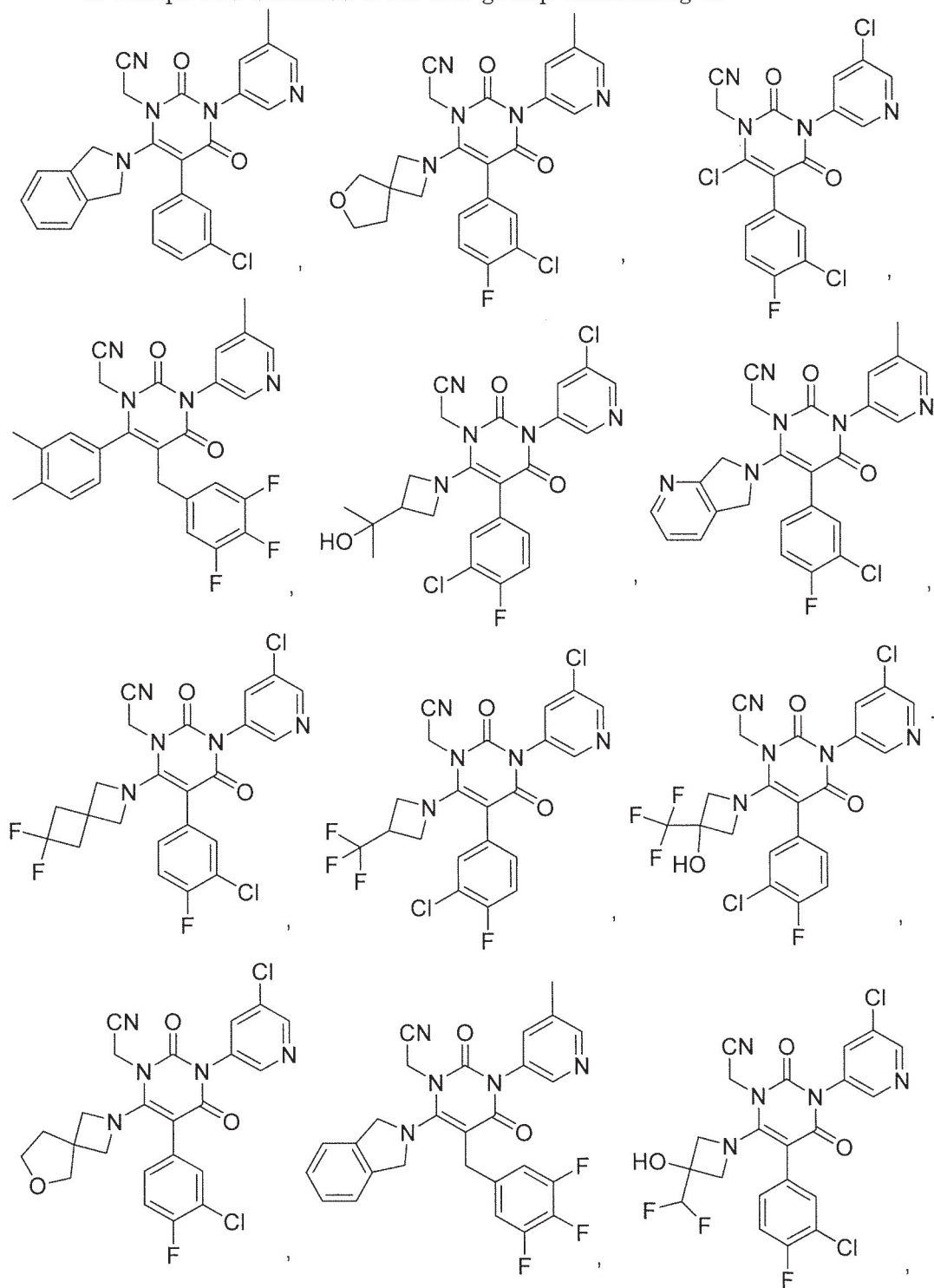
[0115]

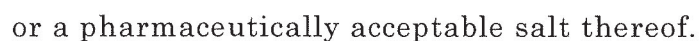
The compound according to the present invention has coronavirus 3CL protease inhibitory activity, and it is considered that the compound is useful as a therapeutic agent and/or a prophylactic agent for a disease or a condition associated with coronavirus 3CL proteases.

CLAIMS

[Claim 1]

A compound selected from the group consisting of:





A pharmaceutical composition comprising the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

A coronavirus 3CL protease inhibitor comprising the compound according to claim1, or a pharmaceutically acceptable salt thereof.

A coronavirus replication inhibitor comprising the compound according to claim

1, or a pharmaceutically acceptable salt thereof.

[Claim 5]

The coronavirus replication inhibitor according to claim 4, wherein the coronavirus is an alphacoronavirus and/or betacoronavirus.

[Claim 6]

The coronavirus replication inhibitor according to claim 4, wherein the coronavirus is SARS-CoV-2.

[Claim 7]

A method for treating and/or preventing a disease associated with coronavirus 3CL proteases, characterized by administering the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

[Claim 8]

The compound according to claim 1, or a pharmaceutically acceptable salt thereof for use in treating and/or preventing a disease associated with coronavirus 3CL proteases.