(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 June 2022 (09.06.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/119899 A1

(51) International Patent Classification:
A61K 31/497 (2006.01) *A61K 31/7048* (2006.01)
A61K 31/4545 (2006.01) *A61K 31/7052* (2006.01)
A61K 31/498 (2006.01) *A61P 31/06* (2006.01)

(21) International Application Number:
PCT/US2021/061365

(22) International Filing Date:
01 December 2021 (01.12.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/120,315 02 December 2020 (02.12.2020) US

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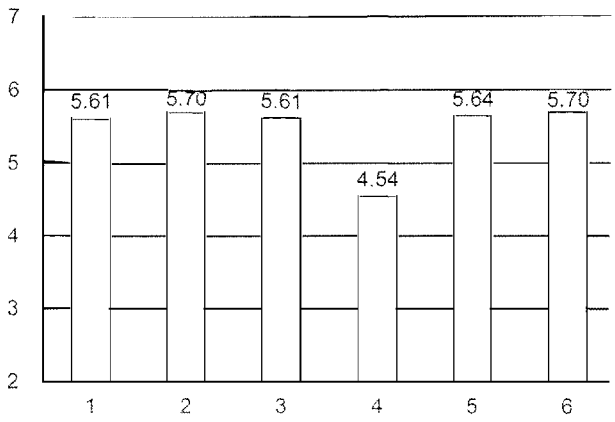
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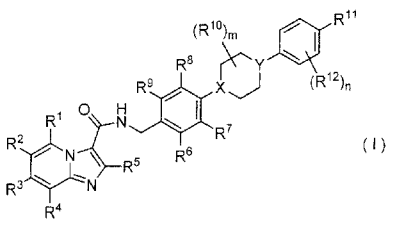
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

(54) Title: A MEDICAMENT FOR TREATING MYCOBACTERIAL INFECTION CHARACTERIZED BY COMBINING A CYTOCHROME BC1 INHIBITOR WITH CLARITHROMYCIN OR AZITHROMYCIN

[Figure 9]





(I)

(57) Abstract: A medicament characterized in that (A) a compound represented by formula (I):, or its pharmaceutically acceptable salt, wherein R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl or the like; R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl or the like; R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen or the like; X is CH or N; Y is CH or N; R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl or the like; m is 0, 1, 2, 3 or 4; R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl or the like; R^{12} is each independently halogen, hydroxy, cyano or the like; n is 0, 1, 2, 3 or 4; is combined with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and (C) clofazimine, or its pharmaceutically acceptable salt.

[Continued on next page]

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SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Description

[Title of Invention] A MEDICAMENT FOR TREATING MYCOBACTERIAL INFECTION CHARACTERIZED BY COMBINING A CYTOCHROME bc1 INHIBITOR WITH CLARITHROMYCIN OR AZITHROMYCIN

[TECHNICAL FIELD]
[0001]

The present invention relates to novel combinations. The invention also relates to such combinations for use as pharmaceuticals, for instance in the treatment of bacterial diseases, including diseased caused by pathogenic mycobacteria such as non-tuberculosis mycobacteria.

In particular, the present invention relates to a medicament characterized in that a compound having a cytochrome bc1 inhibitory activity or its pharmaceutically acceptable salt is combined with clarithromycin or azithromycin or their pharmaceutically acceptable salts, or a medicament characterized in that a compound having a cytochrome bc1 inhibitory activity or its pharmaceutically acceptable salt is combined with clarithromycin or azithromycin, and clofazimine, or their pharmaceutically acceptable salts.

[BACKGROUND]
[0002]

Genus Mycobacterium has 95 well-characterized species. Over the centuries two well known mycobacterial species, namely, *Mycobacterium tuberculosis* and *M. Leprae* have been the known causes of immense human suffering. Most of other mycobacteria are present in the environment and their pathogenic potential has been recognized since the beginning of the last century. These mycobacteria are called non-tuberculous mycobacteria (NTM). Whereas the incidence of tuberculosis (TB) is decreasing, a new health concern has been raised globally by NTM. Pulmonary disease caused by NTM is characterized by progressive, irreversible pulmonary damage and increased mortality. About 80% of pulmonary NTM disease is caused by Mycobacterium avium complex (MAC: *M. avium, M. intracellulare, M. chimaera, M. colombiense, M. arosiense, M. vulneris, M. bouchedurhonense, M. timonense, M. marseillense, M. yongonense, M. paraintracellulare and M. lepraemurium*).

The annual prevalence of NTM pulmonary disease varies in different regions, ranging from 0.2/100,000 to 14.7/100,000 with an overall alarming growth rate. The disease is more prevalent after age 60 where the estimated prevalence is from 19.6/100,000 during 1994-1996 to 26.7/100,000 during 2004-2006 in the US.

Different from TB, NTM are opportunistic pathogens, causing mostly TB-like pulmonary diseases in immunocompromised patients or patients with pre-existing lung conditions, such as cystic fibrosis (CF), bronchiectasis or chronic obstructive pulmonary disease (COPD). In addition, post-menopausal women without pre-existing structural pulmonary disease represent another risk group for NTM lung disease. These women, primarily older women of Caucasian or Asian descent, present with nodular bronchiectasis as their NTM lung disease.
[0003]

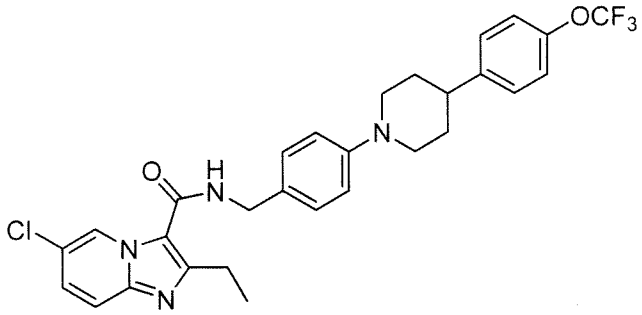
Currently, for most patients with MAC pulmonary disease, a combination therapy is recommended by the American Thoracic Society and the

Infectious Diseases Society of America (ATS/IDSA). For most patients with nodular/bronchiectatic disease, a three-times-weekly regimen of macrolide (clarithromycin or azithromycin), rifampin, and ethambutol is recommended. For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of macrolide (clarithromycin or azithromycin), rifampin or rifabutin, and ethambutol with consideration of three times-weekly amikacin or streptomycin early in therapy is recommended. Patients should be treated until culture negative on therapy for 1 year. Many patients, however, are refractory to the above first-line therapy and do not achieve sustained culture conversion. The limited success of current treatment regimens is in part caused by an insufficient bactericidal activity and challenging compliance due to the frequent occurrence of adverse drug reactions. Therefore, there is a high medical need for new therapies (e.g. combinations) likely to demonstrate activity against drug-resistant mycobacteria, in particular NTM.

[0004]

Patent Documents 1 to 8 disclose a variety of compounds having a cytochrome bc1 inhibitory activity.

Patent Document 9 discloses a variety of compounds having a cytochrome bc1 inhibitory activity. For example, the following compound is disclosed.



This compound is known as Telacebec and is a new clinical candidate for the treatment of tuberculosis.

Patent Document 10 discloses a combination of bedaquiline, Telacebec and pyrazinamide.

Patent Document 11 discloses a combination of rifabutin, clarithromycin and clofazimine.

Non-Patent Document 1 discloses a combination of clarithromycin and clofazimine.

Non-Patent Document 2 discloses a combination of a compound having a cytochrome bc1 inhibitory activity and rifampin.

[PATENT DOCUMENTS]

[0005]

Patent Document 1: WO2011/057145
Patent Document 2: WO2014/015167
Patent Document 3: WO2017/049321
Patent Document 4: US2017/0313697
Patent Document 5: WO2017/001660
Patent Document 6: WO2017/001661
Patent Document 7: WO2017/216281

Patent Document 8: WO2017/216283
Patent Document 9: WO2011/113606
Patent Document 10: WO2018/158280
Patent Document 11: US2016/0228464

[NON-PATENT DOCUMENT]
[0006]

Non-Patent Document 1: Antimicrobial Agents and Chemotherapy, February 2016, Volume 60, Number 2, 1097-1105

Non-Patent Document 2: Antimicrobial Agents and Chemotherapy, August 2016, Volume 60, Number 8, 5018-5022

[DISCLOSURE OF INVENTION]
[PROBLEMS TO BE SOLVED BY THE INVENTION]
[0007]

An object of the present invention is to provide a medicament useful for treating or preventing mycobacterial infections which has few side effects.

[MEANS FOR SOLVING THE PROBLEMS]
[0008]

As a result of intensive studies in order to solve the above problems, the present inventors have newly found that new combinations of a cytochrome bc1 inhibitor, and clarithromycin or azithromycin, or pharmaceutically acceptable salts thereof, or new combinations of a cytochrome bc1 inhibitor, clarithromycin or azithromycin, and clofazimine, or pharmaceutically acceptable salts thereof are particularly effective in the prevention and/or treatment of a mycobacterial infection, especially non-tuberculous mycobacterial infection, as compared to cases where the agents are administered alone.
[0009]

Clarithromycin is one of the macrolides of a combination regimen that the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) recommended as a first-line therapy for MAC disease. Clarithromycin, azithromycin as well, is/are the only (single) agents used for treatment of MAC disease for which there is a correlation between *in vitro* susceptibility and *in vivo* (clinical) response. Specifically, treatment success correlates with *in vitro* macrolide susceptibility, while conversely, patients who have MAC isolates that are macrolide resistant do not respond favorably to macrolide-containing regimens. This fundamental relationship has not been established for any other agent in the treatment of MAC lung disease.
[0010]

Clofazimine is an orally administered drug approved for the treatment of leprosy, currently repurposed as an anti-TB drug. A retrospective review reported that a significantly greater proportion of pulmonary disease patients infected by MAC treated with clofazimine converted to negative cultures, although relapse still occurred. *In vitro*, its MIC ranges from 1-4 μg/mL against *M. avium* and is <1 μg/mL against the majority of *M. intracellulare* isolates.
[0011]

Azithromycin is one of the macrolides of a combination regimen that the ATS/IDSA recommended as a first-line therapy for MAC disease.

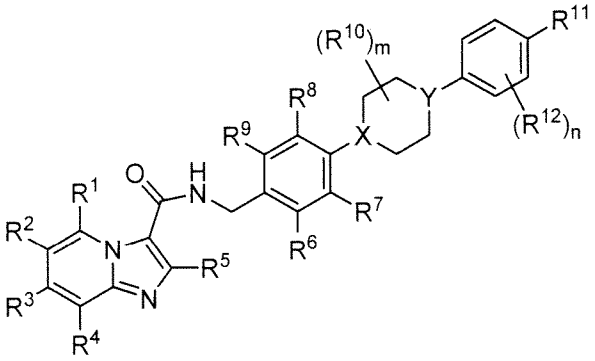
Since clarithromycin inhibits cytochrome P-450 (CYP) 3A and affects the metabolism of other drugs but azithromycin does not inhibit CYP3A, azithromycin is preferentially used for treatment of MAC disease.

[0012]

Recently, with the advent of bedaquiline for treatment of multidrug-resistant tuberculosis, oxidative phosphorylation has been validated as an important target and a vulnerable component of mycobacterial metabolism. Exploiting the dependence of TB on oxidative phosphorylation for energy production, several components of this pathway have been targeted for the development of new antimycobacterial agents. The cytochrome bc1 complex is one of the validated targets for anti-mycobacteria drug development. The complex is assembled with three subunits, qcrA, qcrB and qcrC. One of the qcrB inhibitors, Telacebec, inhibited the growth of TB not only *in vitro* but an *in vivo* mouse model.

[0013]

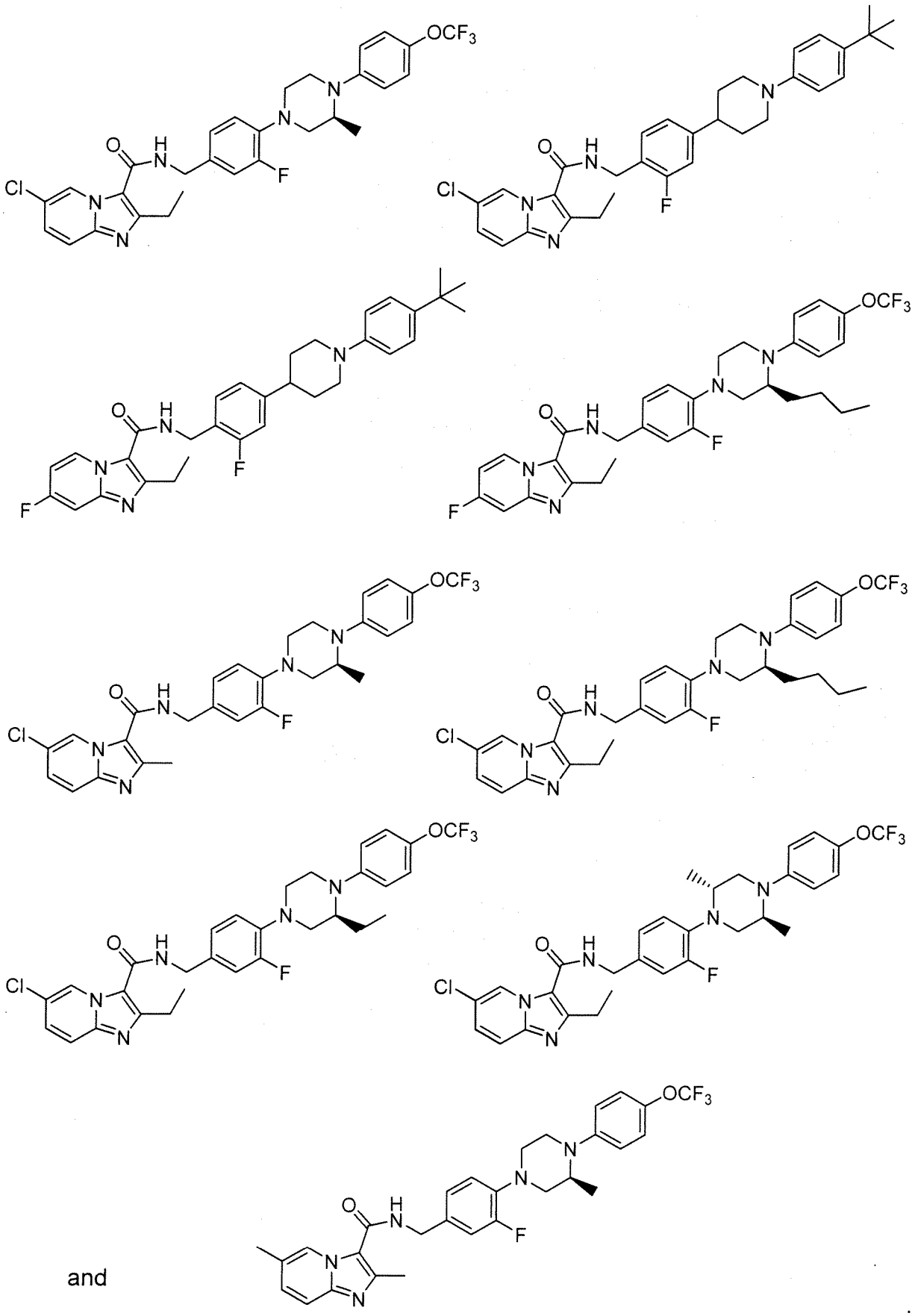
The cytochrome bc1 inhibitor of the present invention may be a compound of the following general formula (I):



(I)

A compound represented by formula (I), or its pharmaceutically acceptable salt has excellent cytochrome bc1 inhibitory activity.

For instance, it is described in WO2021/050708 that the following compounds which fall within formula (I) have excellent cytochrome bc1 inhibitory activity:

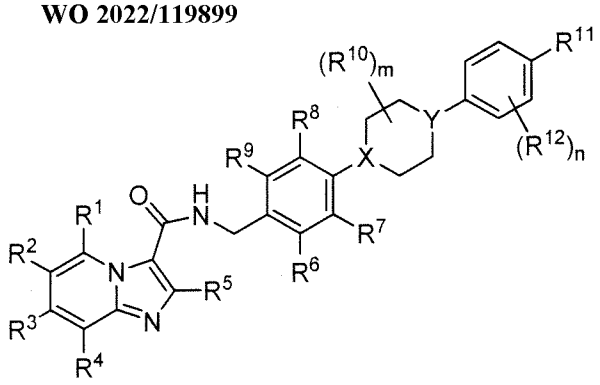


and

[BRIEF DESCRIPTION OF SEVERAL EMBODIMENTS OF THE INVENTION]

[0014]

(1) A medicament characterized in that (A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
is combined with
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(2) The medicament according to the above (1), wherein R^1 and R^4 are hydrogen atom.

(3) The medicament according to the above (1) or (2), wherein R^2 is hydrogen atom, halogen or substituted or unsubstituted alkyl.

(4) The medicament according to any one of the above (1) to (3), wherein R^3 is hydrogen atom or halogen.

(5) The medicament according to any one of the above (1) to (4), wherein R^5 is substituted or unsubstituted alkyl.

(6) The medicament according to any one of the above (1) to (5), wherein R^6, R^8 and R^9 are hydrogen atom, and R^7 is halogen.

(7) The medicament according to any one of the above (1) to (6), wherein X is N.

(8) The medicament according to any one of the above (1) to (7), wherein Y is N.

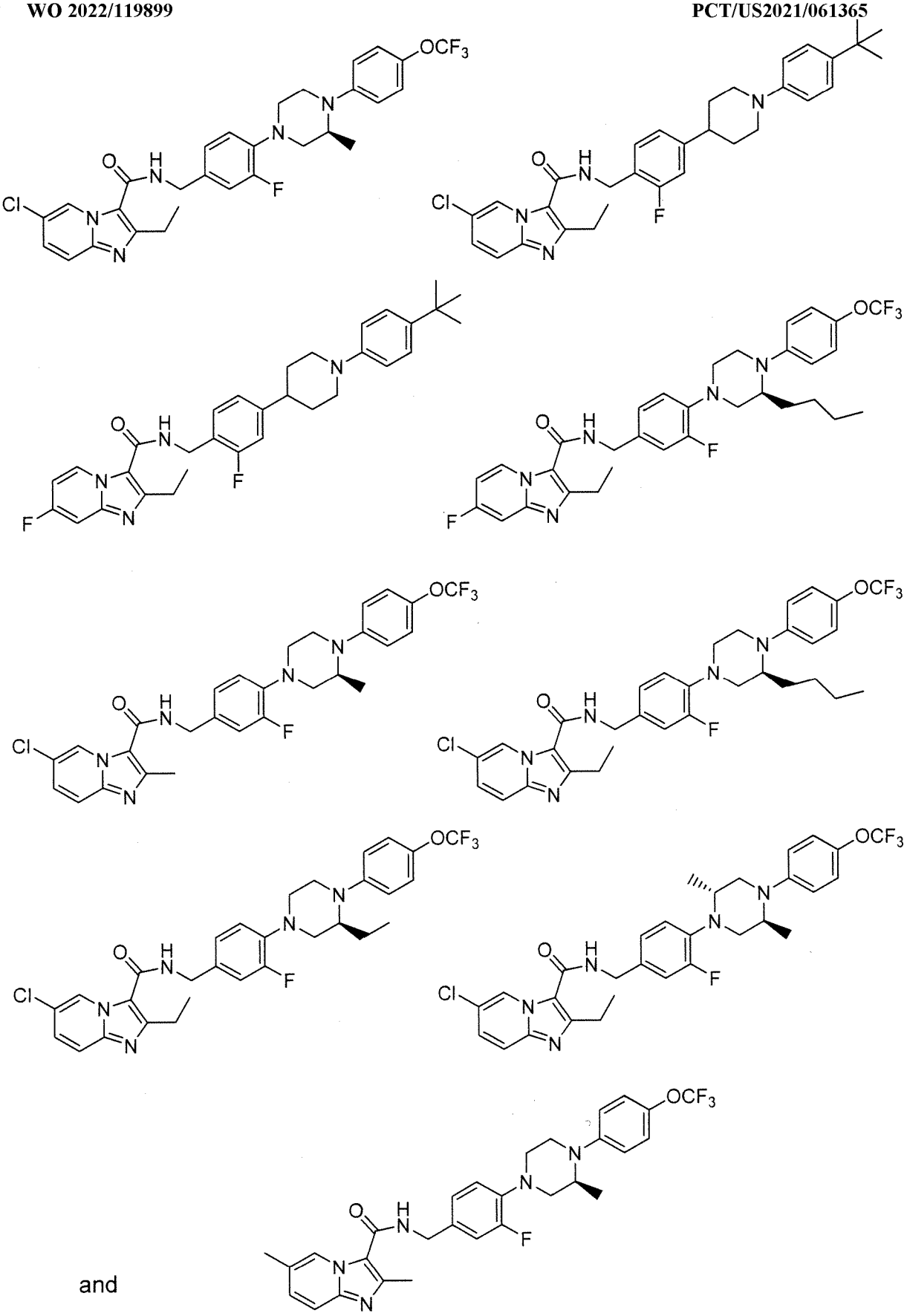
(9) The medicament according to any one of the above (1) to (8), wherein m is 1.

(10) The medicament according to the above (9), wherein R^{10} is substituted or unsubstituted alkyl.

(11) The medicament according to any one of the above (1) to (10), wherein R^{11} is substituted or unsubstituted alkyloxy.

(12) The medicament according to any one of the above (1) to (11), wherein n is 0.

(13) The medicament according to the above (1), wherein (A) is the compound selected from the group consisting of



and

, or its pharmaceutically acceptable salt.

(14) The medicament according to any one of the above (1) to (13), wherein (B) is clarithromycin or its pharmaceutically acceptable salt.

(15) The medicament according to any one of the above (1) to (14), wherein (A) and (B) are simultaneously, sequentially or at intervals administered.

(16) The medicament according to any one of the above (1) to (14), wherein the medicament is combination drugs.

(17) The medicament according to any one of the above (1) to (16), wherein the medicament is used for the treatment or prevention of mycobacterial infection.

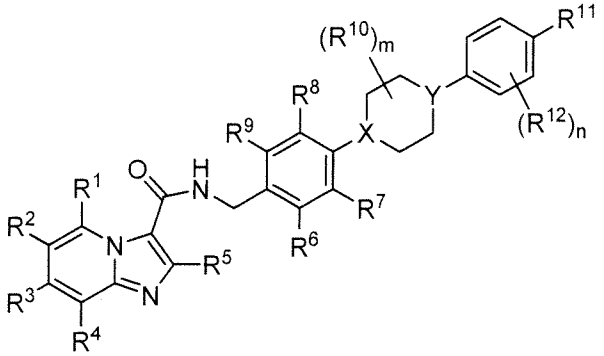
(18) A method of enhancing the anti-bacterial activity of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, comprising administering the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt with a compound represented by formula (I) in the above (1), or its pharmaceutically acceptable salt.

(19) A method of enhancing the anti-bacterial activity of a compound represented by formula (I) in the above (1), or its pharmaceutically acceptable salt, comprising administering the compound represented by formula (I) in the above (1), or its pharmaceutically acceptable salt with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(20) The method according to the above (18), wherein the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of the compound represented by formula (I) in the above (1), or its pharmaceutically acceptable salt.

(21) The method according to the above (19), wherein the compound represented by formula (I) in the above (1), or its pharmaceutically acceptable salt, is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(22) A method of treating mycobacterial infection comprising administering a combination of
(A) a compound represented by formula (I):



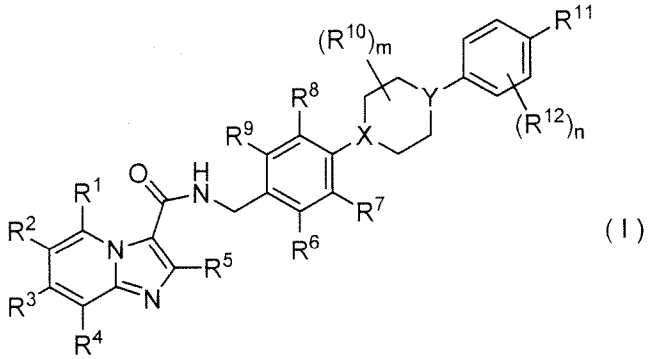
(I)

, or its pharmaceutically acceptable salt,

wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4; and
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, in a therapeutically effective amount thereof to an individual in need of treatment for mycobacterial infection.

(23) The method according to the above (22), wherein (A) a compound represented by formula (I), or its pharmaceutically acceptable salt and (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt are administered simultaneously, sequentially or at intervals.

(24) A pharmaceutical composition or kit, comprising:
(A) a compound represented by formula (I):

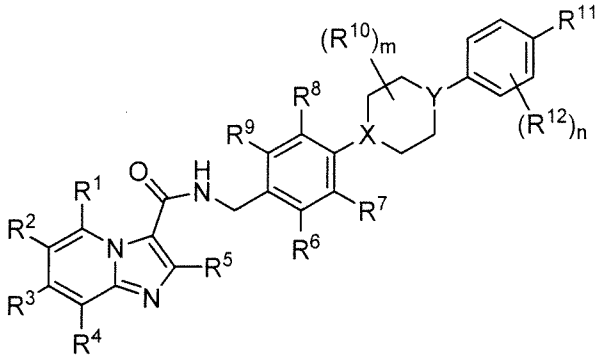


(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy,

cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4; and
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(25) A medicament characterized in that (A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;

X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
is combined with
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

(26) The medicament according to the above (25), wherein R^1 and R^4 are hydrogen atom.

(27) The medicament according to the above (25) or (26), wherein R^2 is hydrogen atom, halogen or substituted or unsubstituted alkyl.

(28) The medicament according to any one of the above (25) to (27), wherein R^3 is hydrogen atom or halogen.

(29) The medicament according to any one of the above (25) to (28), wherein R^5 is substituted or unsubstituted alkyl.

(30) The medicament according to any one of the above (25) to (29), wherein R^6, R^8 and R^9 are hydrogen atom, and R^7 is halogen.

(31) The medicament according to any one of the above (25) to (30), wherein X is N.

(32) The medicament according to any one of the above (25) to (31), wherein Y is N.

(33) The medicament according to any one of the above (25) to (32), wherein m is 1.

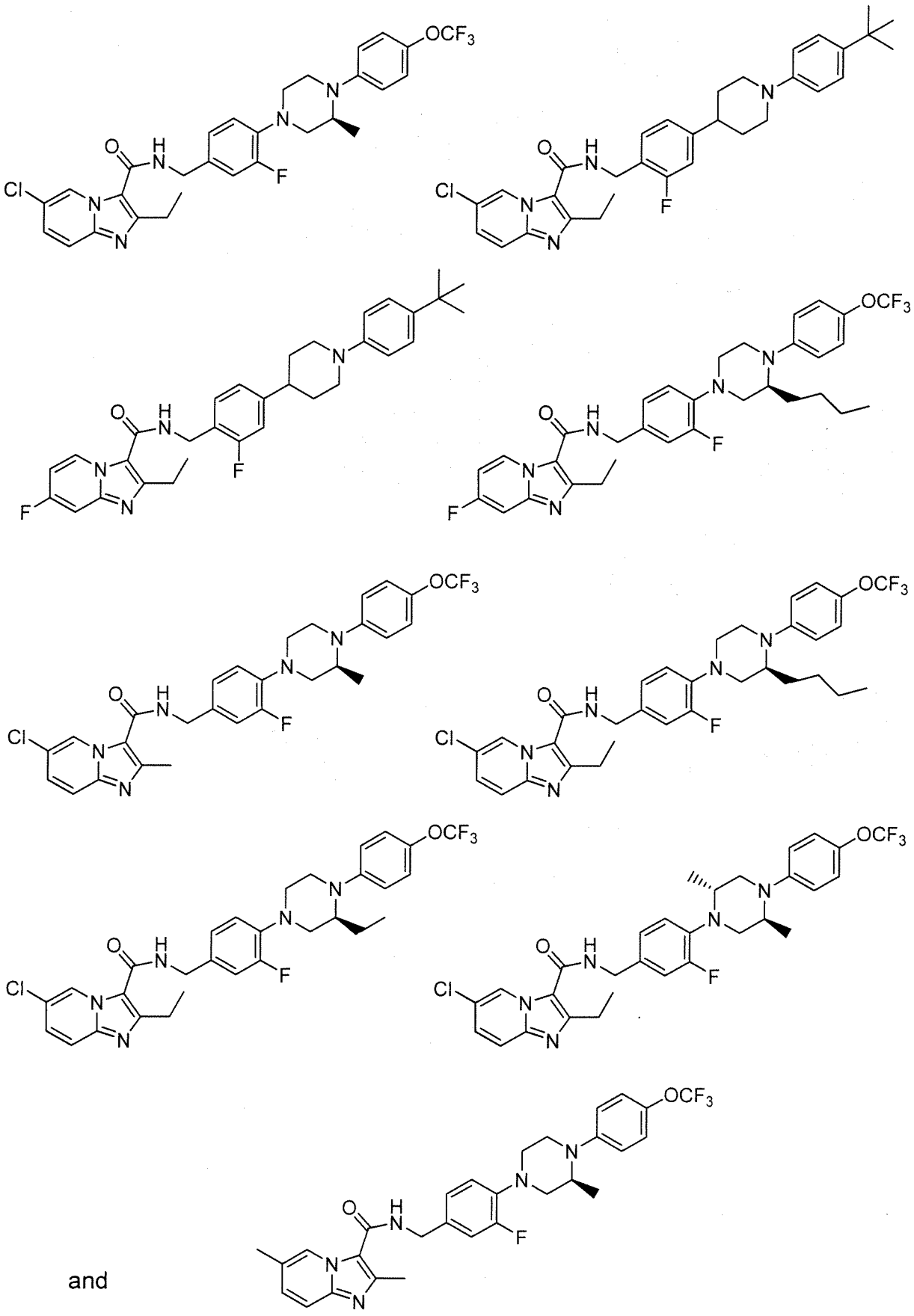
(34) The medicament according to the above (33), wherein R^{10} is substituted or unsubstituted alkyl.

(35) The medicament according to any one of the above (25) to (34), wherein R^{11} is substituted or unsubstituted alkyloxy.

(36) The medicament according to any one of the above (25) to (35), wherein n is 0.

(37) The medicament according to the above (25), wherein (A) is the compound

selected from the group consisting of



and

, or its pharmaceutically acceptable salt.

(38) The medicament according to any one of the above (25) to (37), wherein (B) is

clarithromycin or its pharmaceutically acceptable salt.

(39) The medicament according to any one of the above (25) to (38), wherein (A), (B) and (C) are simultaneously, sequentially or at intervals administered.

(40) The medicament according to any one of the above (25) to (38), wherein the medicament is combination drugs.

(41) The medicament according to any one of the above (25) to (40), wherein the medicament is used for the treatment or prevention of mycobacterial infection.

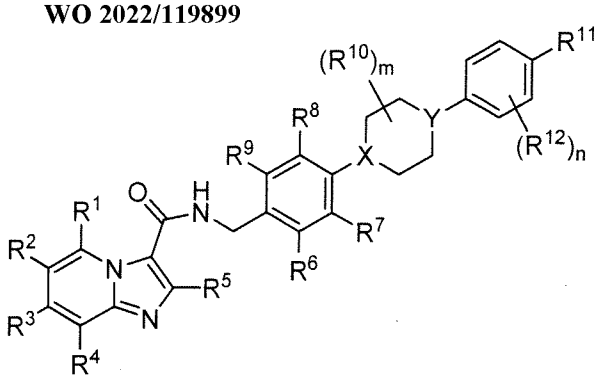
(42) A method of enhancing the anti-bacterial activity of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt, comprising administering the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt with a compound represented by formula (I) in the above (25), or its pharmaceutically acceptable salt.

(43) A method of enhancing the anti-bacterial activity of a compound represented by formula (I) in the above (25), or its pharmaceutically acceptable salt, comprising administering the compound represented by formula (I) in the above (25), or its pharmaceutically acceptable salt with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt.

(44) The method according to the above (42), wherein the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt is/are administered simultaneously, sequentially or at intervals with a therapeutically effective amount of the compound represented by formula (I) in the above (25), or its pharmaceutically acceptable salt.

(45) The method according to the above (43), wherein the compound represented by formula (I) in the above (25), or its pharmaceutically acceptable salt, is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt.

(46) A method of treating mycobacterial infection comprising administering a combination of
(A) a compound represented by formula (I):

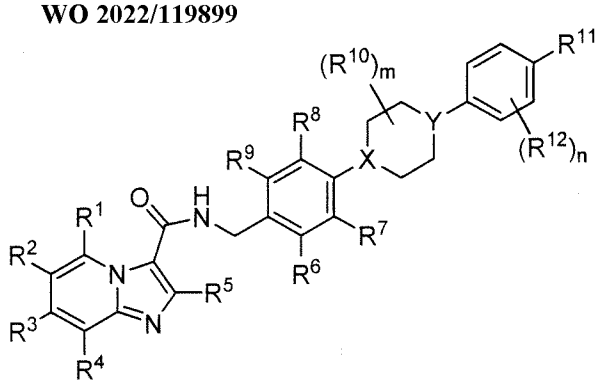


(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and
(C) clofazimine, or its pharmaceutically acceptable salt, in a therapeutically effective amount thereof to an individual in need of treatment for mycobacterial infection.

(47) The method according to the above (46), wherein (A) a compound represented by formula (I), or its pharmaceutically acceptable salt, (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt, are administered simultaneously, sequentially or at intervals.

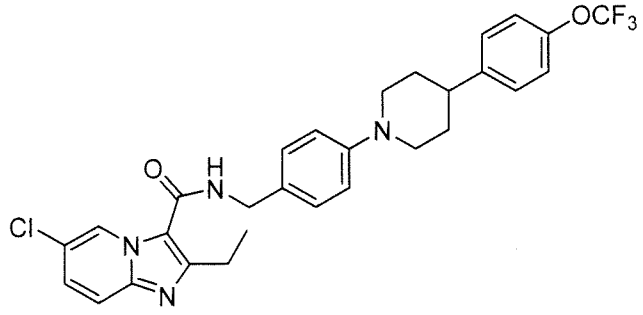
(48) A pharmaceutical composition or kit, comprising:
(A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

(49) A medicament characterized in that (A) a compound defined below



, or its pharmaceutically acceptable salt;
is combined with
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(50) The medicament according to the above (49), wherein (B) is clarithromycin or its pharmaceutically acceptable salt.

(51) The medicament according to the above (49) or (50), wherein (A) and (B) are simultaneously, sequentially or at intervals administered.

(52) The medicament according to the above (49) or (50), wherein the medicament is combination drugs.

(53) The medicament according to any one of the above (49) to (52), wherein the medicament is used for the treatment or prevention of mycobacterial infection.

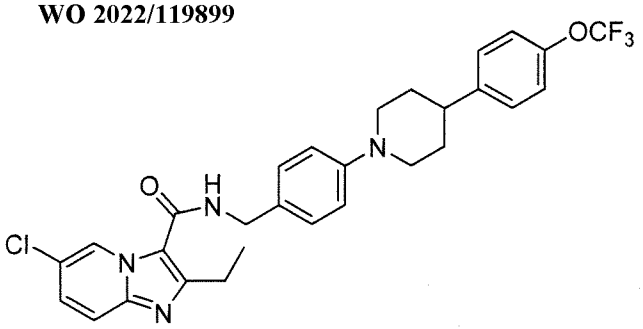
(54) A method of enhancing the anti-bacterial activity of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, comprising administering the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt with a compound (A) in the above (49), or its pharmaceutically acceptable salt.

(55) A method of enhancing the anti-bacterial activity of a compound (A) in the above (49), or its pharmaceutically acceptable salt, comprising administering the compound (A) in the above (49), or its pharmaceutically acceptable salt with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(56) The method according to the above (54), wherein the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of the compound (A) in the above (49), or its pharmaceutically acceptable salt.

(57) The method according to the above (55), wherein the compound (A) in the above (49), or its pharmaceutically acceptable salt, is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

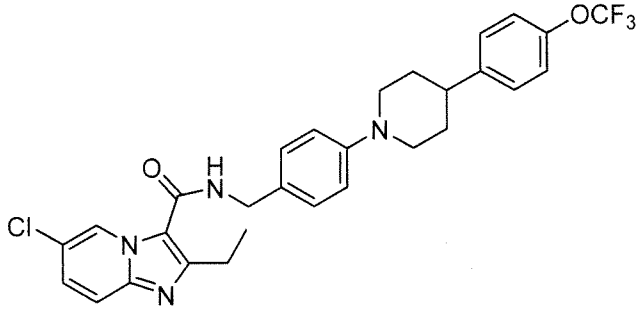
(58) A method of treating mycobacterial infection comprising administering a combination of
(A) a compound defined below



, or its pharmaceutically acceptable salt; and
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, in a therapeutically effective amount thereof to an individual in need of treatment for mycobacterial infection.

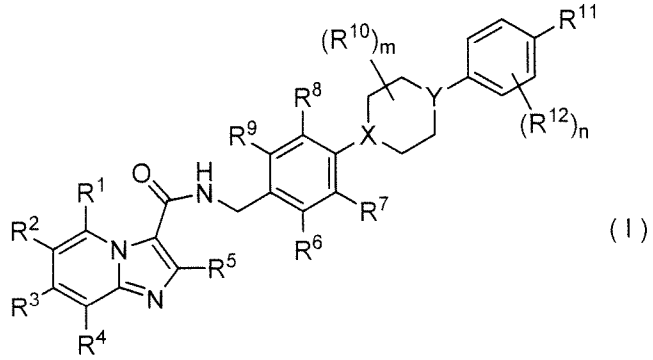
(59) The method according to the above (58), wherein the compound (A), or its pharmaceutically acceptable salt and (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt are administered simultaneously, sequentially or at intervals.

(60) A pharmaceutical composition or kit, comprising:
(A) a compound defined below



, or its pharmaceutically acceptable salt; and
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

(1') A medicament characterized in that (A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
is combined with
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

(2') The medicament according to the above (1'), wherein R^1 and R^4 are hydrogen atom.

(3') The medicament according to the above (1'), wherein R^2 is hydrogen atom, halogen or substituted or unsubstituted alkyl.

(4') The medicament according to the above (1'), wherein R^3 is hydrogen atom or halogen.

(5') The medicament according to the above (1'), wherein R^5 is substituted or unsubstituted alkyl.

(6') The medicament according to the above (1'), wherein R^6, R^8 and R^9 are hydrogen atom, and R^7 is halogen.

(7') The medicament according to the above (1'), wherein X is N.

(8') The medicament according to the above (1'), wherein Y is N.

(9') The medicament according to the above (1'), wherein m is 1.

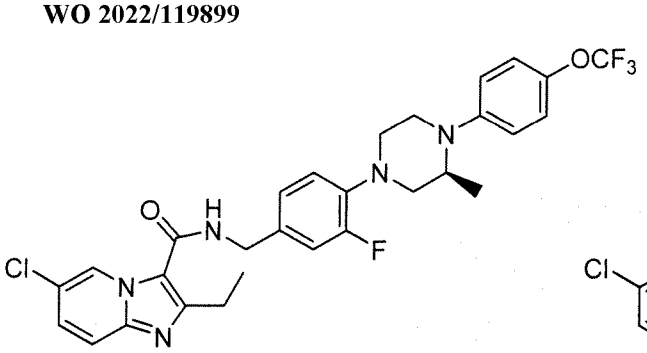
(10') The medicament according to the above (9'), wherein R^{10} is substituted or

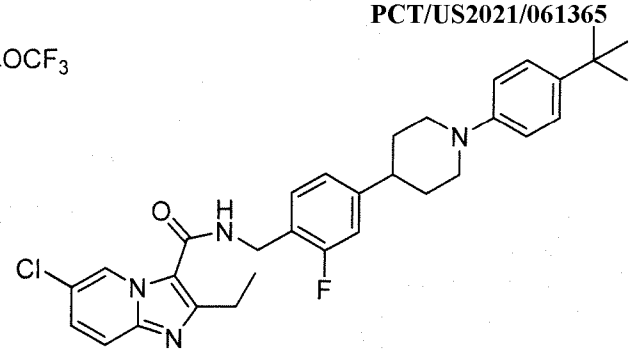
unsubstituted alkyl.

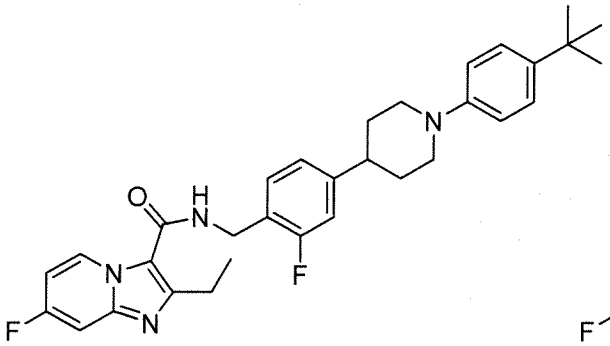
(11') The medicament according to the above (1'), wherein R^{11} is substituted or unsubstituted alkyloxy.

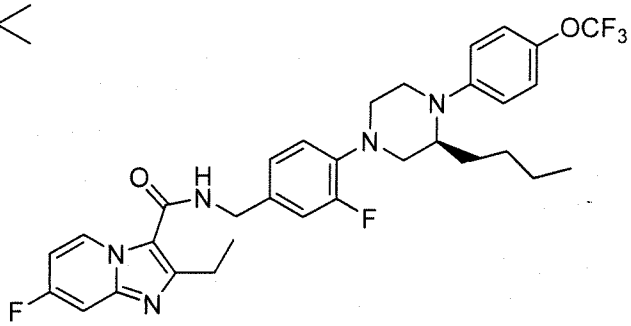
(12') The medicament according to the above (1'), wherein n is 0.

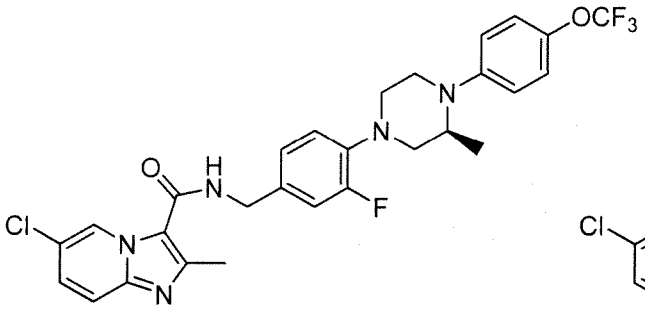
(13') The medicament according to the above (1'), wherein (A) is the compound selected from the group consisting of

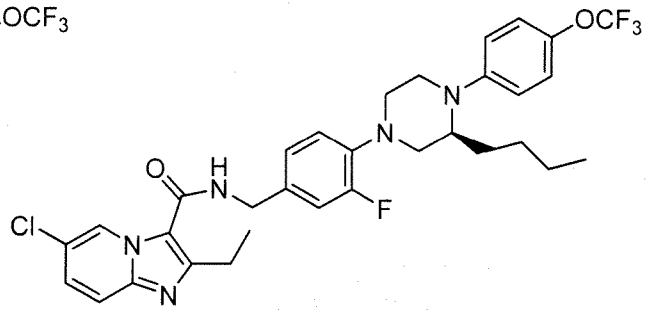


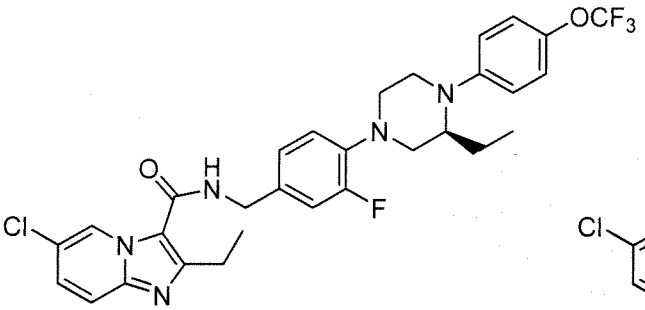


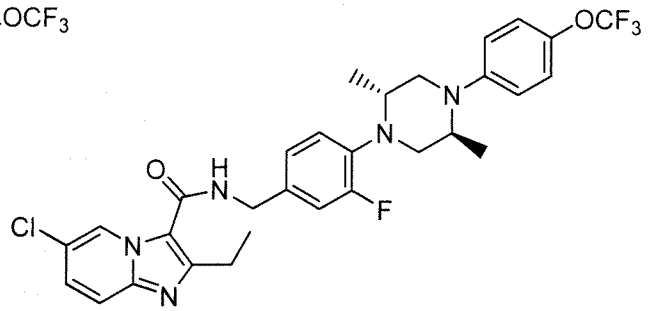




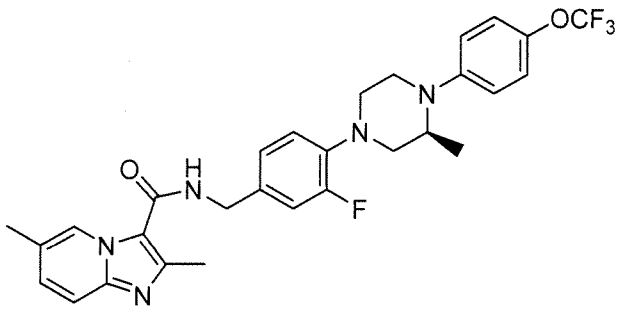








and



, or its pharmaceutically acceptable salt.

(14') The medicament according to the above (1'), wherein (B) is clarithromycin or its pharmaceutically acceptable salt.

(15') The medicament according to the above (1'), wherein (A), (B) and (C) are simultaneously, sequentially or at intervals administered.

(16') The medicament according to the above (1'), wherein the medicament is combination drugs.

(17') The medicament according to the above (1'), wherein the medicament is used for the treatment or prevention of mycobacterial infection.

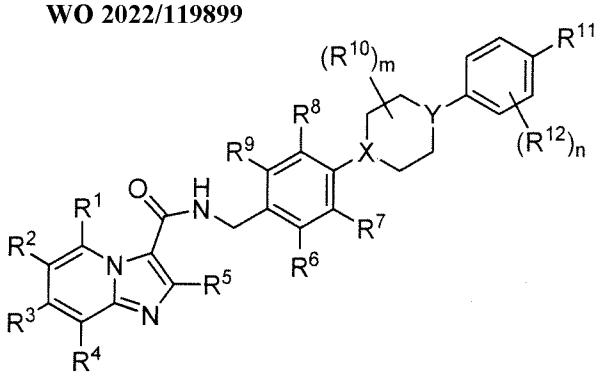
(18') A method of enhancing the anti-bacterial activity of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt, comprising administering the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt with a compound represented by formula (I) in the above (1'), or its pharmaceutically acceptable salt.

(19') A method of enhancing the anti-bacterial activity of a compound represented by formula (I) in the above (1'), or its pharmaceutically acceptable salt, comprising administering the compound represented by formula (I) in the above (1'), or its pharmaceutically acceptable salt with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt.

(20') The method according to the above (18'), wherein the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt is/are administered simultaneously, sequentially or at intervals with a therapeutically effective amount of the compound represented by formula (I) in the above (1'), or its pharmaceutically acceptable salt.

(21') The method according to the above (19'), wherein the compound represented by formula (I) in the above (1'), or its pharmaceutically acceptable salt, is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt.

(22') A method of treating mycobacterial infection comprising administering a combination of
(A) a compound represented by formula (I):

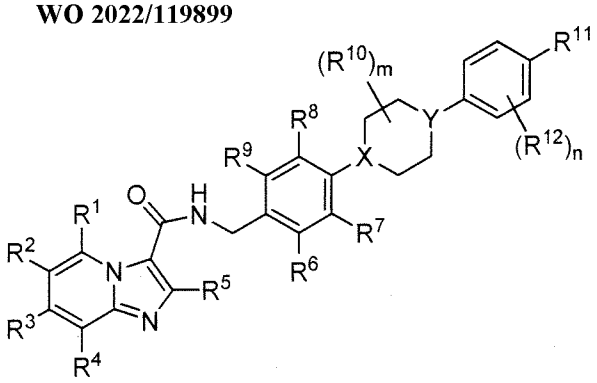


(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and
(C) clofazimine, or its pharmaceutically acceptable salt, in a therapeutically effective amount thereof to an individual in need of treatment for mycobacterial infection.

(23') The method according to the above (22'), wherein (A) a compound represented by formula (I), or its pharmaceutically acceptable salt, (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt, are administered simultaneously, sequentially or at intervals.

(24') A pharmaceutical composition or kit, comprising:
(A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

[EFFECT OF THE INVENTION]

[0015]

The medicament of the present invention is useful in the treatment of a mycobacterial infection, especially non-tuberculous mycobacterial infection.

[BRIEF DESCRIPTION OF DRAWINGS]

[0016]

[Figure 1] Figure 1 shows the mean log10 value for CFUs of each lung

of the 15 study groups after the end of treatment, as described hereinafter (13 study groups comprise treatment regimens comprising Clarithromycin (CAM) , Clofazimine (CFZ), cytochrome bc1 inhibitors and various combinations, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the mean log10 value for CFUs.

[Figure 2] Figure 2 shows the mean log10 value for CFUs of each lung of the 6 study groups after the end of treatment, as described hereinafter (4 study groups comprise treatment regimens comprising Clarithromycin (CAM) ,CFZ, cytochrome bc1 inhibitors and various combinations, and 2 study groups are control groups) . X axis indicates each study groups. Y axis indicates the mean log10 value for CFUs.

[Figure 3] Figure 3 shows the mean log10 value for CFUs of each lung of the 15 study groups after the end of treatment, as described hereinafter (13 study groups comprise treatment regimens comprising Clarithromycin (CAM) ,CFZ, cytochrome bc1 inhibitors and various combinations, and 2 study groups are control groups) . X axis indicates each study groups. Y axis indicates the mean log10 value for CFUs.

[Figure 4] Figure 4 shows the mean log10 value for CFUs of each lung of the 6 study groups after the end of treatment, as described hereinafter (4 study groups comprise treatment regimens comprising Azithromycin (AZM) , Rifampicin (RFP), Ethambutol (ETB), CFZ, cytochrome bc1 inhibitor and various combinations, and 2 study groups are control groups) . X axis indicates each study groups. Y axis indicates the mean log10 value for CFUs.

[Figure 5] Figure 5 shows the log10 value for CFUs of each of the 12 study groups, as described hereinafter (10 study groups comprise conditions containing either Clarithromycin (CAM) or cytochrome bc1 inhibitors, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[Figure 6] Figure 6 shows the log10 value for CFUs of each of the 30 study groups, as described hereinafter (28 study groups comprise conditions containing either Clarithromycin (CAM) or combination of CAM and cytochrome bc1 inhibitors, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[Figure 7] Figure 7 shows the log10 value for CFUs of each of the 11 study groups, as described hereinafter (9 study groups comprise conditions containing either Clarithromycin (CAM) or combination of CAM and cytochrome bc1 inhibitors, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[Figure 8] Figure 8 shows the log10 value for CFUs of each of the 26 study groups, as described hereinafter (24 study groups comprise conditions containing either Clarithromycin (CAM), I-1-3 or combination of CAM and I-1-3, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[Figure 9] Figure 9 shows the log10 value for CFUs of each of the 6 study groups, as described hereinafter (4 study groups comprise conditions containing either Clarithromycin (CAM), I-1-3, combination of CAM and Clofazimine (CFZ) or combination of CAM, CFZ and I-1-3, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[Figure 10] Figure 10 shows the mean log10 value for CFUs of each

lung of the 6 study groups after the end of treatment, as described hereinafter (6 study groups comprise treatment regimens comprising Clarithromycin (CAM) ,Rifampicin (RFP), Ethambutol (ETB), CFZ, cytochrome bc1 inhibitor and various combinations, and 2 study groups are control groups) . X axis indicates each study groups. Y axis indicates the mean log10 value for CFUs of each lung.

[Figure 11] Figure 11 shows the log10 value for CFUs of each of the 7 study groups, as described hereinafter (5 study groups comprise conditions containing either Clarithromycin (CAM), Clofazimine (CFZ), I-1-3, combination of CAM and CFZ or combination of CAM, CFZ and I-1-3, and 2 study groups are control groups). X axis indicates each study groups. Y axis indicates the log10 value for CFUs.

[DETAILED DESCRIPTION OF SEVERAL EMBODIMENTS OF THE INVENTION]

[0017]

Each term used in this description will be described below. In this description, even when each term is used individually or used together with other terms, the term has the same meaning.

The term, "consisting of" means having only the recited components or elements.

The term, "comprising" means not restricting with components and not excluding undescribed factors.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

[0018]

The compound represented by formula (I) in (A), or its pharmaceutically acceptable salt is described hereinabove and below.

[0019]

The term "halogen" includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. A fluorine atom and a chlorine atom are especially preferable.

[0020]

The term "alkyl" includes a C1 to C15, preferably C1 to C10, more preferably C1 to C6 and further preferably C1 to C4 linear or branched hydrocarbon group. 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.

A preferred embodiment of "alkyl" is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or n-pentyl. A more preferred embodiment is methyl, ethyl, n-propyl, isopropyl, n-butyl or tert-butyl.

[0021]

The term "alkenyl" includes a C2 to C15, preferably a C2 to C10, more preferably a C2 to C6 and further preferably a C2 to C4 linear or branched hydrocarbon group having one or more double bond(s) at any position(s). 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.

A preferred embodiment of "alkenyl" is vinyl, allyl, propenyl,

isopropenyl or butenyl.
[0022]
The term "alkynyl" includes C2 to C8 straight or branched alkynyl having one or more triple bond(s) in the above "alkyl", and examples thereof include ethynyl, propynyl, butynyl and the like. Furthermore, an "alkynyl" may have a double bond.
[0023]
The term "alkyloxy" means a group wherein the above "alkyl" is bonded to an oxygen atom. Examples include methyloxy, ethyloxy, n-propyloxy, isopropyloxy, n-butyloxy, tert-butyloxy, isobutyloxy, sec-butyloxy, pentyloxy, isopentyloxy, and hexyloxy.
A preferred embodiment of "alkyloxy" is methyloxy, ethyloxy, n-propyloxy, isopropyloxy or tert-butyloxy.
[0024]
The term "alkenyloxy" means a group wherein the above "alkenyl" is bonded to an oxygen atom. Examples include vinyloxy, allyloxy, 1-n-propenyloxy, 2-n-butenyloxy, 2-n-pentenyloxy, 2-n-hexenyloxy, 2-n-heptenyloxy, and 2-n-octenyloxy.
[0025]
The term "alkynyloxy" means a group wherein the above "alkynyl" is bonded to an oxygen atom. Examples include ethynyloxy, 1-n-propynyloxy, 2-n-propynyloxy, 2-n-butynyloxy, 2-n-pentynyloxy, 2-n-hexynyloxy, 2-n-heptynyloxy, and 2-n-octynyloxy.
[0026]
The substituents of "substituted alkyl", "substituted alkenyl", "substituted alkynyl", "substituted alkyloxy", "substituted alkenyloxy" and "substituted alkynyloxy" include the following substituents. A carbon atom at any positions may be bonded to one or more group(s) selected from the following substituents.
A substituent: halogen, hydroxy, carboxy, amino, imino, hydroxyamino, hydroxyimino, formyl, formyloxy, carbamoyl, sulfamoyl, sulfanyl, sulfino, sulfo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, cyano, nitro, nitroso, azido, hydrazino, ureido, amidino, guanidino, trialkylsilyl, alkyloxy, alkenyloxy, alkynyloxy, haloalkyloxy, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylamino, alkenylamino, alkynylamino, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, alkylimino, alkenylimino, alkynylimino, alkylcarbonylimino, alkenylcarbonylimino, alkynylcarbonylimino, alkyloxyimino, alkenyloxyimino, alkynyloxyimino, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylsulfanyl, alkenylsulfanyl, alkynylsulfanyl, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkylcarbamoyl, alkenylcarbamoyl, alkynylcarbamoyl, alkylsulfamoyl, alkenylsulfamoyl, alkynylsulfamoyl, aromatic carbocyclyl, non-aromatic carbocyclyl, aromatic heterocyclyl, non-aromatic heterocyclyl, aromatic carbocyclyloxy, non-aromatic carbocyclyloxy, aromatic heterocyclyloxy, non-aromatic heterocyclyloxy, aromatic carbocyclylcarbonyl, non-aromatic carbocyclylcarbonyl, aromatic heterocyclylcarbonyl, non-aromatic heterocyclylcarbonyl, aromatic carbocyclyloxycarbonyl, non-aromatic carbocyclyloxycarbonyl, aromatic heterocyclyloxycarbonyl, non-aromatic heterocyclyloxycarbonyl, aromatic

carbocyclylalkyloxy, non-aromatic carbocyclylalkyloxy, aromatic heterocyclylalkyloxy, non-aromatic heterocyclylalkyloxy, aromatic carbocyclylalkyloxycarbonyl, non-aromatic carbocyclylalkyloxycarbonyl, aromatic heterocyclylalkyloxycarbonyl, non-aromatic heterocyclylalkyloxycarbonyl, aromatic carbocyclylalkylamino, non-aromatic carbocyclylalkylamino, aromatic heterocyclylalkylamino, non-aromatic heterocyclylalkylamino, aromatic carbocyclylsulfanyl, non-aromatic carbocyclylsulfanyl, aromatic heterocyclylsulfanyl, non-aromatic heterocyclylsulfanyl, non-aromatic carbocyclylsulfonyl, aromatic carbocyclylsulfonyl, aromatic heterocyclylsulfonyl, and non-aromatic heterocyclylsulfonyl.

A preferable substituent: halogen, hydroxy, carboxy, amino, imino, hydroxyamino, hydroxyimino, formyl, formyloxy, carbamoyl, sulfamoyl, sulfanyl, sulfino, sulfo, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, cyano, nitro, nitroso, azido, hydrazino, ureido, amidino, guanidino, trialkylsilyl, alkyloxy, alkenyloxy, alkynyloxy, haloalkyloxy, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylamino, alkenylamino, alkynylamino, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, alkylimino, alkenylimino, alkynylimino, alkylcarbonylimino, alkenylcarbonylimino, alkynylcarbonylimino, alkyloxyimino, alkenyloxyimino, alkynyloxyimino, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylsulfanyl, alkenylsulfanyl, alkynylsulfanyl, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkylcarbamoyl, alkenylcarbamoyl, alkynylcarbamoyl, alkylsulfamoyl, alkenylsulfamoyl, and alkynylsulfamoyl.

A more preferable substituent: halogen, hydroxy, amino, cyano, alkyloxy, alkenyloxy, alkynyloxy, haloalkyloxy, alkylamino, alkenylamino, and alkynylamino.

An especially preferable substituent: halogen, hydroxy, amino, cyano, alkyloxy, and alkylamino.

[0027]

The term "haloalkyl" includes a group wherein one or more hydrogen atom(s) attached to a carbon atom of the above "alkyl" is replaced with the above "halogen". Examples include monofluoromethyl, monofluoroethyl, monofluoro-n-propyl, 2,2,3,3,3-n-pentafluoropropyl, monochloromethyl, trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 1,2-dibromoethyl, and 1,1,1-trifluoro-n-propan-2-yl.

A preferred embodiment of "haloalkyl" is trifluoromethyl and trichloromethyl.

[0028]

The term "haloalkyloxy" means a group wherein the above "haloalkyl" is bonded to an oxygen atom. Examples include monofluoromethoxy, monofluoroethoxy, trifluoromethoxy, trichloromethoxy, trifluoroethoxy, and trichloroethoxy.

A preferred embodiment of "haloalkyloxy" is trifluoromethoxy and trichloromethoxy.

[0029]

The term "alkylcarbonyl" means a group wherein the above "alkyl" is bonded to a carbonyl group. Examples include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, tert-butylcarbonyl,

isobutylcarbonyl, sec-butylcarbonyl, n-pentylcarbonyl, isopentylcarbonyl, and n-hexylcarbonyl.

A preferred embodiment of "alkylcarbonyl" is methylcarbonyl, ethylcarbonyl and n-propylcarbonyl.

[0030]

The term "alkenylcarbonyl" means a group wherein the above "alkenyl" is bonded to a carbonyl group. Examples include vinylcarbonyl, allylcarbonyl and n-propenylcarbonyl.

[0031]

The term "alkynylcarbonyl" means a group wherein the above "alkynyl" is bonded to a carbonyl group. Examples include ethynylcarbonyl and n-propynylcarbonyl.

[0032]

The term "alkylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with the above "alkyl". Examples include methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, N,N-diisopropylamino, and N-methyl-N-ethylamino.

A preferred embodiment of "alkylamino" is methylamino and ethylamino.

[0033]

The term "alkenylamino" means a group wherein a hydrogen atom attached to a nitrogen atom of an amino group is replaced with the above "alkenyl". For example, it includes ethylenylamino, propenylamino and the like. Another hydrogen atom attached to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0034]

The term "Alkynylamino" means a group wherein a hydrogen atom attached to a nitrogen atom of an amino group is replaced with the above "alkynyl". For example, it includes ethynylamino, propynylamino and the like. Another hydrogen atom attached to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0035]

The term "alkylsulfonyl" means a group wherein the above "alkyl" is bonded to a sulfonyl group. Examples include methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, tert-butylsulfonyl, isobutylsulfonyl, and sec-butylsulfonyl.

A preferred embodiment of "alkylsulfonyl" is methylsulfonyl and ethylsulfonyl.

[0036]

The term "alkenylsulfonyl" means a group wherein the above "alkenyl" is bonded to a sulfonyl group. Examples include vinylsulfonyl, allylsulfonyl, and n-propenylsulfonyl.

[0037]

The term "alkynylsulfonyl" means a group wherein the above "alkynyl" is bonded to a sulfonyl group. Examples include ethynylsulfonyl, and n-propynylsulfonyl.

[0038]

The term "alkylcarbonylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with

the above "alkylcarbonyl". Examples include methylcarbonylamino, dimethylcarbonylamino, ethylcarbonylamino, diethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, N,N-diisopropylcarbonylamino, n-butylcarbonylamino, tert-butylcarbonylamino, isobutylcarbonylamino, and sec-butylcarbonylamino. Another hydrogen atom bonded to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0039]

The term "alkenylcarbonylamino" means a group wherein a hydrogen atom bonded to a nitrogen atom of an amino group is replaced with the above "alkenylcarbonyl". For example, it includes ethylenylcarbonylamino, propenylcarbonylamino and the like. Another hydrogen atom bonded to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0040]

The term "alkynylcarbonylamino" means a group wherein a hydrogen atom bonded to a nitrogen atom of an amino group is replaced with the above "alkynylcarbonyl". For example, it includes ethynylcarbonylamino, propynylcarbonylamino and the like. Another hydrogen atom bonded to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0041]

The term "alkylsulfonylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with the above "alkylsulfonyl". Examples include methylsulfonylamino, dimethylsulfonylamino, ethylsulfonylamino, diethylsulfonylamino, n-propylsulfonylamino, isopropylsulfonylamino, N,N-diisopropylsulfonylamino, n-butylsulfonylamino, tert-butylsulfonylamino, isobutylsulfonylamino, and sec-butylsulfonylamino.

A preferred embodiment of "alkylsulfonylamino" is methylsulfonylamino and ethylsulfonylamino.

[0042]

The term "alkenylsulfonylamino" means a group wherein a hydrogen atom bonded to a nitrogen atom of an amino group is replaced with the above "alkenylsulfonyl". For example, it includes ethylenylsulfonylamino, propenylsulfonylamino and the like. Another hydrogen atom bonded to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0043]

The term "alkynylsulfonylamino" means a group wherein a hydrogen atom bonded to a nitrogen atom of an amino group is replaced with the above "alkynylsulfonyl". For example, it includes ethynylsulfonylamino, propynylsulfonylamino and the like. Another hydrogen atom bonded to the nitrogen atom of the amino group may be replaced with the above "alkyl".

[0044]

The term "alkylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkyl". Examples include methylimino, ethylimino, n-propylimino, and isopropylimino.

[0045]

The term "alkenylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkenyl". Examples include ethylenylimino, and n-propenylimino.

[0046]

The term "alkynylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkynyl". Examples include ethynylimino, and n-propynylimino.

[0047]

The term "alkylcarbonylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkylcarbonyl". Examples include methylcarbonylimino, ethylcarbonylimino, n-propylcarbonylimino, and isopropylcarbonylimino.

[0048]

The term "alkenylcarbonylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkenylcarbonyl". Examples include ethylenylcarbonylimino, and n-propenylcarbonylimino.

[0049]

The term "alkynylcarbonylimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkynylcarbonyl". Examples include ethynylcarbonylimino and n-propynylcarbonylimino.

[0050]

The term "alkyloxyimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkyloxy". Examples include methyloxyimino, ethyloxyimino, n-propyloxyimino, and isopropyloxyimino.

[0051]

The term "alkenyloxyimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkenyloxy". Examples include ethylenyloxyimino, and n-propenyloxyimino.

[0052]

The term "alkynyloxyimino" means a group wherein a hydrogen atom attached to a nitrogen atom of an imino group is replaced with the above "alkynyloxy". Examples include ethynyloxyimino, and n-propynyloxyimino.

[0053]

The term "alkylcarbonyloxy" means a group wherein the above "alkylcarbonyl" is bonded to an oxygen atom. Examples include methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, tert-butylcarbonyloxy, isobutylcarbonyloxy, and sec-butylcarbonyloxy.

A preferred embodiment of "alkylcarbonyloxy" is methylcarbonyloxy and ethylcarbonyloxy.

[0054]

The term "alkenylcarbonyloxy" means a group wherein the above "alkenylcarbonyl" is bonded to an oxygen atom. Examples include ethylenylcarbonyloxy and n-propenylcarbonyloxy.

[0055]

The term "alkynylcarbonyloxy" means a group wherein the above "alkynylcarbonyl" is bonded to an oxygen atom. Examples include ethynylcarbonyloxy and n-propynylcarbonyloxy.

[0056]

The term "alkyloxycarbonyl" means a group wherein the above

"alkyloxy" is bonded to a carbonyl group. Examples include methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, tert-butyloxycarbonyl, isobutyloxycarbonyl, sec-butyloxycarbonyl, n-pentyloxycarbonyl, isopentyloxycarbonyl, and n-hexyloxycarbonyl.

A preferred embodiment of "alkyloxycarbonyl" is methyloxycarbonyl, ethyloxycarbonyl and n-propyloxycarbonyl.

[0057]

The term "alkenyloxycarbonyl" means a group wherein the above "alkenyloxy" is bonded to a carbonyl group. Examples include ethylenyloxycarbonyl and n-propenyloxycarbonyl.

[0058]

The term "alkynyloxycarbonyl" means a group wherein the above "alkynyloxy" is bonded to a carbonyl group. Examples include ethynyloxycarbonyl and n-propynyloxycarbonyl.

[0059]

The term "alkylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the above "alkyl". Examples include methylsulfanyl, ethylsulfanyl, n-propylsulfanyl, and isopropylsulfanyl.

[0060]

The term "alkenylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the above "alkenyl". Examples include ethylenylsulfanyl, and n-propenylsulfanyl.

[0061]

The term "alkynylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the above "alkynyl". Examples include ethynylsulfanyl, and n-propynylsulfanyl.

[0062]

The term "alkylsulfinyl" means a group wherein the above "alkyl" is bonded to a sulfinyl group. Examples include methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, and isopropylsulfinyl.

[0063]

The term "alkenylsulfinyl" means a group wherein the above "alkenyl" is bonded to a sulfinyl group. Examples include ethylenylsulfinyl, and n-propenylsulfinyl.

[0064]

The term "alkynylsulfinyl" means a group wherein the above "alkynyl" is bonded to a sulfinyl group. Examples include ethynylsulfinyl and n-propynylsulfinyl.

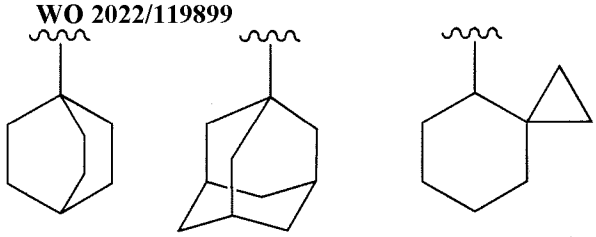
[0065]

The term "alkylcarbamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a carbamoyl group is replaced with the above "alkyl". For example, it includes methylcarbamoyl, ethylcarbamoyl and the like. Another hydrogen atom bonded to the nitrogen atom of the carbamoyl group may be replaced with the above "alkyl".

[0066]

The term "alkenylcarbamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a carbamoyl group is replaced with the above "alkenyl". For example, it includes ethylenylcarbamoyl, propenylcarbamoyl and the like.

Another hydrogen atom bonded to the nitrogen atom of the carbamoyl group may be replaced with the above "alkyl".
[0067]
The term "alkynylcarbamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a carbamoyl group is replaced with the above "alkynyl". For example, it includes ethynylcarbamoyl, propynylcarbamoyl and the like. Another hydrogen atom bonded to the nitrogen atom of the carbamoyl group may be replaced with the above "alkyl".
[0068]
The term "alkylsulfamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a sulfamoyl group is replaced with the above "alkyl". For example, it includes methylsulfamoyl, dimethylsulfamoyl and the like. Another hydrogen atom bonded to the nitrogen atom of the sulfamoyl group may be replaced with the above "alkyl".
[0069]
The term "alkenylsulfamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a sulfamoyl group is replaced with the above "alkenyl". For example, it includes ethylenylsulfamoyl, propenylsulfamoyl and the like. Another hydrogen atom bonded to the nitrogen atom of the carbamoyl group may be replaced with the above "alkyl".
[0070]
The term "alkynylsulfamoyl" means a group wherein a hydrogen atom bonded to a nitrogen atom of a sulfamoyl group is replaced with the above "alkynyl". For example, it includes ethynylsulfamoyl, propynylsulfamoyl and the like. Another hydrogen atom bonded to the nitrogen atom of the carbamoyl group may be replaced with the above "alkyl".
[0071]
The term "aromatic carbocyclyl" means a cyclic aromatic hydrocarbon group which is monocyclic or polycyclic having two or more rings. Examples include phenyl, naphthyl, anthryl, and phenanthryl.
A preferred embodiment of "aromatic carbocyclyl" is phenyl.
[0072]
The term "aromatic carbocycle" means a cyclic aromatic hydrocarbon ring which is monocyclic or polycyclic having two or more rings. Examples include a benzene ring, a naphthalene ring, an anthracene ring, and a phenanthrene ring.
A preferred embodiment of "aromatic carbocycle" is a benzene ring or a naphthalene ring.
[0073]
The term "non-aromatic carbocyclyl" means a cyclic saturated hydrocarbon group or a cyclic unsaturated non-aromatic hydrocarbon group, which is monocyclic or polycyclic having two or more rings. The "non-aromatic carbocyclyl" which is polycyclic having two or more rings includes a fused ring group wherein a non-aromatic carbocyclyl, which is monocyclic or polycyclic having two or more rings, is fused with a ring of the above "aromatic carbocyclyl".
In addition, examples of the "non-aromatic carbocyclyl" also include a group having a bridge or a group to form a spiro ring as follows:



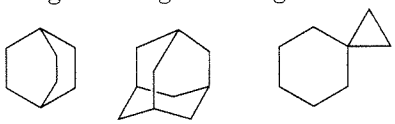
The non-aromatic carbocyclyl which is monocyclic is preferably C3 to C16, more preferably C3 to C12 and further preferably C4 to C8 carbocyclyl. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclohexadienyl.

Examples of non-aromatic carbocyclyl, which is polycyclic having two or more rings, include indanyl, indenyl, acenaphthyl, tetrahydronaphthyl, and fluorenyl.

[0074]

The term "non-aromatic carbocycle" means a cyclic saturated hydrocarbon ring or a cyclic unsaturated non-aromatic hydrocarbon ring, which is monocyclic or polycyclic having two or more rings. The "non-aromatic carbocycle", which is polycyclic having two or more rings, includes a fused ring wherein the non-aromatic carbocycle, which is monocyclic or polycyclic having two or more rings, is fused with a ring of the above "aromatic carbocycle".

In addition, examples of the "non-aromatic carbocycle" also include a ring having a bridge or a ring to form a spiro ring as follows:



The non-aromatic carbocycle which is monocyclic is preferably C3 to C16, more preferably C3 to C12 and further preferably C4 to C8 carbocyclyl. Examples include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, and cyclohexadiene.

Examples of a non-aromatic carbocycle, which is polycyclic having two or more rings, include indane, indene, acenaphthene, tetrahydronaphthalene, and fluorene.

[0075]

The term "aromatic heterocyclyl" means an aromatic cyclyl, which is monocyclic or polycyclic having two or more rings, containing one or more, same or different heteroatom(s) selected independently from O, S and N. The "aromatic heterocyclyl", which is polycyclic having two or more rings, includes a fused ring group wherein an aromatic heterocyclyl, which is monocyclic or polycyclic having two or more rings, is fused with a ring of the above "aromatic carbocyclyl".

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

Examples of aromatic heterocyclyl, which is bicyclic, include indolyl,

isoindolyl, indazolyl, indolizinyl, 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 aromatic heterocyclyl, which is polycyclic having three or more rings, include carbazolyl, acridinyl, xanthenyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, and dibenzofuryl.

[0076]

The term "aromatic heterocycle" means an aromatic ring, which is monocyclic or polycyclic having two or more rings, containing one or more, same or different heteroatom(s) selected independently from O, S and N.

The "aromatic heterocycle", which is polycyclic having two or more rings, includes a fused ring wherein an aromatic heterocycle, which is monocyclic or polycyclic having two or more rings, is fused with a ring of the above "aromatic carbocycle".

The aromatic heterocycle, which is monocyclic, is preferably a 5- to 8-membered ring and more preferably a 5- or 6- membered ring. Examples include pyrrole, imidazole, pyrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazole, triazine, tetrazole, furan, thiophen, isoxazole, oxazole, oxadiazole, isothiazole, thiazole, and thiadiazole.

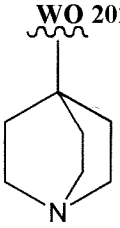
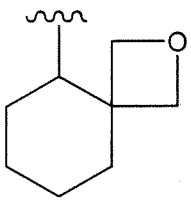
Examples of an aromatic heterocycle, which is bicyclic, include indole, isoindole, indazole, indolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, naphthyridine, quinoxaline, purine, pteridine, benzimidazole, benzisoxazole, benzoxazole, benzoxadiazole, benzisothiazole, benzothiazole, benzothiadiazole, benzofuran, isobenzofuran, benzothiophene, benzotriazole, imidazopyridine, triazolopyridine, imidazothiazole, pyrazinopyridazine, oxazolopyridine, and thiazolopyridine.

Examples of an aromatic heterocycle, which is polycyclic having three or more rings, include carbazole, acridine, xanthene, phenothiazine, phenoxathiine, phenoxazine, and dibenzofuran.

[0077]

The term "non-aromatic heterocyclyl" means a non-aromatic cyclyl, which is monocyclic or polycyclic having two or more rings, containing one or more, same or different heteroatom(s) selected independently from O, S and N. The "non-aromatic heterocyclyl", which is polycyclic having two or more rings, includes an above-mentioned non-aromatic heterocyclyl fused with a ring of the above "aromatic carbocyclyl", "non-aromatic carbocyclyl" and/or "aromatic heterocyclyl". The "non-aromatic heterocyclyl", which is polycyclic having two or more rings, includes an aromatic heterocyclyl, which is monocyclic or polycyclic having two or more rings, fused with a ring of the above "non-aromatic carbocyclyl" and/or "aromatic heterocyclyl".

In addition, examples of the "non-aromatic heterocyclyl" also include a group having a bridge or a group to form a spiro ring as follows:

The non-aromatic heterocyclyl, which is monocyclic, is preferably a 3- to 8-membered and more preferably a 5- to 6- membered ring. Examples include dioxanyl, thiiranyl, oxiranyl, oxetanyl, oxathiolanyl, azetidinyl, thianyl, thiazolidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, dihydropyridyl, tetrahydropyridyl, tetrahydrofuryl, tetrahydropyranyl, dihydrothiazolyl, tetrahydroisothiazolyl, dihydrooxazinyl, hexahydroazepinyl, tetrahydrodiazepinyl, tetrahydropyridazinyl, hexahydropyrimidinyl, dioxolanyl, dioxazinyl, aziridinyl, dioxolynyl, oxepanyl, thiolanyl, thiinyl, and thiazinyl.

Examples of non-aromatic heterocyclyl, which is polycyclic having two or more rings, include indolinyl, isoindolinyl, chromanyl, and isochromanyl.

[0078]

The term "non-aromatic heterocycle" means a cyclic non-aromatic ring, which is monocyclic or polycyclic having two or more rings, containing one or more, same or different heteroatom(s) selected from O, S and N.

The "non-aromatic heterocycle", which is polycyclic having two or more rings, includes an above-mentioned non-aromatic heterocycle fused with a ring of the above "aromatic carbocycle", "non-aromatic carbocycle" and/or "aromatic heterocycle".

In addition, the "non-aromatic heterocycle" also includes a ring having a bridge or a ring to form a spiro ring.

The non-aromatic heterocycle which is non-bridged is preferably a 3 to 8-membered ring, more preferably a 4 to 8-membered ring, and further preferably a 5 or 6-membered ring.

The non-aromatic heterocycle which is bridged is preferably a 6 to 10-membered ring and more preferably a 8 or 9-membered ring. Herein, a number of members mean a number of all annular atoms of a bridged non-aromatic heterocycle.

The non-aromatic heterocycle which is monocyclic is preferably a 3 to 8-membered ring, and more preferably a 5 or 6-membered ring. Examples include dioxane, thiirane, oxirane, oxetane, oxathiolane, azetidine, thiane, thiazolidine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, pyridone, morpholine, thiomorpholine, dihydropyridine, tetrahydropyridine, tetrahydrofuran, tetrahydropyran, dihydrothiazole, tetrahydrothiazole, tetrahydroisothiazole, dihydrooxazine, hexahydroazepine, tetrahydrodiazepine, tetrahydropyridazine, hexahydropyrimidine, dioxolane, dioxazine, aziridine, dioxoline, oxepane, thiolane, thiine, and thiazine.

Examples of a non-aromatic heterocycle, which is polycyclic having two or more rings, include indoline, isoindoline, chromane, and isochromane.

[0079]

The term "aromatic carbocyclyloxy" means a group wherein the "aromatic carbocycle" is bonded to an oxygen atom. Examples include phenyloxy and naphthyloxy.

[0080]

The term "non-aromatic carbocyclyloxy" means a group wherein the

"non-aromatic carbocycle" is bonded to an oxygen atom. Examples include cyclopropyloxy, cyclohexyloxy, and cyclohexenyloxy.
[0081]

The term "aromatic heterocyclyloxy" means a group wherein the "aromatic heterocycle" is bonded to an oxygen atom. Examples include pyridyloxy and oxazolyloxy.
[0082]

The term "non-aromatic heterocyclyloxy" means a group wherein the "non-aromatic heterocycle" is bonded to an oxygen atom. Examples include piperidinyloxy and tetrahydrofuryloxy.
[0083]

The term "aromatic carbocyclylcarbonyl" means a group wherein the "aromatic carbocycle" is bonded to a carbonyl group. Examples include phenylcarbonyl and naphthylcarbonyl.
[0084]

The term "non-aromatic carbocyclylcarbonyl" means a group wherein the "non-aromatic carbocycle" is bonded to a carbonyl group. Examples include cyclopropylcarbonyl, cyclohexylcarbonyl, and cyclohexenylcarbonyl.
[0085]

The term "non-aromatic carbocyclylcarbonyloxy" means a group wherein the "non-aromatic carbocyclylcarbonyl" is bonded to an oxygen atom. Examples include cyclopropylcarbonyloxy, cyclohexylcarbonyloxy, and cyclohexenylcarbonyloxy.
[0086]

The term "aromatic heterocyclylcarbonyl" means a group wherein the "aromatic heterocycle" is bonded to a carbonyl group. Examples include pyridylcarbonyl and oxazolylcarbonyl.
[0087]

The term "non-aromatic heterocyclylcarbonyl" means a group wherein the "non-aromatic heterocycle" is bonded to a carbonyl group. Examples include piperidinylcarbonyl, and tetrahydrofurylcarbonyl.
[0088]

The term "aromatic carbocyclyloxycarbonyl" means a group wherein the "aromatic carbocyclyloxy" is bonded to a carbonyl group. Examples include phenyloxycarbonyl and naphthyloxycarbonyl.
[0089]

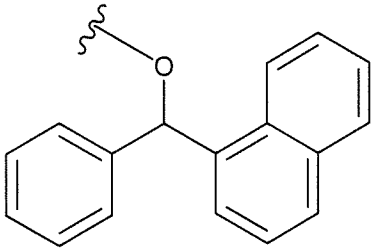
The term "non-aromatic carbocyclyloxycarbonyl" means a group wherein the "non-aromatic carbocyclyloxy" is bonded to a carbonyl group. Examples include cyclopropyloxycarbonyl, cyclohexyloxycarbonyl, and cyclohexenyloxycarbonyl.
[0090]

The term "aromatic heterocyclyloxycarbonyl" means a group wherein the "aromatic heterocyclyloxy" is bonded to a carbonyl group. Examples include pyridyloxycarbonyl and oxazolyloxycarbonyl.
[0091]

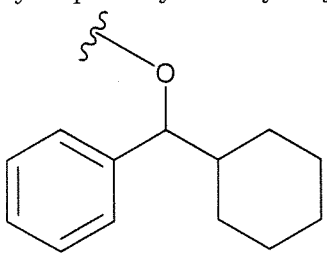
The term "non-aromatic heterocyclyloxycarbonyl" means a group wherein the "non-aromatic heterocyclyloxy" is bonded to a carbonyl group. Examples include piperidinyloxycarbonyl, and tetrahydrofuryloxycarbonyl.
[0092]

The term "aromatic carbocyclylalkyloxy" means an alkyloxy

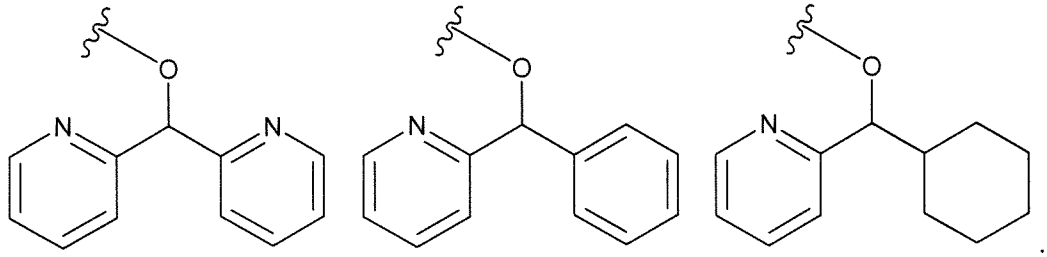
substituted with one or more "aromatic carbocyclyl" described above. Examples include benzyloxy, phenethyloxy, phenyl-n-propyloxy, benzhydryloxy, trityloxy, naphthylmethyloxy, and a group of the following formula:



[0093] The term "non-aromatic carbocyclylalkyloxy" means an alkyloxy substituted with one or more "non-aromatic carbocyclyl" described above. The "non-aromatic carbocyclylalkyloxy" also includes "non-aromatic carbocyclylalkyloxy" wherein the alkyl part is substituted with the above "aromatic carbocyclyl". Examples include cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopenthylmethyloxy, cyclohexylmethyloxy, and a group of the following formula:

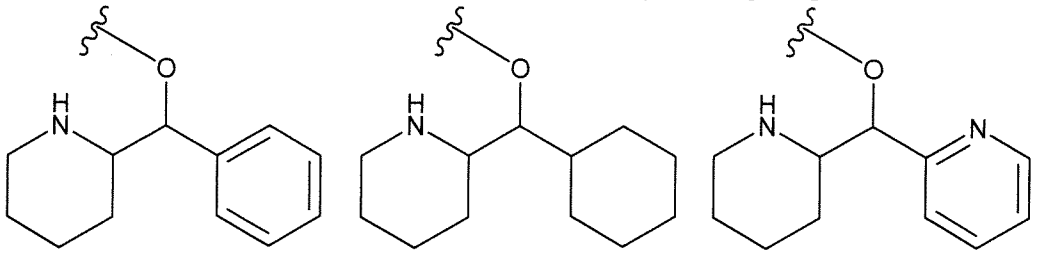


[0094] The term "aromatic heterocyclylalkyloxy" means an alkyloxy substituted with one or more "aromatic heterocyclyl" described above. The "aromatic heterocyclylalkyloxy" also includes "aromatic heterocyclylalkyloxy" wherein the alkyl part is substituted with the above "aromatic carbocyclyl" and/or "non-aromatic carbocyclyl". Examples include pyridylmethyloxy, furanylmethyloxy, imidazolylmethyloxy, indolylmethyloxy, benzothiophenylmethyloxy, oxazolylmethyloxy, isoxazolylmethyloxy, thiazolylmethyloxy, isothiazolylmethyloxy, pyrazolylmethyloxy, isopyrazolylmethyloxy, pyrrolidinylmethyloxy, benzoxazolylmethyloxy, and groups of the following formulae:

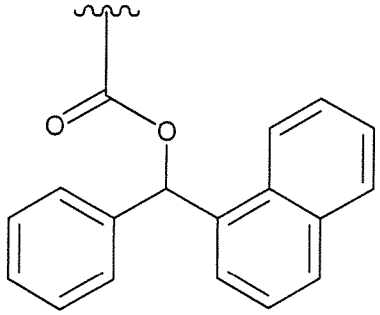


[0095] The term "non-aromatic heterocyclylalkyloxy" means an alkyloxy substituted with one or more "non-aromatic heterocyclyl" described above. The "non-aromatic heterocyclylalkyloxy" also includes "non-aromatic heterocyclylalkyloxy" wherein the alkyl part is substituted with the above "aromatic carbocyclyl", "non-aromatic carbocyclyl" and/or "aromatic heterocyclyl". Examples include

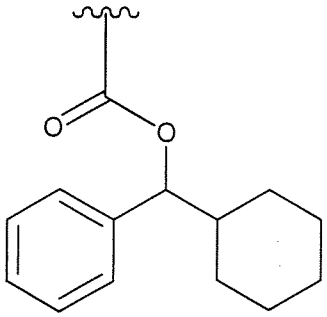
tetrahydropyranylmethyloxy, morpholinylmethyloxy, morpholinylethyloxy, piperidinylmethyloxy, piperazinylmethyloxy, and groups of the following formulae:



[0096] The term "aromatic carbocyclylalkyloxycarbonyl" means an alkyloxycarbonyl substituted with one or more "aromatic carbocyclyl" described above. Examples include benzyloxycarbonyl, phenethyloxycarbonyl, phenyl-n-propyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, naphthylmethyloxycarbonyl, and a group of the following formula:

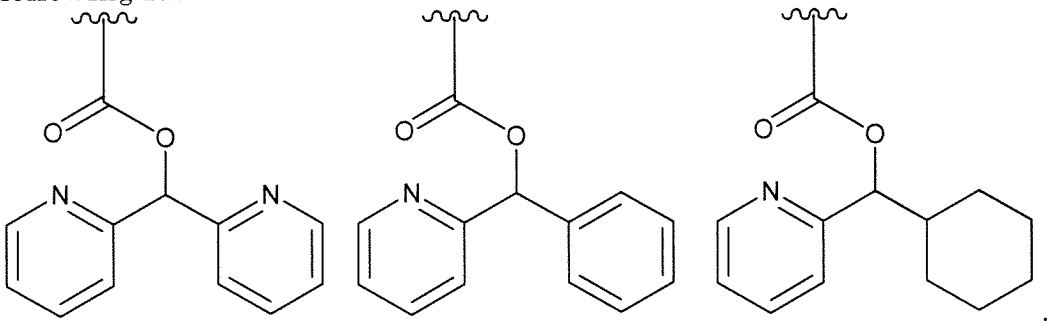


[0097] The term "non-aromatic carbocyclylalkyloxycarbonyl" means an alkyloxycarbonyl substituted with one or more "non-aromatic carbocyclyl" described above. The "non-aromatic carbocyclylalkyloxycarbonyl" also includes "non-aromatic carbocyclylalkyloxycarbonyl" wherein the alkyl part is substituted with the above "aromatic carbocyclyl". Examples include cyclopropylmethyloxycarbonyl, cyclobutylmethyloxycarbonyl, cyclopenthylmethyloxycarbonyl, cyclohexylmethyloxycarbonyl, and a group of the following formula:



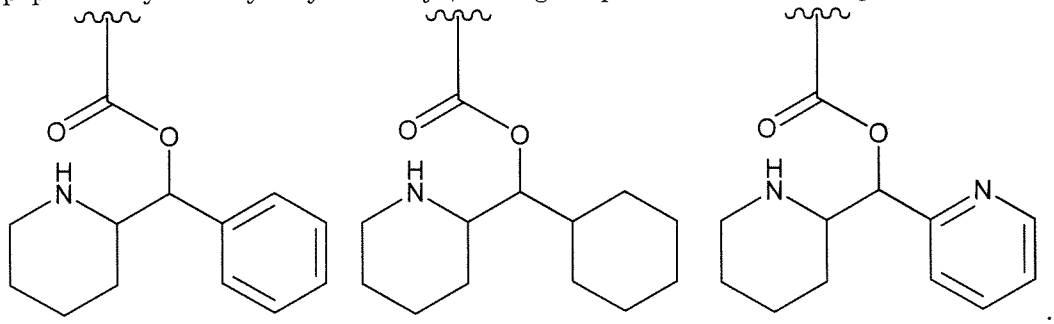
[0098] The term "aromatic heterocyclylalkyloxycarbonyl" means an alkyloxycarbonyl substituted with one or more "aromatic heterocyclyl" described above. The "aromatic heterocyclylalkyloxycarbonyl" also include "aromatic heterocyclylalkyloxycarbonyl" wherein the alkyl part is substituted with the above "aromatic carbocyclyl" and/or "non-aromatic carbocyclyl". Examples include pyridylmethyloxycarbonyl, furanylmethyloxycarbonyl, imidazolylmethyloxycarbonyl,

indolylmethyloxycarbonyl, benzothiophenylmethyloxycarbonyl, oxazolylmethyloxycarbonyl, isoxazolylmethyloxycarbonyl, thiazolylmethyloxycarbonyl, isothiazolylmethyloxycarbonyl, pyrazolylmethyloxycarbonyl, isopyrazolylmethyloxycarbonyl, pyrrolidinylmethyloxycarbonyl, benzoxazolylmethyloxycarbonyl, and groups of the following formulae:



[0099]

The term "non-aromatic heterocyclylalkyloxycarbonyl" means an alkyloxycarbonyl substituted with one or more "non-aromatic heterocyclyl" described above. The "non-aromatic heterocyclylalkyloxycarbonyl" also includes "non-aromatic heterocyclylalkyloxycarbonyl" wherein the alkyl part is substituted with the above "aromatic carbocyclyl", "non-aromatic carbocyclyl" and/or "aromatic heterocyclyl". Examples include tetrahydropyranylmethyloxycarbonyl, morpholinylethyloxycarbonyl, piperidinylmethyloxycarbonyl, piperazinylmethyloxycarbonyl, and groups of the following formulae:



[0100]

The term "aromatic carbocyclylalkylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with the above "aromatic carbocyclylalkyl". Examples include benzylamino, phenethylamino, phenylpropylamino, benzhydrylamino, tritylamino, naphthylmethylamino, and dibenzylamino.

[0101]

The term "non-aromatic carbocyclylalkylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with the above "non-aromatic carbocyclylalkyl". Examples include cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, and cyclohexylmethylamino.

[0102]

The term "aromatic heterocyclylalkylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are)

replaced with the above "aromatic heterocyclylalkyl". Examples include pyridylmethylamino, furanylmethylamino, imidazolylmethylamino, indolylmethylamino, benzothiophenylmethylamino, oxazolylmethylamino, isoxazolylmethylamino, thiazolylmethylamino, isothiazolylmethylamino, pyrazolylmethylamino, isopyrazolylmethylamino, pyrrolylmethylamino, and benzoxazolylmethylamino.

[0103]

The term "non-aromatic heterocyclylalkylamino" means a group wherein one or two hydrogen atom(s) attached to a nitrogen atom of an amino group is(are) replaced with the above "non-aromatic heterocyclylalkyl". Examples include tetrahydropyranylmethylamino, morpholinylethylamino, piperidinylmethylamino, and piperazinylmethylamino.

[0104]

The term "aromatic carbocyclylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the "aromatic carbocycle". Examples include phenylsulfanyl and naphthylsulfanyl.

[0105]

The term "non-aromatic carbocyclylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the "non-aromatic carbocycle". Examples include cyclopropylsulfanyl, cyclohexylsulfanyl, and cyclohexenylsulfanyl.

[0106]

The term "aromatic heterocyclylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the "aromatic heterocycle". Examples include pyridylsulfanyl and oxazolylsulfanyl.

[0107]

The term "non-aromatic heterocyclylsulfanyl" means a group wherein a hydrogen atom attached to a sulfur atom of a sulfanyl group is replaced with the "non-aromatic heterocycle". Examples include piperidinylsulfanyl and tetrahydrofurylsulfanyl.

[0108]

The term "non-aromatic carbocyclylsulfonyl" means a group wherein the "non-aromatic carbocycle" is bonded to a sulfonyl group. Examples include cyclopropylsulfonyl, cyclohexylsulfonyl, and cyclohexenylsulfonyl.

[0109]

The term "aromatic carbocyclylsulfonyl" means a group wherein the "aromatic carbocycle" is bonded to a sulfonyl group. Examples include phenylsulfonyl and naphthylsulfonyl.

[0110]

The term "aromatic heterocyclylsulfonyl" means a group wherein the "aromatic heterocycle" is bonded to a sulfonyl group. Examples include pyridylsulfonyl and oxazolylsulfonyl.

[0111]

The term "non-aromatic heterocyclylsulfonyl" means a group wherein the "non-aromatic heterocycle" is bonded to a sulfonyl group. Examples include piperidinylsulfonyl and tetrahydrofurylsulfonyl.

[0112]

Preferred embodiments of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X, Y, m and n in the compound represented by formula (I) are

described below. A compound having any possible combination of those described below is preferable.

[0113]

R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy.

[0114]

Preferably, R^1 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

Further preferably, R^1 is a hydrogen atom, halogen or substituted or unsubstituted alkyl.

Particularly preferably, R^1 is a hydrogen atom.

[0115]

When R^1 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

When R^1 is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0116]

Preferably, R^2 is a hydrogen atom, halogen, cyano or substituted or unsubstituted alkyl.

Further preferably, R^2 is a hydrogen atom, halogen or substituted or unsubstituted alkyl.

Particularly preferably, R^2 is a hydrogen atom or halogen.

[0117]

When R^2 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

When R^2 is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0118]

Preferably, R^3 is a hydrogen atom, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

Further preferably, R^3 is a hydrogen atom, halogen or substituted or unsubstituted alkyl.

Particularly preferably, R^3 is a hydrogen atom or halogen.

[0119]

When R^3 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

When R^3 is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0120]

Preferably, R^4 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

Further preferably, R^4 is a hydrogen atom, halogen or substituted or unsubstituted alkyl.

Particularly preferably, R^4 is a hydrogen atom.

[0121]

When R^4 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

When R^4 is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0122]

R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

Preferably, R^5 is halogen or substituted or unsubstituted alkyl.

Further preferably, R^5 is substituted or unsubstituted alkyl.

[0123]

When R^5 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

When R^5 is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0124]

R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom.

[0125]

Preferably, R^6 is a hydrogen atom or halogen. Further preferably, R^6 is a hydrogen atom.

[0126]

Preferably, R^7 is a hydrogen atom or halogen. Further preferably, R^7 is halogen.

[0127]

Preferably, R^8 is a hydrogen atom or halogen. Further preferably, R^8 is a hydrogen atom.

[0128]

Preferably, R^9 is a hydrogen atom or halogen. Further preferably, R^9 is a hydrogen atom.

[0129]

Embodiments in which R^7 is halogen, and R^6, R^8 and R^9 are hydrogen atom are also preferred.

[0130]

Embodiments in which R^6 is halogen, and R^7, R^8 and R^9 are hydrogen atom are also preferred.

[0131]

Embodiments in which R^7 and R^8 are each independently halogen, and R^6 and R^9 are hydrogen atom are also preferred.

[0132]

Embodiments in which R^6 and R^7 are each independently halogen, and R^8 and R^9 are hydrogen atom are also preferred.

[0133]

Embodiments in which R^7 and R^9 are each independently halogen, and R^6 and R^8 are hydrogen atom are also preferred.

[0134]

When R^6 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, alkyloxy and the like.

When R^6 is a substituted group, a further preferable substituent on said substituted group is selected from halogen.

[0135]

When R^7 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, alkyloxy and the like.

When R^7 is a substituted group, a further preferable substituent on said substituted group is selected from halogen.

[0136]

When R^8 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, alkyloxy and the like.

When R^8 is a substituted group, a further preferable substituent on said substituted group is selected from halogen.

[0137]

When R^9 is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, alkyloxy and the like.

When R^9 is a substituted group, a further preferable substituent on said substituted group is selected from halogen.

[0138]

X is CH or N.

[0139]

Y is CH or N.

[0140]

Embodiments in which X is N, and Y is N are also preferred.

[0141]

Embodiments in which X is N, and Y is CH are also preferred.

[0142]

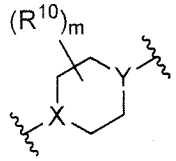
Embodiments in which X is CH, and Y is N are also preferred.

[0143]

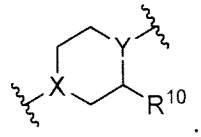
m is 0, 1, 2, 3 or 4. Preferably, m is 0, 1 or 2. Further preferably, m is 1 or 2. Particularly preferably, m is 1.

[0144]

In case that m is 1, a group represented by formula:

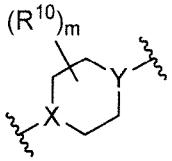


in formula (I) is preferably a group represented by formula:

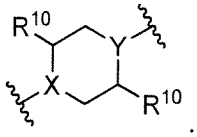


[0145]

In case that m is 2, a group represented by formula:



in formula (I) is preferably a group represented by formula:



[0146]

R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl.

Preferably, R^{10} is each independently halogen or substituted or unsubstituted alkyl.

Further preferably, R^{10} is each independently substituted or unsubstituted alkyl.

[0147]

When R^{10} is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, cyano, alkyloxy, alkylamino and the like.

[0148]

R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio. Preferably, R^{11} is halogen, substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

Further preferably, R^{11} is substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

Particularly preferably, R^{11} is substituted or unsubstituted alkyloxy, including trihaloalkyloxy (like OCF_3).

[0149]

When R^{11} is a substituted group, a preferable substituent on said substituted group is selected from halogen, hydroxy, amino, alkyloxy, alkylamino, non-aromatic carbocyclyl and the like.

When R^{11} is a substituted group, a further preferable substituent on said substituted group is selected from halogen and the like.

[0150]

R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy.

Preferably, R^{12} is each independently halogen, substituted or unsubstituted alkyl or substituted or unsubstituted alkyloxy.

[0151]

When R^{12} is a substituted group, a preferable substituent on said

substituted group is selected from halogen and the like.

[0152]

n is 0, 1, 2, 3 or 4. Preferably, n is 0, 1 or 2. Further preferably, n is 0 or 1. Particularly preferably, n is 0.

[0153]

Preferred combinations of substituents of a compound represented by formula (I) include the following 1) to 6):

1) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is halogen; R^3 is a hydrogen atom; R^5 is substituted or unsubstituted alkyl; R^6, R^8 and R^9 are hydrogen atom; R^7 is halogen; X is N; Y is N; m is 1; R^{10} is substituted or unsubstituted alkyl; R^{11} is substituted or unsubstituted alkyloxy; n is 0;

2) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is halogen; R^3 is a hydrogen atom; R^5 is substituted or unsubstituted alkyl; R^7, R^8 and R^9 are hydrogen atom; R^6 is halogen; X is CH; Y is N; m is 0; R^{11} is substituted or unsubstituted alkyl; n is 0;

3) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is a hydrogen atom; R^3 is halogen; R^5 is substituted or unsubstituted alkyl; R^7, R^8 and R^9 are hydrogen atom; R^6 is halogen; X is CH; Y is N; m is 0; R^{11} is substituted or unsubstituted alkyl; n is 0;

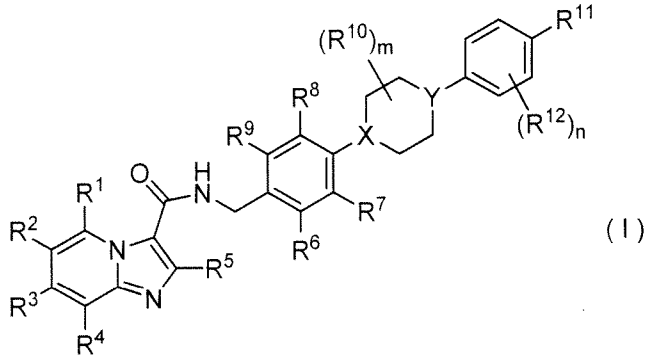
4) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is a hydrogen atom; R^3 is halogen; R^5 is substituted or unsubstituted alkyl; R^6, R^8 and R^9 are hydrogen atom; R^7 is halogen; X is N; Y is N; m is 1; R^{10} is substituted or unsubstituted alkyl; R^{11} is substituted or unsubstituted alkyloxy; n is 0;

5) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is halogen; R^3 is a hydrogen atom; R^5 is substituted or unsubstituted alkyl; R^6, R^8 and R^9 are hydrogen atom; R^7 is halogen; X is N; Y is N; m is 2; R^{10} is each independently substituted or unsubstituted alkyl; R^{11} is substituted or unsubstituted alkyloxy; n is 0;

6) a compound wherein R^1 and R^4 are hydrogen atom; R^2 is substituted or unsubstituted alkyl; R^3 is hydrogen atom; R^5 is substituted or unsubstituted alkyl; R^6, R^8 and R^9 are hydrogen atom; R^7 is halogen; X is N; Y is N; m is 1; R^{10} is substituted or unsubstituted alkyl; R^{11} is substituted or unsubstituted alkyloxy; n is 0.

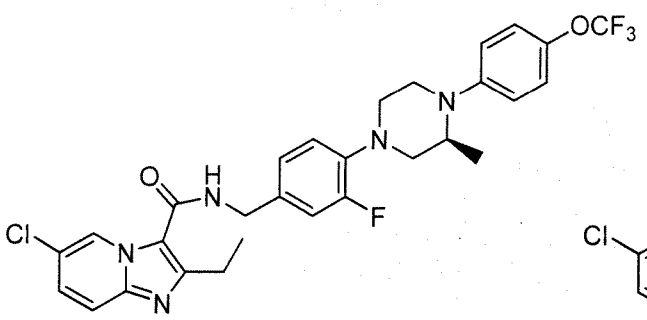
[0154]

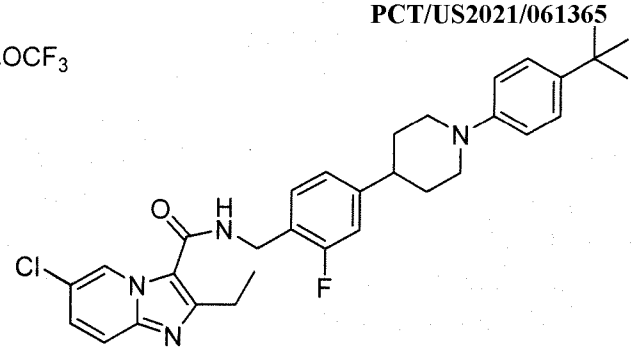
A compound represented by formula (I):

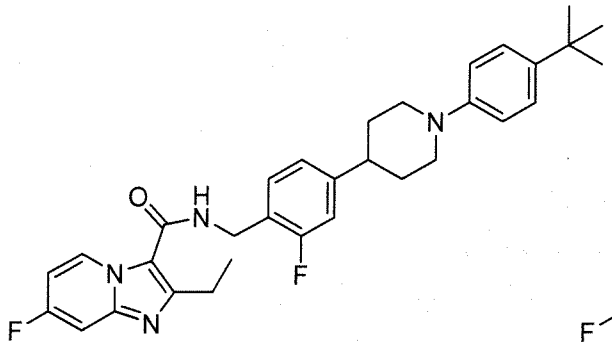


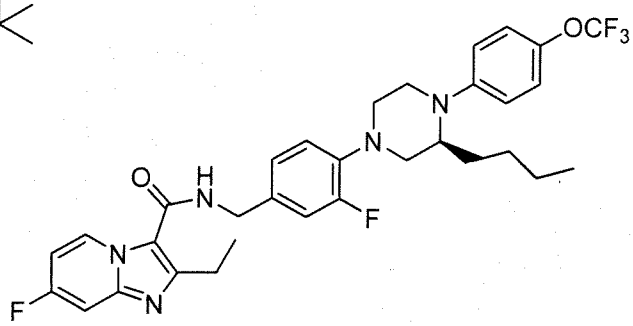
(I)

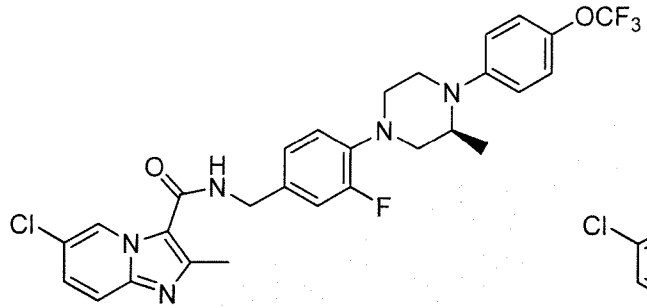
, or its pharmaceutically acceptable salt is particularly preferably the compound selected from the group consisting of

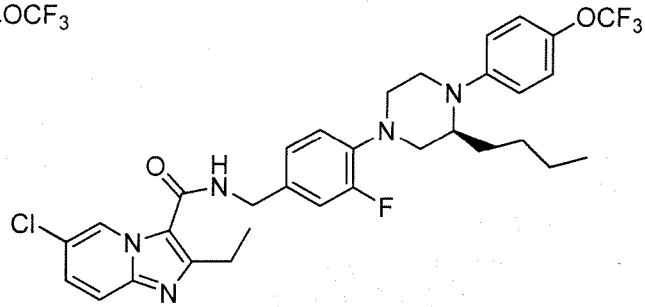


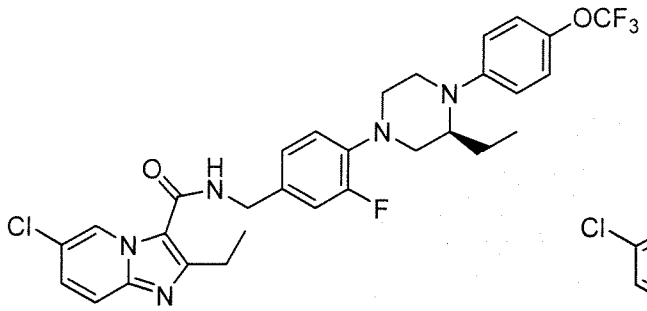


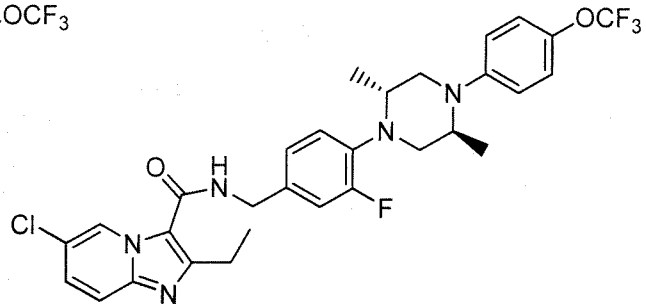




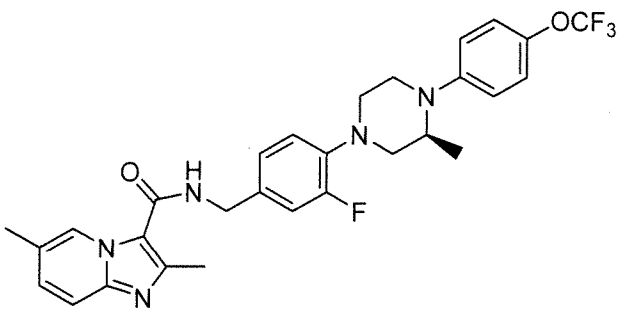








and



, or its pharmaceutically acceptable salt.

[0155] If desired, any one of more of the compounds of the present invention

(a compound represented by formula (I), clarithromycin, azithromycin or clofazimine) may be in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts of the compounds include, for example, salts with alkaline metal (e.g., lithium, sodium or potassium), alkaline earth metal (e.g., calcium or barium), magnesium, transition metal (e.g., zinc or iron), ammonia, organic bases (e.g., trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, pyridine, picoline or quinoline) or amino acids, or salts with inorganic acids (e.g., hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid, or hydroiodic acid) or organic acids (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid). Especially, salts with hydrochloric acid, sulfuric acid, phosphoric acid, tartaric acid, methanesulfonic acid and the like are included. These salts can be formed by the usual methods.
[0156]

The compounds of formula (I) are not limited to specific isomers but include all possible isomers (e.g., keto-enol isomers, imine-enamine isomers, diastereoisomers, enantiomers, or rotamers), racemates or mixtures thereof.
[0157]

One or more hydrogen, carbon and/or other atom(s) in the compounds of formula (I) may be replaced with isotopes of hydrogen, carbon and/or other atoms respectively. Examples of isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine and chlorine, such as ^{2}H, ^{3}H, ^{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 of formula (I) include the compounds replaced with these isotopes. The compounds replaced with the above isotopes are useful as medicines and include all of radiolabeled compounds of the compound of formula (I). A "method of radiolabeling" in the manufacture of the "radiolabeled compounds" is encompassed by the present invention, and the "radiolabeled compounds" are useful for studies on metabolized drug pharmacokinetics, studies on binding assay and/or diagnostic tools.
[0158]

A radiolabeled compound of the compounds of formula (I) can be prepared using well-known methods in this field of the invention. For example, a tritium-labeled compound of formula (I) can be prepared by introducing a tritium to a certain compound of formula (I) through a catalytic dehalogenation reaction using a tritium. This method comprises reacting an appropriately-halogenated precursor of the compound of formula (I) with tritium gas in the presence of an appropriate catalyst, such as Pd/C, and in the presence or absent of a base. The other appropriate method of preparing a tritium-labeled compound can be referred to "Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987)". A ^{14}C-labeled compound can be prepared by using a raw material having ^{14}C.
[0159]

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

compounds of formula (I) or pharmaceutically acceptable salts thereof are allowed to stand in the atmosphere, the compounds may absorb water, resulting in attachment of adsorbed water or formation of hydrates. Recrystallization of the compounds of formula (I) or pharmaceutically acceptable salts thereof may produce crystal polymorphs. "Co-crystal" means that a compound of formula (I) or a salt thereof and a counter-molecule exist in the same crystal lattice, and it can be formed with any number of counter-molecules.

[0160]

The compounds of formula (I) of the present invention or pharmaceutically acceptable salts thereof may form prodrugs. The present invention also encompasses such various prodrugs. Prodrugs are derivatives of the compounds of the present invention that have chemically or metabolically degradable groups, and compounds that are converted to the pharmaceutically active compounds of the present invention through solvolysis or under physiological conditions in vivo. Prodrugs include compounds that are converted to the compounds of formula (I) through enzymatic oxidation, reduction, hydrolysis or the like under physiological conditions in vivo, compounds that are converted to the compounds of formula (I) through hydrolysis by gastric acid etc., and the like. Methods for selecting and preparing suitable prodrug derivatives are described in, for example, "Design of Prodrugs, Elsevier, Amsterdam, 1985". Prodrugs themselves may have some activity.

[0161]

When the compounds of formula (I) or pharmaceutically acceptable salts thereof have hydroxyl group(s), prodrugs include acyloxy derivatives and sulfonyloxy derivatives that are prepared by, for example, reacting compounds having hydroxyl group(s) with suitable acyl halide, suitable acid anhydride, suitable sulfonyl chloride, suitable sulfonyl anhydride and mixed anhydride, or with a condensing agent. For example, they include CH_3COO^-, $C_2H_5COO^-$, tert-$BuCOO^-$, $C_{15}H_{31}COO^-$, $PhCOO^-$, (m-$NaOOCPh)COO^-$, $NaOOCCH_2CH_2COO^-$, $CH_3CH(NH_2)COO^-$, $CH_2N(CH_3)_2COO^-$, $CH_3SO_3^-$, $CH_3CH_2SO_3^-$, $CF_3SO_3^-$, $CH_2FSO_3^-$, $CF_3CH_2SO_3^-$, p-CH_3O-$PhSO_3^-$, $PhSO_3^-$ and p-$CH_3PhSO_3^-$.

[0162]

The term "pharmaceutically acceptable" means preventively or therapeutically harmless.

[0163]

General procedures for the synthesis of the compounds of the present invention are described below. Starting materials and reaction reagents used in such synthesis are commercially available or can be synthesized according to methods well known in the art using compounds commercially available. Further, extraction, purification and the like may be performed in accordance with the methods carried out in the art.

In the following all steps, when a substituent which impedes a reaction, e.g. hydroxy, mercapto, amino, formyl, carbonyl, carboxy, is possessed, the substituent is protected by the method described in Protective Groups in organic Synthesis, and Theodora W Greene (John Wiley & Sons, hereinafter referred to as literature A) in advance, and the protecting group may be removed at a desirable stage. In addition, in the all steps, an order of steps to be implemented may be appropriately changed, and each intermediate may be isolated, and used in a next step. All of reaction time, reaction temperature, solvents, reagents, protecting

groups, etc. are mere exemplification and not limited as long as they do not cause an adverse effect on a reaction.

[0164]

For example, the compounds represented by Formula (I) of the present invention can be produced according to general procetures as described below. Also, the compounds of the invention can be prepared according to other methods based on the knowledge in organic chemistry.

[0165]

Preparation of Compound a3



a1 a2 a3

wherein

PG is an amino protecting group such as Boc, Cbz and etc., R^{a1} is halogen, triflate, nonaflate, mesylate or tosylate, the other symbols are as defined above.

Compound a1 is reacted with Compound a2 in the presence of the base to obtain Compound a3.

Examples of the solvent include toluene, DMF, DMA, tetrahydrofuran, ethanol, water, toluene, acetonitrile, 1,4-dioxane and the like, and these solvents may be used alone or in combination.

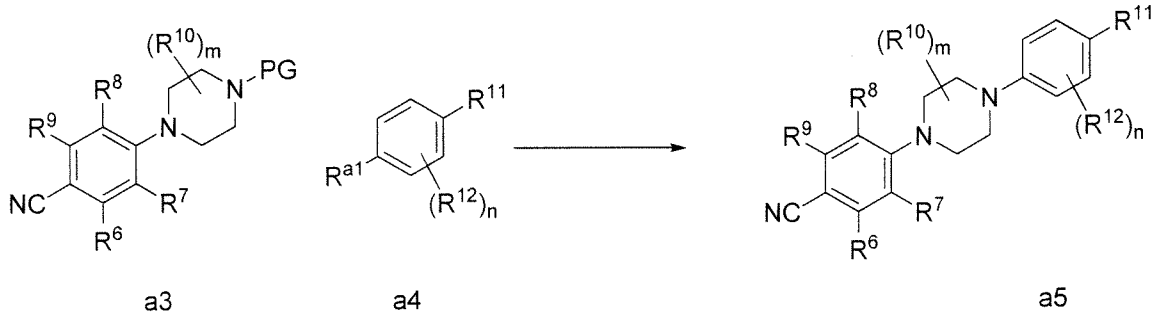
Examples of the base include potassium tert-butoxide, sodium hydride, potassium carbonate, cesium carbonate, triethylamine, diisopropylethylamine, DBU and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a1.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0166]

Preparation of Compound a5



a3 a4 a5

wherein each symbol is as defined above.

Compound a5 can be obtained by reacting with Compound a4 in the presense of Palladium, Ligand and base after reacting Compound a3 with

deprotecting agents.

Examples of the reaction solvent for deprotecting reaction include ethyl acetate, water, dicloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

Examples of the deprotecting agent include hydrochloric acid / ethyl acetate, methane sulfonic acid, trifluoroacetic acid, sulfuric acid, iodotrimethylsilane, aluminium trichloride, bromocatechol borane, trimethylsilyl chloride, trimethylsilyl triflate and the like. The amount of the deprotecting agent may be 1 to 100 mole equivalents, preferably 1 to 50 mole equivalents of Compound a4.

Examples of the Palladium include palladium acetate, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$ and the like. The amount of the Palladium may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a4.

Examples of the Ligand include 2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, Dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) and the like. The amount of the Ligand may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a3.

Examples of the base include cesium carbonate, potassium carbonate, sodium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a4.

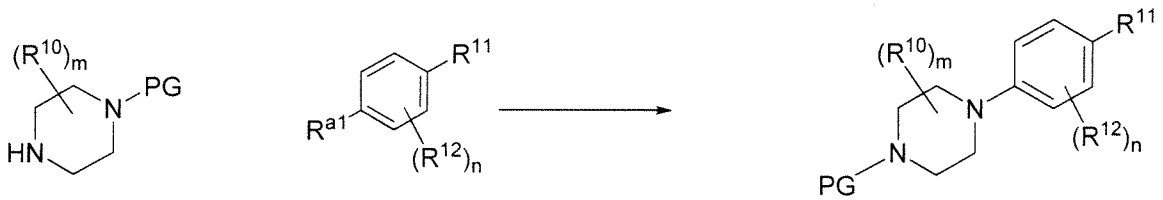
Examples of the reaction solvent include methanol, N,N-dimethylformamide, N, N-dimethylacetamide, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0167]

Preparation of Compound a6



a2 a4 a6

wherein each symbol is as defined above.

Compound a6 can be obtained by reacting with Compound a2 and Compound a4 in the presense of Palladium, Ligand and base.

Examples of the Palladium include palladium acetate, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$ and the like. The amount of the Palladium may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a2.

Examples of the Ligand include 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) and the like. The amount of the Ligand may be 0.01 to 5

mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a2.

Examples of the base include cesium carbonate, potassium carbonate, sodium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a2.

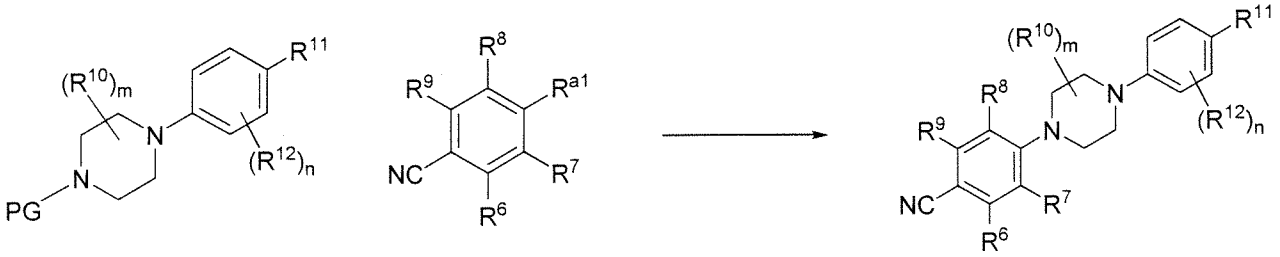
Examples of the reaction solvent include methanol, N,N-dimethylformamide, N, N-dimethylacetamide, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0168]

Preparation of Compound a5



a6 a1 a5

wherein each symbol is as defined above.

Compound a5 can be obtained by reacting with Compound a1 in the presence of the base after reacting Compound a6 with deprotecting agents.

Examples of the reaction solvent for deprotecting reaction include ethyl acetate, water, dicloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

Examples of the deprotecting agent include hydrochloric acid / ethyl acetate, methane sulfonic acid, trifluoroacetic acid, sulfuric acid, iodotrimethylsilane, aluminium trichloride, bromocatechol borane, trimethylsilyl chloride, trimethylsilyl triflate and the like. The amount of the deprotecting agent may be 1 to 100 mole equivalents, preferably 1 to 50 mole equivalents of Compound a1.

Examples of the solvent include toluene, DMF, DMA, dimethyl sulfoxide tetrahydrofuran, ethanol, water, toluene, acetonitrile, 1,4-dioxane and the like, and these solvents may be used alone or in combination.

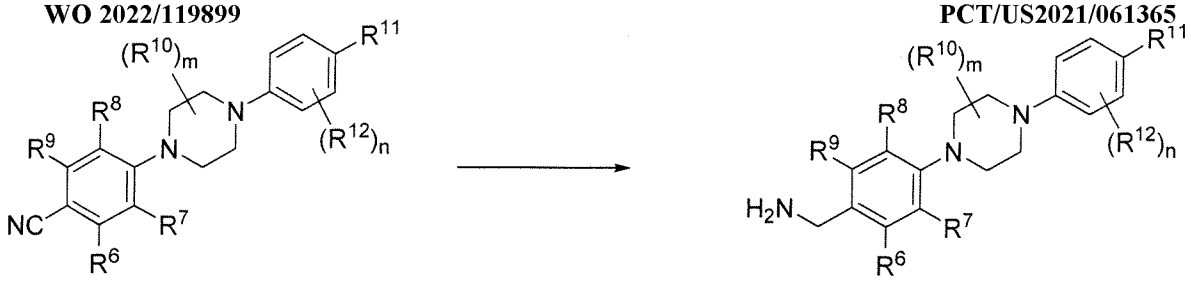
Examples of the base include potassium tert-butoxide, sodium hydride, potassium carbonate, cesium carbonate, triethylamine, diisopropylethylamine, DBU and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a1.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0169]

Preparation of Compound a7



a5 a7

wherein each symbol is as defined above.

Compound a7 can be obtained by reacting Compound a5 with reductants.

Examples of the reaction solvent include ethyl acetate, water, dicloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, acetic acid, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

Examples of the reductants include hydrogen with Pd carbon, hydrogen with $Pd(OH)_2$, sodium borohydrodie with $NiCl_2(H_2O)_6$, lithium aluminumhydride and the like. The amount of the reductants may be 1 to 100 mole equivalents, preferably 1 to 10 mole equivalents of Compound a5.

The reaction temperature may be 0°C to 200°C, preferably 0°C to 100°C.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0170]

Preparation of Compound a10



a8 a9 a10

wherein

R^{a2} is halogen, triflate, nonaflate, mesylate, tosylate, bornic acid or boronate, R^{a3} is triflate, nonaflate, mesylate, tosylate, bornic acid or boronate, the other symbols are as defined above.

The compound a8 is reacted with a9 in the presence of the Palladium and base to obtain Compound a10.

Examples of the Palladium include palladium acetate, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $PdCl_2(dppf)$ and the like. The amount of the Palladium may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a8.

Examples of the base include cesium carbonate, potassium carbonate, sodium carbonate and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a8.

Examples of the reaction solvent include water, DMF, DMA, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and

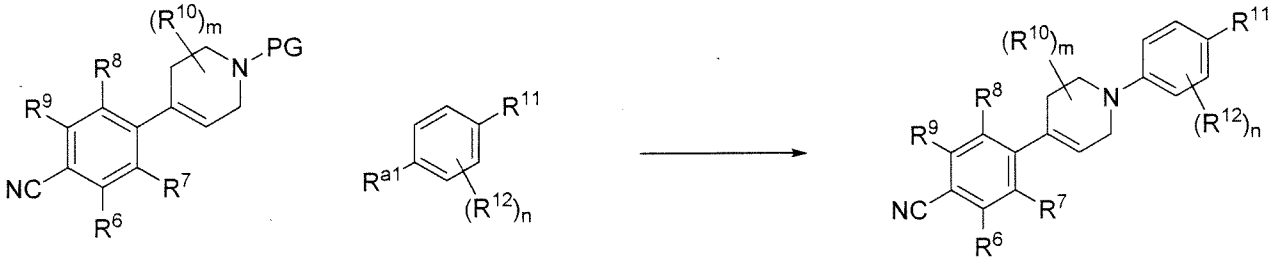
these solvents may be used alone or in combination.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0171]

Preparation of Compound a11



a10 a4 a11

wherein each symbol is as defined above.

Compound a11 can be obtained by reacting with Compound a10 in the presense of Palladium, ligand and base after reacting Compound a4 with deprotecting agents.

Examples of the reaction solvent for deprotecting reaction include ethyl acetate, water, dicloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

Examples of the deprotecting agent include hydrochloric acid / ethyl acetate, methane sulfonic acid, trifluoroacetic acid, sulfuric acid, iodotrimethylsilane, aluminium trichloride, bromocatechol borane, trimethylsilyl chloride, trimethylsilyl triflate and the like. The amount of the deprotecting agent may be 1 to 100 mole equivalents, preferably 1 to 50 mole equivalents of Compound a4.

Examples of the Palladium include palladium acetate, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$ and the like. The amount of the Palladium may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a4.

Examples of the Ligand include 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl, dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) and the like. The amount of the Ligand may be 0.01 to 5 mole equivalents, preferably 0.01 to 1 mole equivalents of Compound a4.

Examples of the base include cesium carbonate, potassium carbonate, sodium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a4.

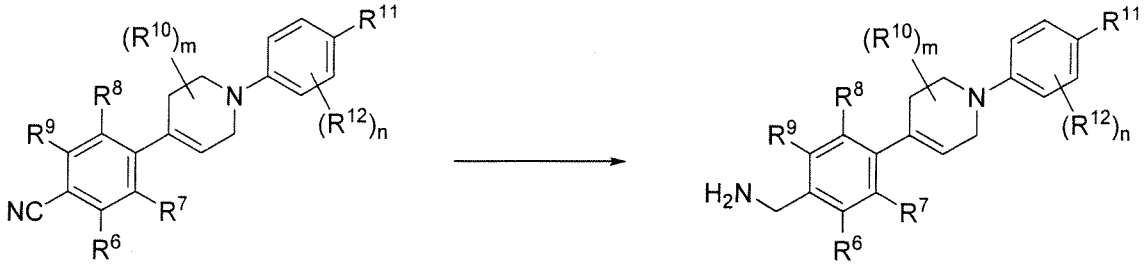
Examples of the reaction solvent include methanol, N,N-dimethylformamide, N, N-dimethylacetamide, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

The reaction temperature may be room temperature to 200°C, preferably 50°C to 150°C, and the reaction can be conducted in seeled tube as required.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0172]

Preparation of Compound a12



a11 a12

wherein each symbol is as defined above.

Compound a12 can be obtained by reacting Compound a11 with reductants.

Examples of the reaction solvent include ethyl acetate, water, dicloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, acetic acid, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

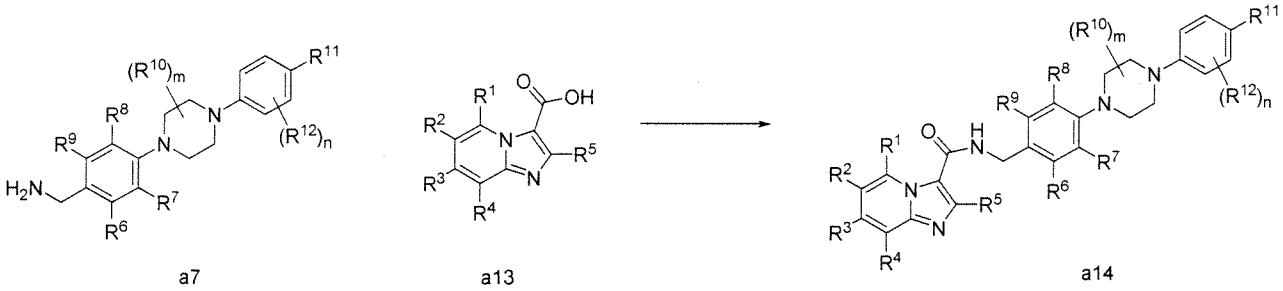
Examples of the reductants includesodium borohydrodie with $NiCl_2(H_2O)_6$, lithium aluminumhydride, borane tetrahydrofran, borane dimethylsulfide and the like. The amount of the reductants may be 1 to 100 mole equivalents, preferably 1 to 10 mole equivalents of Compound a11.

The reaction temperature may be 0°C to 200°C, preferably 0°C to 100°C.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0173]

Preparation of Compound a14



a7 a13 a14

wherein each symbol is as defined above.

Compound a14 can be obtained by reacting Compound a7 with carbocylic acid (Compound a13) in the presence of condensing agents and base.

Examples of the reaction solvent include N,N-dimethylformamide, ethanol, water, dichloromethane, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

Examples of the base include triethylamine, potassium tert-butoxide, potassium carbonate, cesium carbonate, diisopropylethylamine, DBU and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

Examples of the condensing agent include HATU, WSC, DCC, HOBt

and the like. The amount of the condensing agent may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

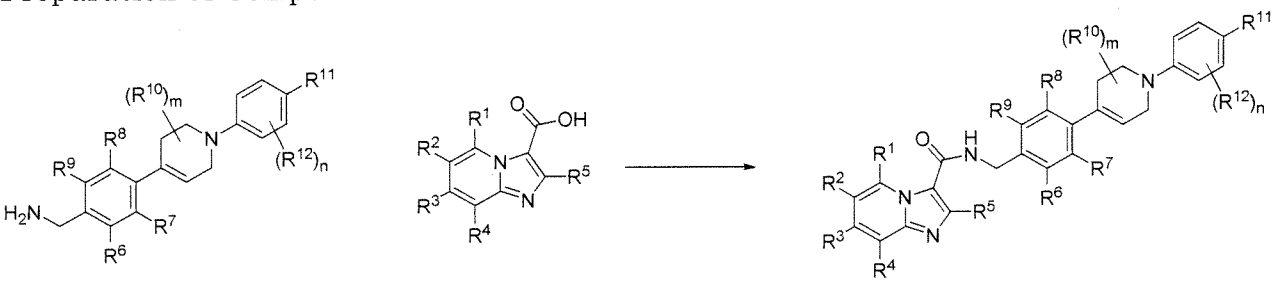
The carboxylic acid may be used in 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a7.

The reaction temperature may be under ice-cooling to reflux temperature, preferably room temperature.

The reaction time may be 0.1 to 24 hours, preferably 1 to 5 hours.

[0174]

Preparation of Compound a15



a12 a13 a15

wherein each symbol is as defined above.

Compound a15 can be obtained by reacting Compound a12 with carbocylic acid (Compound a13) in the presence of condensing agents and base.

Examples of the reaction solvent include N,N-dimethylformamide, ethanol, water, dichloromethane, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

Examples of the base include triethylamine, potassium tert-butoxide, potassium carbonate, cesium carbonate, diisopropylethylamine, DBU and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

Examples of the condensing agent include HATU, WSC, DCC, HOBt and the like. The amount of the condensing agent may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

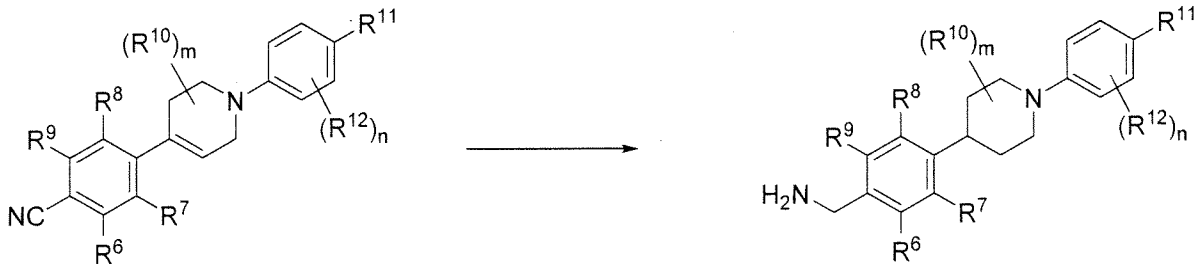
The carboxylic acid may be used in 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a12.

The reaction temperature may be under ice-cooling to reflux temperature, preferably room temperature.

The reaction time may be 0.1 to 24 hours, preferably 1 to 5 hours.

[0175]

Preparation of Compound a16



a11 a16

wherein each symbol is as defined above.

Compound a16 can be obtained by reacting Compound a11 with

reductants.

Examples of the reaction solvent include ethyl acetate, water, dichloromethane, N, N-dimethylformamide, ethanol, tetrahydrofuran, methanol, acetic acid, 1,4-dioxane, acetonitrile, toluene and the like, and these solvents may be used alone or in combination.

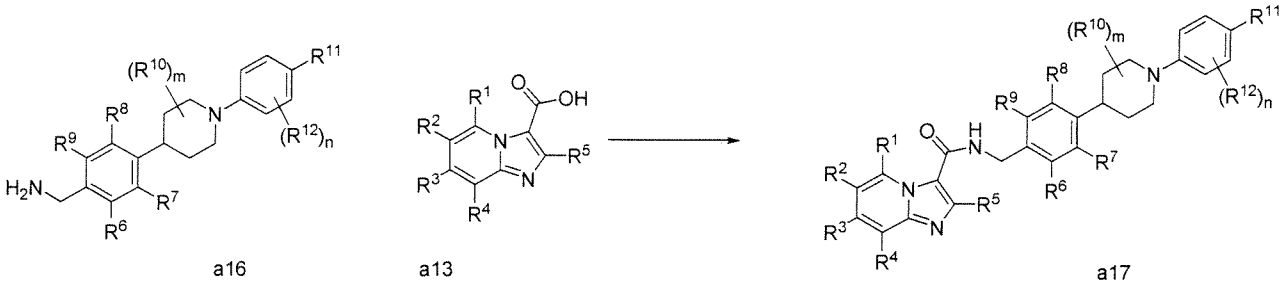
Examples of the reductants include hydrogen with Pd carbon, hydrogen with $Pd(OH)_2$, and the like. The amount of the reductants may be 1 to 100 mole equivalents, preferably 1 to 10 mole equivalents of Compound a11.

The reaction temperature may be 0°C to 200°C, preferably 0°C to 100°C.

The reaction time may be 0.1 to 24 hours, preferably 1 to 12 hours.

[0176]

Preparation of Compound a17



wherein each symbol is as defined above.

Compound a17 can be obtained by reacting Compound a16 with carbocylic acid (Compound a13) in the presence of condensing agents and base.

Examples of the reaction solvent include N,N-dimethylformamide, ethanol, water, dichloromethane, tetrahydrofuran, methanol, 1,4-dioxane, acetonitrile, toluene, ethyl acetate and the like, and these solvents may be used alone or in combination.

Examples of the base include triethylamine, potassium tert-butoxide, potassium carbonate, cesium carbonate, diisopropylethylamine, DBU and the like. The amount of the base may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

Examples of the condensing agent include HATU, WSC, DCC, HOBt and the like. The amount of the condensing agent may be 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a13.

The carboxylic acid may be used in 1 to 10 mole equivalents, preferably 1 to 5 mole equivalents of Compound a16.

The reaction temperature may be under ice-cooling to reflux temperature, preferably room temperature.

The reaction time may be 0.1 to 24 hours, preferably 1 to 5 hours.

[0177]

The compound represented by formula (I) of the present invention or pharmaceutically acceptable salts thereof are useful in the treatment or prevention of a mycobacterial infection, especially non-tuberculous mycobacterial infection. Such compounds may work by interfering with ATP synthase in pathogenic mycobacteria, with the inhibition of cytochrome bc1 activity as the primary mode of action.

The compound represented by formula (I) of the present invention or pharmaceutically acceptable salts thereof have not only the above described activity but also usefulness as a medicine, and have any or all of the following superior features:

a) The inhibitory activity for CYP enzymes (e.g., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and the like) is weak.

b) The compound demonstrates good pharmacokinetics, such as a high bioavailability, moderate clearance, high distribution to a targeted tissue and the like.

c) The compound has a high metabolic stability.

d) The compound has no irreversible inhibitory effect against CYP enzymes (e.g., CYP3A4) when the concentration is within the range described in the present description as the measurement conditions.

e) The compound has no mutagenicity.

f) The compound is associated with a low cardiovascular risk.

g) The compound has a high solubility.

h) The compound causes less induction of drug-metabolizing enzyme

i) The compound has less risk of phototoxicity,

j) The compound has less risk of hepatotoxicity,

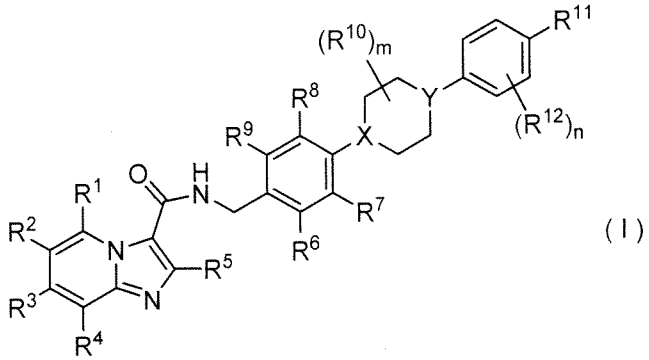
k) The compound has less risk of kidney toxicity,

l) The compound has less risk of gastrointestinal disorders, and

m) The compound has intense efficacy.

[0178]

In embodiments, the medicament includes (A) a compound represented by formula (I):



(I)

wherein each symbol has the same meaning as above

, or its pharmaceutically acceptable salt, is combined with

(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

The term "medicament characterized by combination" includes an embodiment in which each compound is used as a combination drug, an embodiment in which each compound is used as a kit, an embodiment in which it is administered simultaneously, an embodiment in which it is administered sequentially, an embodiment in which it is administered at intervals and an embodiment in which they are used in combination with other drugs.

Referring to administration, the term, "simultaneously" means that the compounds (A) and (B) are administered to the subject at the same time, for example in a single dose or bolus. The term, "sequentially" means that the compounds (A) and (B) are administered to the subject in a certain pre-determined

sequence within a certain pre-determined time interval of one another. For example, administration sequences of (A)-(B) or (B)-(A) are possible, wherein administration of each is carried out within a few seconds to a few hours of each other. The term administered at "intervals" means that the compounds (A) and (B) are administered to the subject in a certain pre-determined sequence within a certain pre-determined time interval of one another. For example, administration sequences of (A)-(B) or (B)-(A) are possible, wherein administration of each is carried out within a few hours to one day of each other.

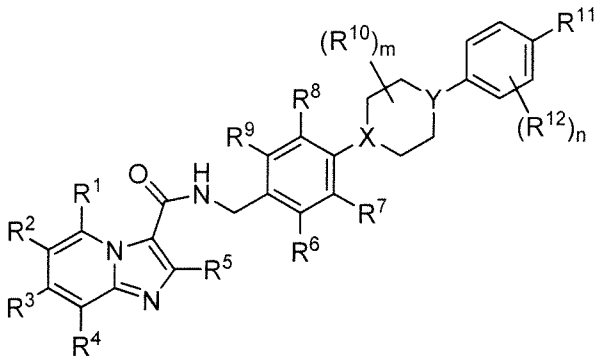
[0179]

The compound represented by formula (I), or its pharmaceutically acceptable salt can be used in combination with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, and it can enhance anti-bacterial effect of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt.

Also, (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt can be used in combination with the compound represented by formula (I), or its pharmaceutically acceptable salt, and it can enhance anti-bacterial effect of the compound represented by formula (I), or its pharmaceutically acceptable salt.

[0180]

In embodiments, the medicament includes (A) a compound represented by formula (I):



(I)

wherein each symbol has the same meaning as above

, or its pharmaceutically acceptable salt, is combined with

(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt.

The term "medicament characterized by combination" includes an embodiment in which each compound is used as a combination drug, an embodiment in which each compound is used as a kit, an embodiment in which it is administered simultaneously, an embodiment in which it is administered sequentially, an embodiment in which it is administered at intervals and an embodiment in which they are used in combination with other drugs.

Referring to administration, the term, "simultaneously" means that the compounds (A), (B), and (C) are administered to the subject at the same time, for example in a single dose or bolus. The term, "sequentially" means that the compounds (A), (B), and (C) are administered to the subject in a certain pre-determined sequence within a certain pre-determined time interval of one another.

For example, administration sequences of (A)-(B)-(C), (B)-(C)-(A), (C)-(A)-(B), (B)-(A)-(C), (A)-(C)-(B), or (C)-(B)-(A) are possible, wherein administration of each is carried out within a few seconds to a few hours of each other. The term administered at "intervals" means that the compounds (A), (B), and (C) are administered to the subject in a certain pre-determined sequence within a certain pre-determined time interval of one another. For example, administration sequences of (A)-(B)-(C), (B)-(C)-(A), (C)-(A)-(B), (B)-(A)-(C), (A)-(C)-(B), or (C)-(B)-(A) are possible, wherein administration of each is carried out within a few hours to one day of each other.

[0181]

The compound represented by formula (I), or its pharmaceutically acceptable salt can be used in combination with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt, and it can enhance anti-bacterial effect of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt, and/or (C) clofazimine, or its pharmaceutically acceptable salt.

Also, (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt can be used in combination with the compound represented by formula (I), or its pharmaceutically acceptable salt, and it can enhance anti-bacterial effect of the compound represented by formula (I), or its pharmaceutically acceptable salt.

[0182]

The route of administration of the medicament of the present invention can be administered by either oral or parenteral methods and is not particularly limited to them.

[0183]

In the case of oral administration, it can be administered by the usual manner in the form of solid preparations for internal use (e.g., tablets, powders, granules, capsules, pills, films), internal solutions (e.g., suspensions, emulsions, elixirs, syrups, limonade agents, alcoholic agents, fragrance solutions, extracts, decoctions, tinctures), and the like. The tablet may be sugar-coated tablets, film-coated tablets, enteric coated tablets, extended release tablets, troches, sublingual tablets, buccal tablets, chewable tablets or orally disintegrating tablets. The powders and granules may be dry syrups. The capsule may be soft capsule, microcapsules or sustained release capsules.

[0184]

In the case of parenteral administration, any forms of injections, drops, external preparations (e.g., eye drops, nasal drops, ear drops, aerosols, inhalants, lotions, infusions, coating agents, gargles, enemas, ointments, plasters, jellies, creams, patches, cataplasms, external powders, suppositories) which are usually used can be suitably administered. The injection may be emulsions such as O/W, W/O, O/W/O or W/O/W type.

[0185]

Optionally, the effective amounts of the compound used in the medicament of the present invention may be mixed as necessary with various pharmaceutical additives such as excipients, binders, disintegrants, and/or lubricants suitable for the dosage form to give the pharmaceutical composition. Furthermore, the pharmaceutical composition can be used for children, the elderly, serious patients

or surgery, by appropriately changing the effective amount of the compound used in the medicament of the present invention, the dosage form and/or various pharmaceutical additives. The pediatric pharmaceutical composition is preferably administered to patients aged under 12 years old or 15 years old. The pediatric pharmaceutical composition can also be administered to patients less than 4 weeks after birth, 4 weeks to less than 1 year old after birth, 1 year old to less than 7 years old, 7 years old to less than 15 years old, or 15 years old to 18 years old. The pharmaceutical composition for the elderly is preferably administered to patients over 65 years old.

[0186]

The dose of the medicament of the present invention can be appropriately selected on the basis of the clinically used dosage. The mixing ratio of (A) the compound represented by formula (I) and (B), or the mixing ratio of (A) the compound represented by formula (I), (B) and (C) can be appropriately selected depending on the administration subject, administration route, target disease, symptom, combination, and the like. For example, when the subject to be administered is a human, 0.01 to 400 parts by weight of (B) and/or (C) the combination drug may be used per 1 part by weight of (A) the compound represented by formula (I).

[0187]

Generally, pharmaceutical compositions contain the active compound in an effective amount to achieve their intended purpose. In one embodiment, a therapeutically effective amount means an amount effective to prevent or inhibit development or progression of a disease characterized by mycobacterial infection or activity in the subject being treated. Determination of the effective amounts is within the capability of those skilled in the art in light of the description provided herein.

[0188]

In some embodiments, the medicament of the present invention is suitable for the treatment and/or prevention of diseases and disorders characterized by mycobacterial activity or infection. The mycobacteria may be pathogenic or non-pathogenic. The mycobacteria may be Gram positive or Gram negative.

[0189]

In some embodiments, the medicament of the present invention is suitable for the treatment in humans (either or both of immunocompetent and immunocompromised) and animals of tuberculous, lepromatous, and non-tuberculous mycobacteria. Non-limiting examples of these include but not limited to the following species and strains: Tuberculous mycobacteria, for example *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*; *Lepromatous mycobacteria*, for example *M. leprae*, *M. Lepromatosis*; *Non-tuberculous mycobacteria*, for example *M. abscessus*, *M. abcessus complex*, *M. avium*, *M. intracellulare*, *M. avium complex*, *M. kansasii*, *M. malmoense*, *M. xenopi*, *M. malmoense*, *M. flavences*, *M. scrofulaceum*, *M. chelonae*, *M. peregrinum*, *M. haemophilum*, *M. fortuitum*, *M. marinum*, *M. ulcerans*, *M. gordonae*, *M. haemophilum*, *M. mucogenicum*, *M. nonchromogenicum*, *M. terrae*, *M. terrae complex*, *M. asiaticum*, *M. celatum*, *M. shimoidei*, *M. simiae*, *M. smegmatis*, *M. szulgai*, *M. celatum*, *M. conspicuum*, *M. genavense*, *M. immunogenum*, *M. xenopi*.

[0190]

In some embodiments, the medicament of the present invention is suitable for the treatment in humans (both immunocompetent and

immunocompromised) and animals of non-mycobacterial infectious diseases.
[0191]

In some embodiments, the subject is known or suspected to need treatment for one or more maladies related to non-pathogenic mycobacterial strain, *M. smegmatis*, *M. vaccae*, *M. aurum*, or combination thereof.
[0192]

In some embodiments, the subject is known or suspected to need treatment for one or more maladies related to Gram positive bacteria, *S. aureus*, *M. luteus*, or combination thereof.
[0193]

In some embodiments, the subject is known or suspected to need treatment for one or more maladies related to Gram negative bacteria, *P. aeruginosa*, *A. baumanii*, or combination thereof.
[0194]

In some embodiments, the subject is known or suspected to need treatment for one or more maladies related to pathogenic mycobacterial strain, *M. tuberculosis*, *M. bovis*, *M. marinum*, *M. kansasaii*, *H37Rv*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. mungi*, *M. pinnipedii*, *M. leprae*, *M. avium*, *myobacterium tuberculosis complex*, *tuberculosis*, or combination thereof.
[0195]

In some embodiments, the subject is known or suspected to need treatment for one or more maladies related to non-pathogenic mycobacterial strain, *M. smegmatis*, *M. vaccae*, *M. aurum*, *Gram positive bacteria*, *S. aureus*, *M. luteus*, Gram negative bacteria, *P. aeruginosa*, *A. baumanii*, pathogenic mycobacterial strain, *M. tuberculosis*, *M. bovis*, *M. marinum*, *M. kansasaii*, *H37Rv*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. mungi*, *M. pinnipedii*, *M. avium*, myobacterium tuberculosis complex, *tuberculosis*, or combination thereof.
[0196]

In some embodiments, a method is provided, which includes killing or inhibiting the growth of a population of one or more of non-pathogenic mycobacterial strain, *M. smegmatis*, *M. vaccae*, *M. aurum*, Gram positive bacteria, *S. aureus*, *M. luteus*, Gram negative bacteria, *P. aeruginosa*, *A. baumanii*, pathogenic mycobacterial strain, *M. tuberculosis*, *M. bovis*, *M. marinum*, *M. kansasaii*, *H37Rv*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M mungi*, *M. pinnipedii*, *M. avium*, *myobacterium tuberculosis complex*, *tuberculosis*, or combination thereof, by contacting one or more member of said population with the compounds used in the present invention or composition.
[EXAMPLES]
[0197]

The present invention is explained in more detail below by Examples, but the present invention is not limited to them.
[0198]

The compound represented by formula (I) used in the present invention (A) can be prepared by reference to WO2011/057145, WO2017/049321, WO2011/113606, WO2021/050708, the entire contents of each of which are hereby incorporated by reference, the same as if set forth at length.
[0199]

Besides, abbreviations used herein have the following meanings:
Me: methyl

Et: ethyl
Bu: butyl
Ph: phenyl
PPh_3: triphenylphosphine
Ac: acetyl
EtOAc: ethyl acetate
DMF: N, N-dimethylformamide
DMA: N, N-dimethylacetoamide
TFA: trifluoroacetic acid
DMSO: dimethyl sulfoxide
THF: tetrahydrofuran
WSC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium; 3-Oxide, hexafluorophosphate
DCC: N,N'-Dicyclohhexylcarbodiimide
HOBt: hydrxybenzotriazole
Boc: t-butoxycarbonyl
t: tertially
Cbz: benzyloxycarbonyl
dppf: 1,1'-Bis(diphenylphosphino)ferrocene
$Pd_2(dba)_3$: Tris(dibezylideneacetone)dipalladium
$PdCl_2(dppf)$: [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride
$Pd(PPh_3)_4$: Tetrakis(triphenylphosphine) palladium(0)
$PdCl_2(PPh_3)_2$: Bis(triphenylphosphine)palladium chloride
[0200]

NMR analysis of each example was performed by 400 MHz using deuterated dimethyl sulfoxide (d6-DMSO) or deuterochloroform ($CDCl_3$). In the case of indicating NMR data, there are cases in which not all measured peaks are described.

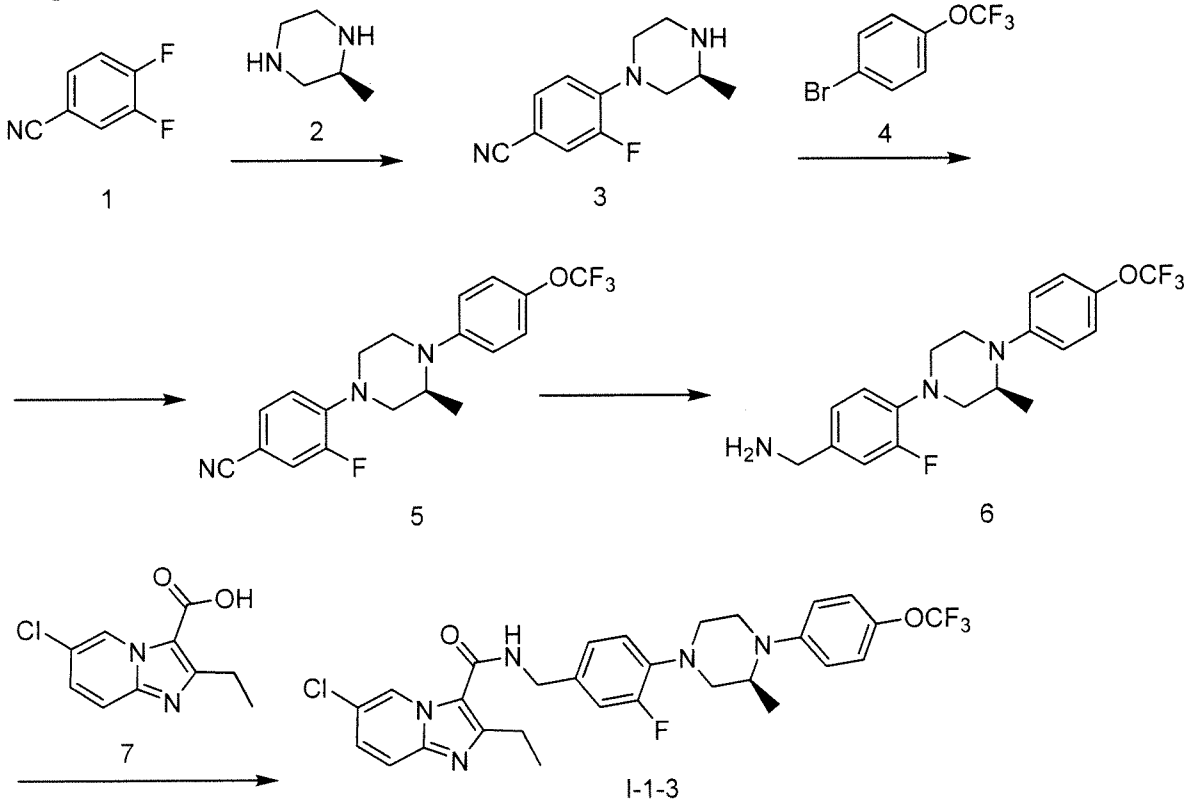
"RT" in the specification means a retention time of LC/MS: liquid chromatography/mass spectrometry, and the measurement conditions are as follows.
(Method A)
UHPLC/MS data of the compounds were measured under the following condition.
Column: ACQUITY UPLC®BEH C18 (1.7μm、i.d.50x2.1mm) (Waters)
Flow rate: 0.8 mL/min
UV detection wavelength: 254nm
Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution.
Gradient: Linear gradient of 5% to 100% solvent [B] for 3.5 minutes was performed, and 100% solvent [B] was maintained for 0.5 minute."

(Method B)
UHPLC/MS data of the compounds were measured under the following condition.
Column: ACQUITY UPLC®BEH C18 (1.7μm、i.d.50x2.1mm) (Waters)
Flow rate: 0.8 mL/min
UV detection wavelength: 254nm
Mobile phase: [A] is 10mM ammonium carbonate-containing aqueous solution, and [B] is acetonitrile.
Gradient: Linear gradient of 5% to 100% solvent [B] for 3.5 minutes was performed,

and 100% solvent [B] was maintained for 0.5 minute.

Hereinafter, MS(m/z) indicates the value observed in the mass spectrometry.

[Example 1]
[0201]
Preparation of Compound I-1-3



Step 1

To a solution of Compound 1 (1 g, 7.19mmol) in DMA (5mL) were added K_2CO_3 (1.49g, 10.78mmol) and Compound 2 (0.792g, 7.91mmol), and the solution was stirred at 100°C for 4.5 hours. After the reaction solution was poured into water, the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried with sodium sulfate and filtered. After the organic layer was concentrated under reduced pressure, the residue was washed with hexanes to yield Compound 3 (1.01g, yield: 64%) as a solid.
1H-NMR (CDCl3) δ: 7.38-7.33 (1H, m), 7.27 (1H, dd, J = 12.9, 1.9 Hz), 6.91 (1H, t, J = 8.2 Hz), 3.50-3.41 (2H, m), 3.12-2.98 (3H, m), 2.88-2.77 (1H, m), 2.52-2.44 (1H, m), 1.12 (3H, d, J = 6.0 Hz).

Step.2

To a solution of Compound 3 (510mg, 2.33mmol) in toluene (5.0mL) were added 1-bromo-4-(trifluoromethyl)benzene 4 (576mg, 2.56mmol), $Pd(OAc)_2$ (52.2mg, 0.233mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (217mg, 0.465mmol) and sodium t-butoxide (447mg, 4.65mmol), the solution was stirred at 100°C for 1 hour. To the reaction solution were added water and ethyl acetate. The oranic layer was washed with water and brine, dried with anhydrous

sodium sulfate and filtered. The organic layer was concentrated under reduced pressure, the residue was purified by silica gel chromatography (hexanes / ethyl acetate) to yield Compound 5 (543mg, yield: 64%) as a yellow solid.
1H-NMR (CDCl3) δ: 7.39 (1H, dd, J = 8.4, 1.9 Hz), 7.30 (1H, dd, J = 12.5, 1.9 Hz), 7.14 (2H, d, J = 8.3 Hz), 6.95 (1H, t, J = 9.2 Hz), 6.92 (2H, d, J = 8.3 Hz), 3.99-3.90 (1H, m), 3.55-3.50 (1H, m), 3.42-3.40 (1H, m), 3.35-3.26 (3H, m), 3.20-3.11 (1H, m), 1.16 (3H, d, J = 6.4 Hz)

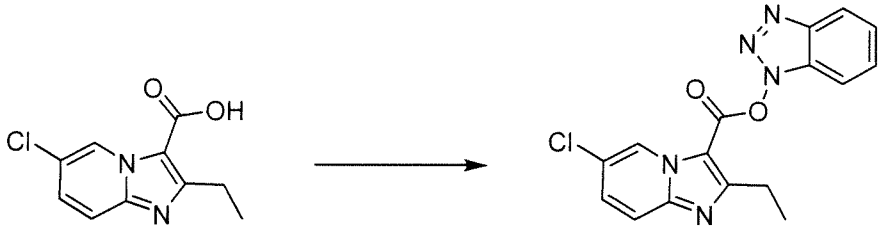
Step.3

To a solution of Compound 5 (546 mg, 1.50mmol) in MeOH (15mL) were added 5% Pd-C (320g, 0.150mmol) and Conc.HCl (1.5mL), and the solution was stirred at room temperature for 5 hours under hydrogen atomosphere. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure. To the reaction mixture were added aqueous NaOH solution and ethyl acetate. The oranic layer was washed with water and brine, dried with anhydrous sodium sulfate and filtered. The organic layer was concentrated under reduced pressure to yield Compound 6 (440mg, yield: 80%) as a yellow solid.
1H-NMR (CDCl3) δ: 7.16-7.10 (2H, m), 7.07-7.00 (2H, m), 6.98-6.88 (3H, m), 3.99-3.91 (1H, m), 3.86-3.80 (2H, m), 3.40-3.21 (4H, m), 3.17-3.10 (1H, m), 3.05-2.99 (1H, m), 1.19 (3H, d, J = 6.4 Hz).

Step.4

To a solution of Compound 6 (80mg, 0.209mmol) in acetonitrile (2.0mL) were added Compound 7 (52mg, 0.230mmol), triethylamine (0.087mL, 0.626mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine (48.6mg, 0.313mmol) and HOBt (28.2mg, 0.209mmol), the solution was stirred at 80°C for 1 hour. To the reaction solution was added water, and extracted with ethyl acetate. The oranic layer was washed with brine, dried with anhydrous sodium sulfate and filtered. The organic layer was concentrated under reduced pressure, the residue was purified by silica gel chromatography ($CHCl_3$ / methanol) to yield Compound I-1-3 (55mg, yield: 45%) as a white solid.
LC/MS Method A: m/z=590.2. [M+H]+, retention time: 3.0 min

[Example 2]
[0202]
Preparation of Compound 8

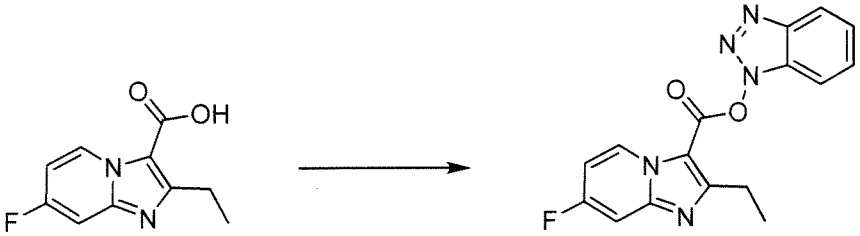


7 8

To a solution of Compound 7 (20g, 89mmol) in acetonitrile (200mL) were added N-methylmorpholine (19.6mL, 178mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (18.8g, 98mmol) and HOBt (18.01g, 98mmol), the solution was stirred at room temperature

for over 15 hours. To the reaction solution was added water, and the reaction mixture was filtered. The residue was washed with water and dried under reduced pressure to yield Compound 8 (19.4g, yield: 64%) as a solid.
1H-NMR (CDCl3) δ: 9.26 (1H, d, J = 1.3 Hz), 8.14 (1H, d, J = 8.4 Hz), 7.74 (1H, d, J = 9.4 Hz), 7.62-7.44 (4H, m), 3.37 (2H, q, J = 7.5 Hz), 1.53 (3H, t, J = 7.5 Hz).

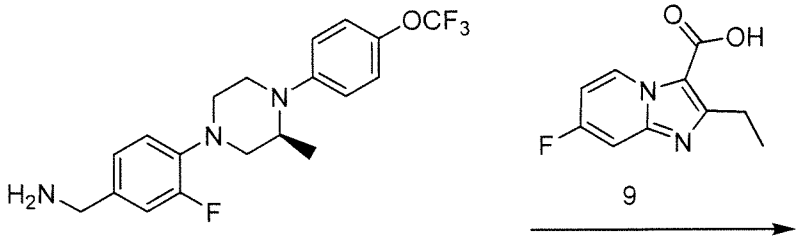
[Example 3]
[0203]
Preparation of Compound 10



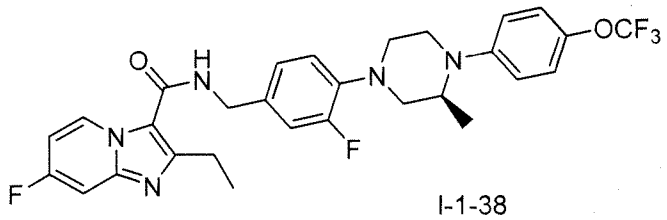
9 10

To a solution of Compound 9 (4.9g, 23.7mmol) in acetonitrile (99mL) were added N-methylmorpholine (2.86mL, 26mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (4.04g, 26mmol) and HOBt (3.2g, 23.7mmol), the solution was stirred at room temperature for over 22 hours. To the reaction solution was added water, and the reaction mixture was filtered. The residue was washed with water and dried under reduced pressure to yield Compound 10 (5.09g, yield: 66%) as a white solid.
1H-NMR (CDCl3) δ: 9.18 (1H, dd, J = 7.5, 5.4 Hz), 8.14 (1H, dt, J = 8.4, 0.9 Hz), 7.59 (1H, dd, J = 16.1, 8.0 Hz), 7.54-7.40 (3H, m), 6.98 (1H, td, J = 7.5, 2.7 Hz), 3.35 (2H, q, J = 7.5 Hz), 1.52 (3H, t, J = 7.5 Hz).

[Example 4]
[0204]
Preparation of Compound I-1-38



6 9

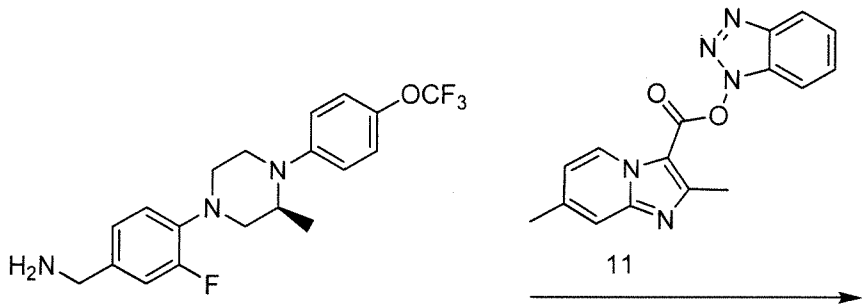


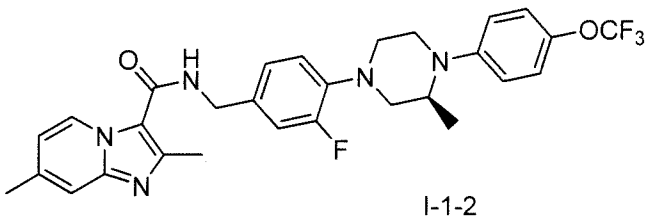
I-1-38

To a solution of Compound 6 (70mg, 0.183mmol) in acetonitrile

(1.0mL) were added Compound 9 (41.8mg, 0.201mmol), triethylamine (0.051mL, 0.365mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (52.5mg, 0.274mmol) and HOBt (24.7mg, 0.183mmol), the solution was stirred at 50°C for 1 hour. To the reaction solution was added saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The oranic layer was washed with water and brine, and dried with anhydrous magnesium sulfate. The organic layer was filtered and concentrated under reduced pressure, the residue was purified by silica gel chromatography (hexane /ethyl acetate) to yield Compound I-1-38 (78mg, yield: 75%) as a white solid.
1H-NMR (CDCl3) δ: 9.44 (1H, t, J = 5.6 Hz), 7.22 (1H, s), 7.14-7.07 (4H, m), 6.97-6.92 (3H, m), 6.80 (1H, t, J = 7.3 Hz), 6.06 (1H, s), 4.63 (2H, d, J = 3.8 Hz), 3.95 (1H, d, J = 2.0 Hz), 3.38-3.27 (4H, m), 3.17-3.14 (1H, m), 3.06-2.95 (3H, m), 1.44-1.40 (3H, m), 1.19 (3H, d, J = 4.5 Hz).
LC/MS Method B: m/z=574.25 [M+H]+, retention time: 2.99 min

[Example 5]
[0205]
Preparation of Compound I-1-2

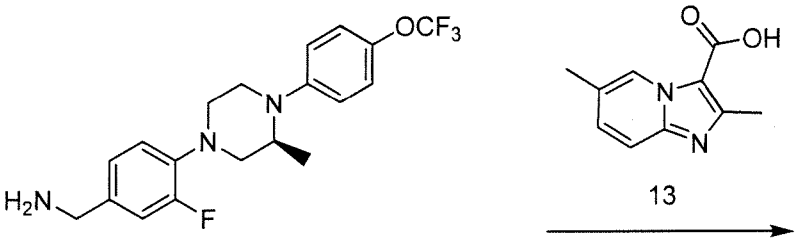


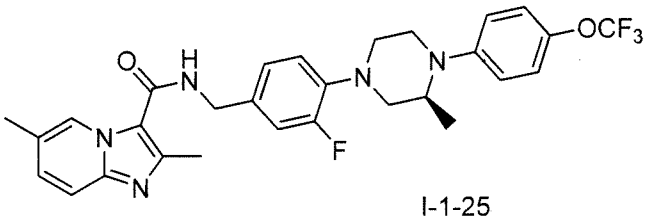


I-1-2

To a solution of Compound 6 (1.5g, 3.91mmol) in dichloromethane (1.0mL) were added Compound 11 (1.32g, 4.3mmol) and triethylamine (0.814mL, 5.87mmol), the solution was stirred at room temperature for 15 hours. The reaction solution was purified by aminosilica gel and silica gel chromatography ($CHCl_3$ /methanol) to yield Compound I-1-2 (1.76g, yield: 81%) as a white solid.
LC/MS Method A: m/z=574.25 [M+H]+, retention time: 2.99 min

[Example 6]
[0206]
Preparation of Compound I-1-25

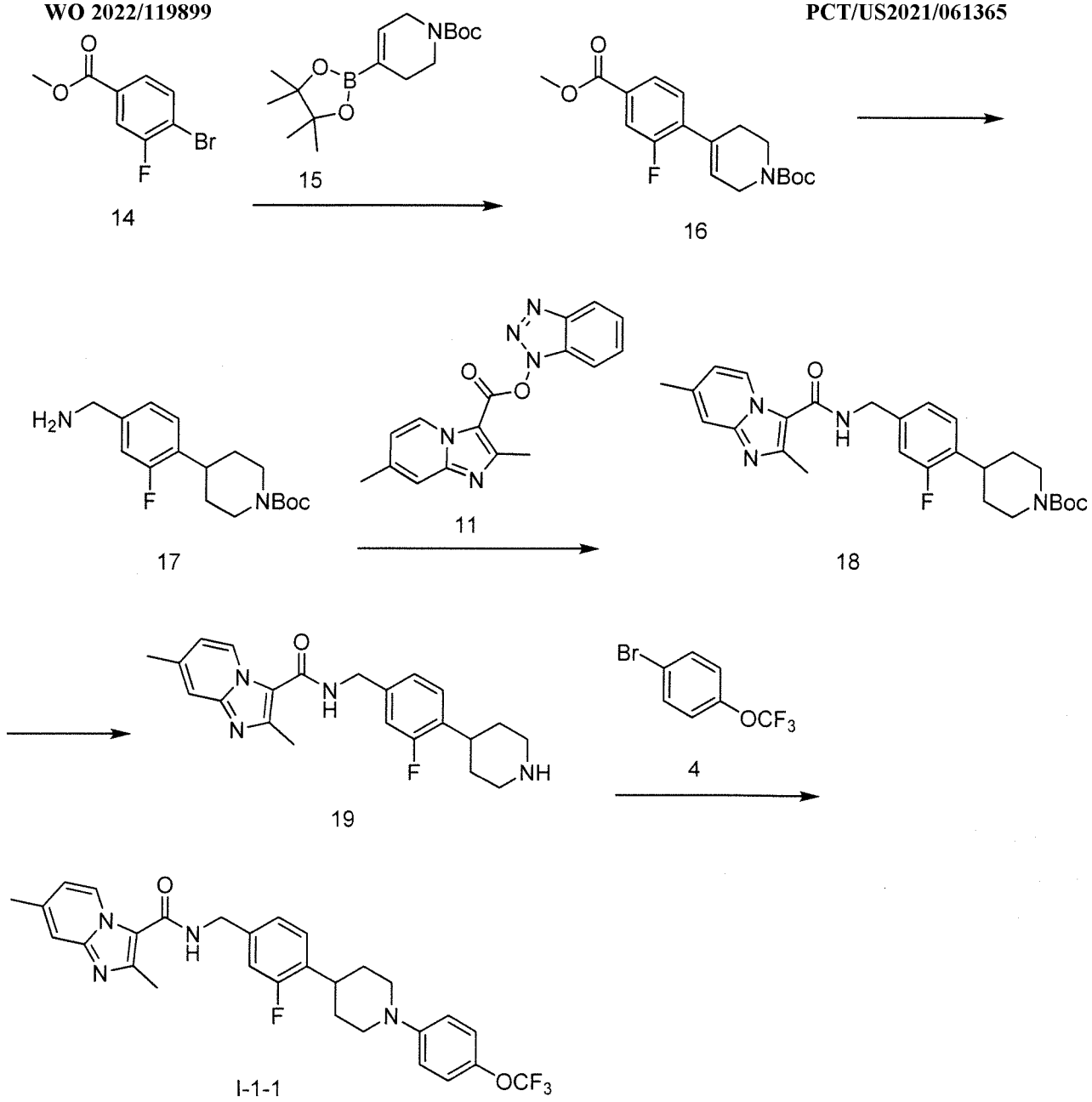




I-1-25

To a solution of Compound 6 (50mg, 0.130mmol) in dichloromethane (0.8mL) were added Compound 13 (29.8g, 0.156mmol), triethylamine (0.054mL, 0.391mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine (30.4mg, 0.196mmol) and HOBt (8.8mg, 0.065mmol), the solution was stirred at room temperature for 15 hours. To the reaction solution was added saturated aqueous NaHCO3 solution, and extracted with dichloromethane. The oranic layer was washed with water and brine, and dried with anhydrous magnesium sulfate. The organic layer was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography ($CHCl_3$ /methanol) to yield Compound I-1-25 (47mg, yield: 74.5%) as a white solid.
LC/MS Method A: m/z=556.3 [M+H]+, retention time: 2.73 min

[Example 7]
[0207]
Preparation of Compound I-1-1



Step 1

To a solution of Compound 14 (5.05 g, 21.7 mmol) in 1,4-dioxane (76mL) were added compound 15 (7.37 g, 23.8mmol), $PdCl_2(PPh_3)_2$ (1.52 g, 2.17 mmol) and 2M Na_2CO_3 aqueous solution (32.5 ml, 65 mmol). The reaction mixture was stirred at 100 °C for 1.5 hours. After the reaction solution was poured into water, the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes-EtOAc) to yield compound 16 (6.59 g, 19.7 mmol, 91%) as a white solid.

1H-NMR (400 MHz, CDCl3) δ: 7.78 (dd, 1H, J = 7.8, 1.3 Hz), 7.70 (dd, 1H, 11.6, 1.3 Hz), 6.04 (m, 1H), 4.15-4.05 (m, 2H), 3.92 (s, 3H), 3.62 (t, 2H, 5.4), 2.56-2.46 (m, 2H), 1.48 (s, 9H)

Step 2

To a solution of compound 16 (6.49 g, 19.4 mmol) in THF (100 ml), purged with inert atmosphere, was added 10% $Pd(OH)_2/C$ (5.44 g, 1.94 mmol). The reaction mixture was charged with hydrogen gas (1 atm). The resulting suspension was vigorously stirred for 6.5 hours. The reaction mixture was purged with an inert atmosphere, filtered through a celite pad. The filter cake was washed with EtOAc, and the filtrate was concentrated under reduce pressure to yield the crude material as an oil. This crude material was used for the next reaction without further purification. The crude material was dissolved in THF (100 ml) and was added to a suspension of $LiAlH_4$ (1.46 g, 38.5 mmol) in THF (100ml) at 0 °C. After stirring for 5 min, to the reaction mixture was added sodium sulfate decahydrate (24.83 g, 77 mmol) and the reaction was stirred for 3 hours. The reaction mixture was filtered through a celite pad. The filter cake was washed with EtOAc, and the filtrate was concentrated under reduce pressure to yield the crude product as an oil. This crude material was used in the next reaction without further purification. To a solution of the crude material in dichloromethane (100 ml) were added Et_3N (7.93 ml, 57.2 mmol) and methansulfonyl chloride (3.28 g, 28.6 mmol) at -78 °C. To the reaction solution was added H_2O, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield the crude material as an oil. This crude material was used in the next reaction without further purification. To a solution of the crude material in DMF (60 ml) was added NaN_3 (2.47 g, 37.9 mmol) and the mixture was stirred at 80 °C for 1 hour. To the reaction solution was added H_2O, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield the crude material as an oil. This crude product was used to the next reaction without further purification. To a solution of the crude product in THF (50 ml) were added PPh_3 (5.55 g, 21.2 mmol) and H_2O (3.18 ml, 176 mmol) and the mixture was stirred at reflux for 2 hours. The mixture was then concentrated under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc-$CHCl_3$-MeOH) to yield compound 17 (4.11 g, 13.3 mmol, 69% for 5 steps) as a white solid.
1H-NMR (400 MHz, CDCl3) δ: 7.15 (t, 1H, J = 7.7 Hz), 7.04 (d, 1H, J = 7.9 Hz), 7.00 (d, 1H, J = 11.3 Hz), 4,24 (s, 2H), 3.84 (s, 2H), 2.98-2.89 (m, 1H), 2.84-2.70 (m, 2H), 1.83-1.75 (m, 2H), 1.68-1.55 (4H, m), 1.48 (s, 9H)
LC/MS Method: A, LC-MS: m/z=253. [M+H]+, retention time: 1.67min

Step 3

To a solution of compound 17 (1.84 g, 5.97 mmol) in dichloromethane (20 ml) were added compound 11 (2.02 g, 6.56 mmol) and Et_3N (1.24 ml, 8.95 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced pressure and the residue was purified by silica gel chromatography ($CHCl_3$ /MeOH) to yield compound 18 (2.83 g, 5.89 mmol, 99%) as a white solid.
LC/MS Method: A, LC-MS: m/z=481. [M+H]+, retention time: 2.17 min

Step 4

To a solution of compound 18 (2.44 g, 5.08 mmol) in dichloromethane (20 ml) was added TFA (3.91 ml, 50.8 mmol) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced

pressure and the residue was purified by amino silica gel chromatography ($CHCl_3$ /MeOH) to yield compound 19 (1.83 g, 4.81 mmol, 95%) as a off-white amorphous.
LC/MS Method: A, LC-MS: m/z=381. [M+H]+, retention time: 1.00 min

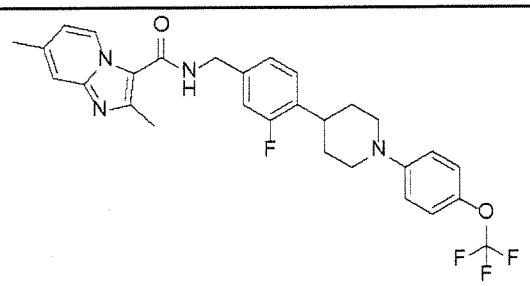
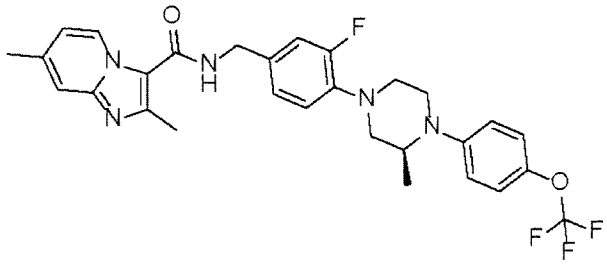
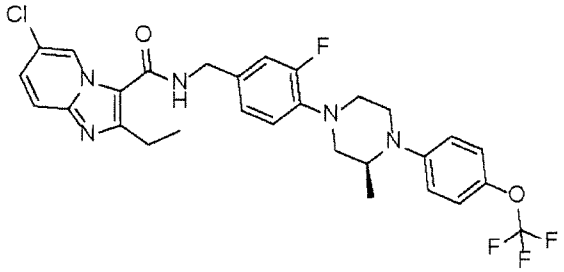
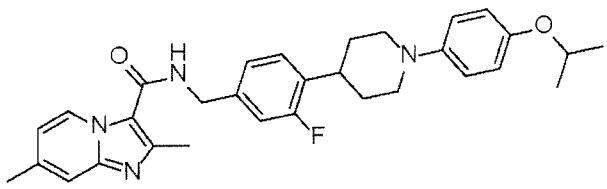
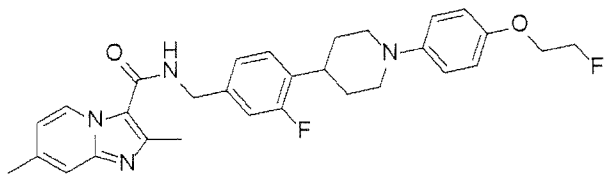
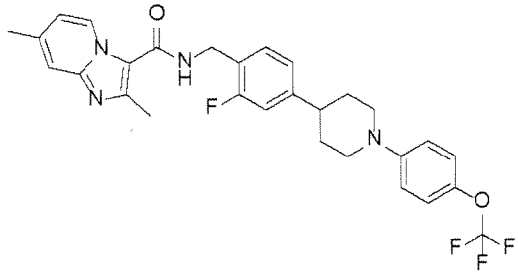
Step 5

To a solution of compound 19 (100 mg, 0.263 mmol) in THF were added compound 4 (95 mg, 0.394 mmol), $Pd_2(dba)_3$ (24.1 mg, 0.0026 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (49.1mg, 0.105 mmol) and NaOtBu (0.789 mmol), and then the reaction was stirred at 60 °C for 1 hour. To the reaction solution was added H_2O, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes /EtOAc) to yield compound I-1-1 (81.7 mg, 0.151 mmol, 57.5%)
1H-NMR (400 MHz, CDCl3) δ: 9.32 (d, 1H, J = 7.5 Hz), 7.33 (s, 1H), 7.28-7.22 (m, 1H), 7.15-7.04 (m, 4H), 6.94 (d, 2H, J = 7.9 Hz), 6.77 (d, 1H, J = 6.5 Hz), 6.06 (s, 1H), 4.67 (d, 2H, J = 5.3 Hz), 3.80-3.72 (m, 2H), 3.05- 2.95 (m, 1H), 2.90-2.80 (m, 2H), 2.69 (s, 3H), 2.43 (s, 3H), 1.95-1.83 (m, 4H)
LC/MS Method: A, LC-MS: m/z=541. [M+H]+, retention time: 2.42 min

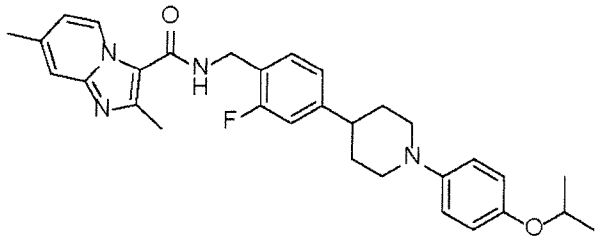
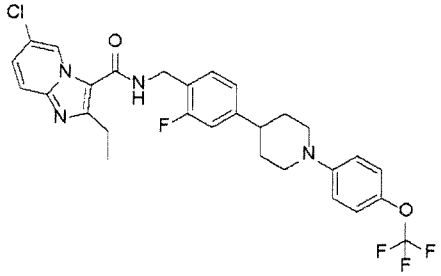
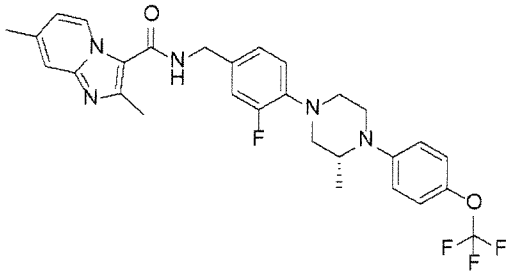
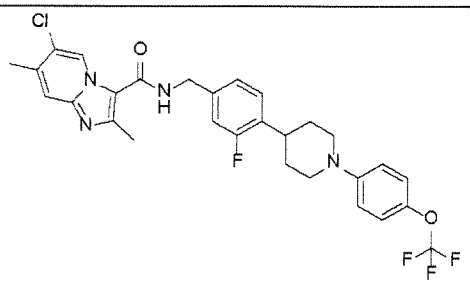
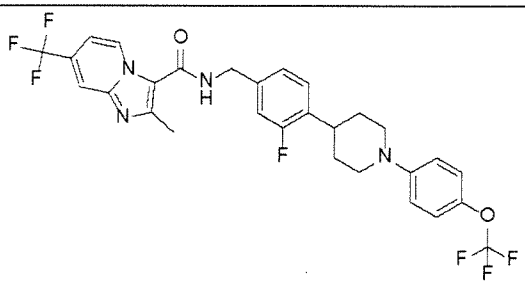
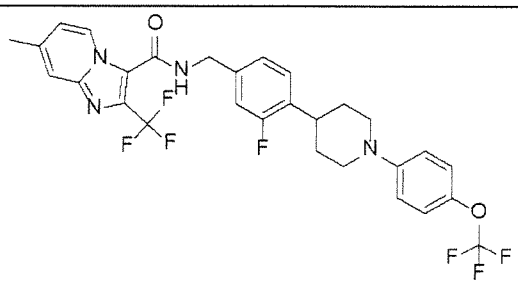
[0208]

The following Compounds were obtained in accordance with the general synthetic methods and Examples. The chemical structures and the physical properties(LC/MS data) of Compounds are described below.

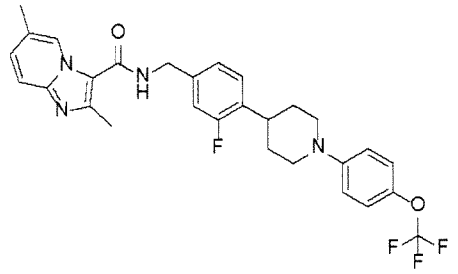
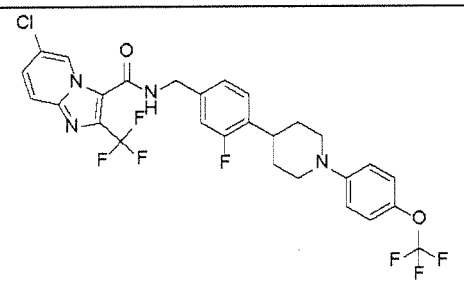
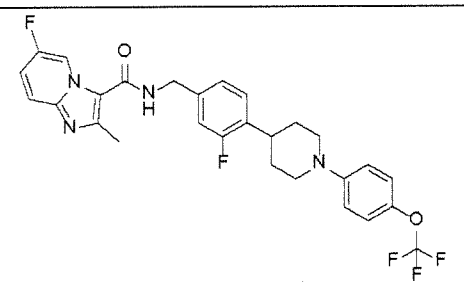
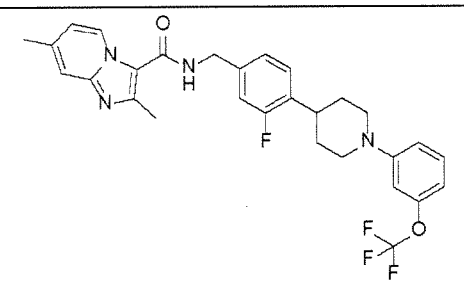
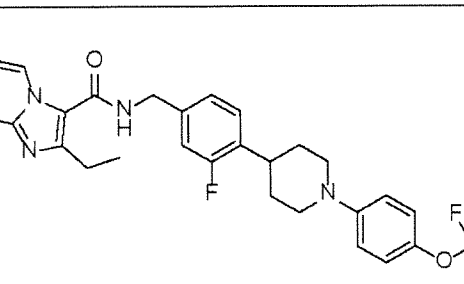
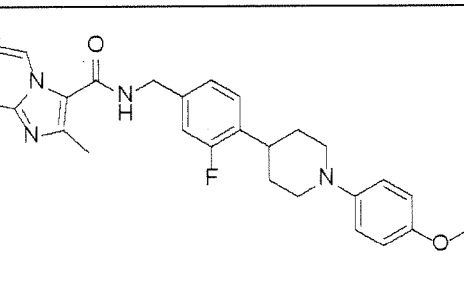
[0209]
[Table 1]

No.	Structure	LCMS method	RT	MS (M+H)
I-1-1		A	2.42	541.2
I-1-2		A	2.52	556.3
I-1-3		A	3	590.2
I-1-4		A	1.8	515.3
I-1-5		A	1.57	519.2
I-1-8		A	2.57	541.2

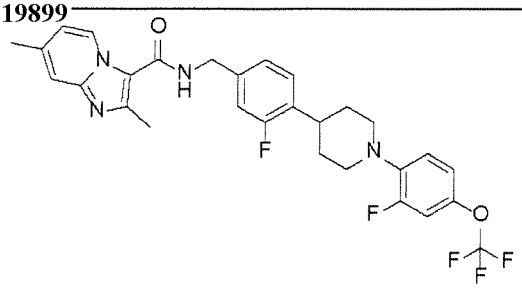
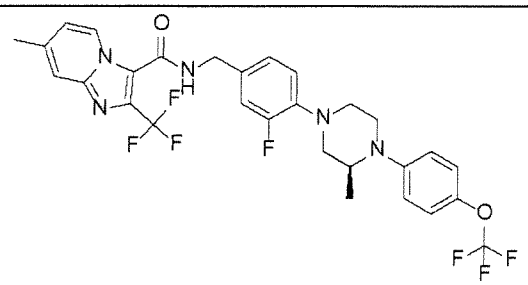
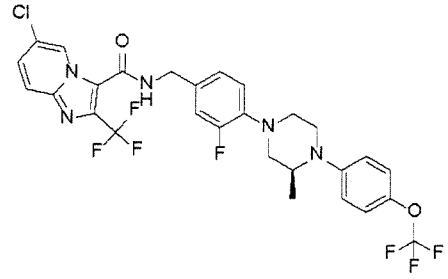
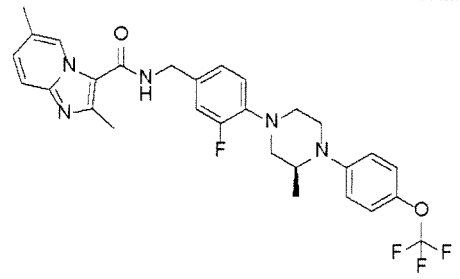
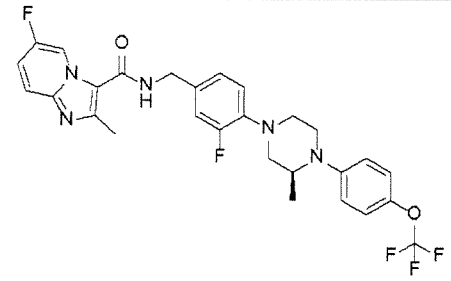
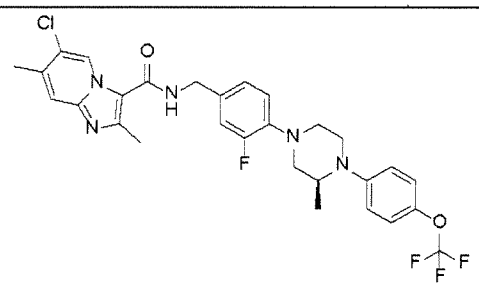
[0210]
[Table 2]

I-1-9		A	1.75	515.25
I-1-10		A	2.98	575.2
I-1-12		A	2.56	556.2
I-1-13		A	3.02	575.2
I-1-14		A	3.11	595.2
I-1-15		A	3.07	595.2

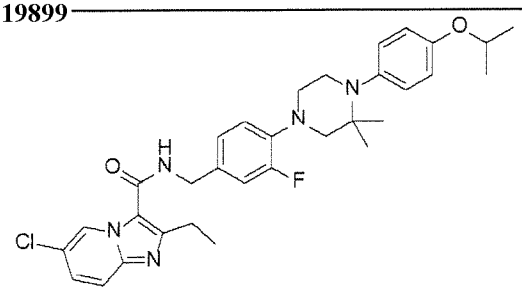
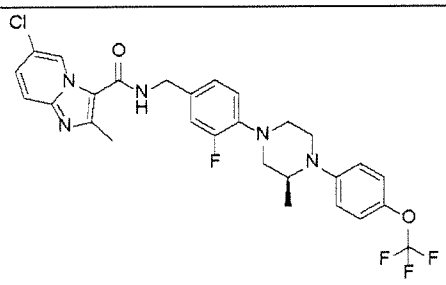
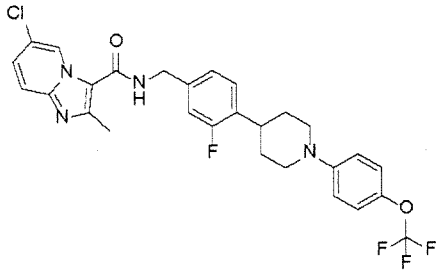
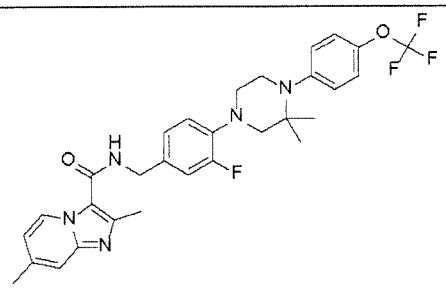
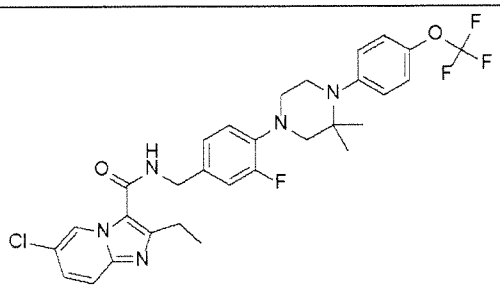
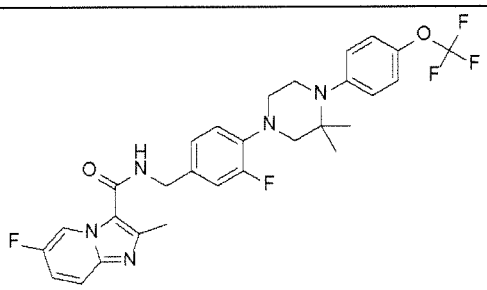
[0211]
[Table 3]

I-1-16		A	2.62	541.3
I-1-17		A	3.21	615.2
I-1-18		A	2.9	545.2
I-1-19		A	2.68	541.2
I-1-20		A	3.12	575.2
I-1-21		A	1.88	555.3

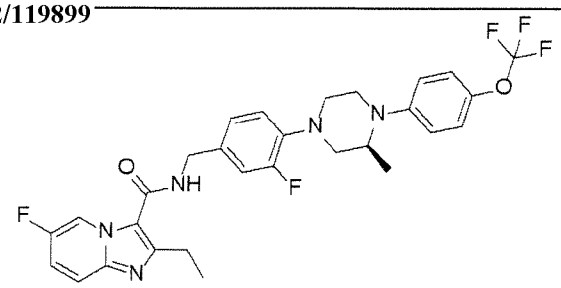
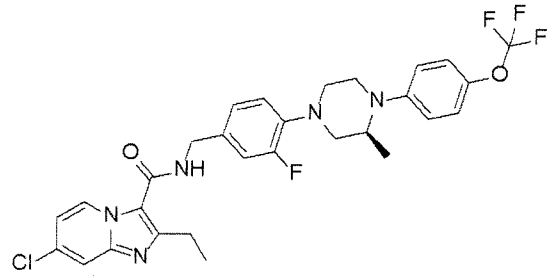
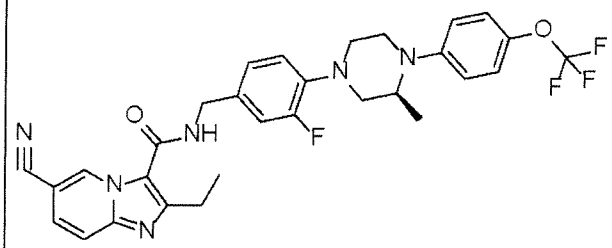
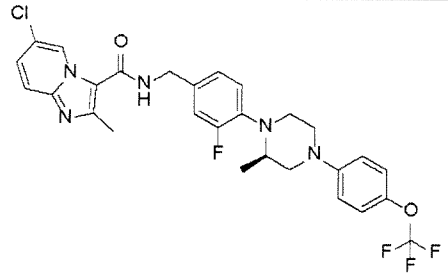
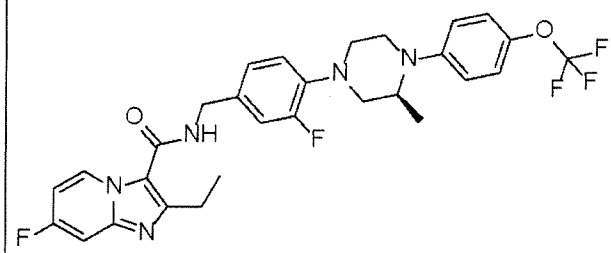
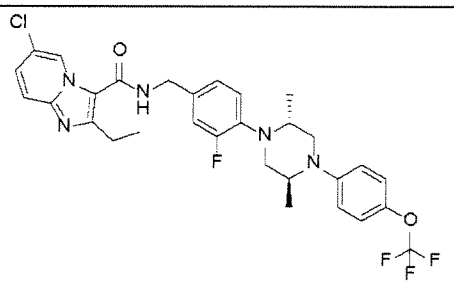
[0212]
[Table 4]

I-1-22		A	2.76	559.3
I-1-23		A	3.09	610.2
I-1-24		A	3.2	630.2
I-1-25		A	2.73	556.3
I-1-26		A	2.78	560.2
I-1-27		A	3.09	590.2

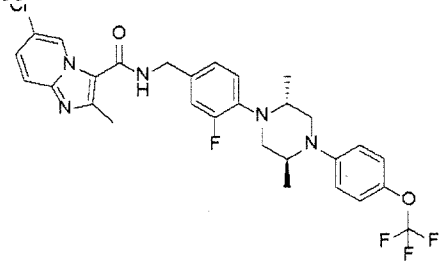
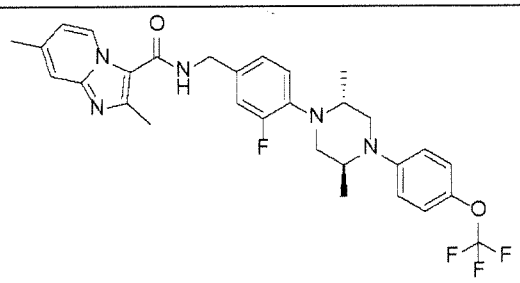
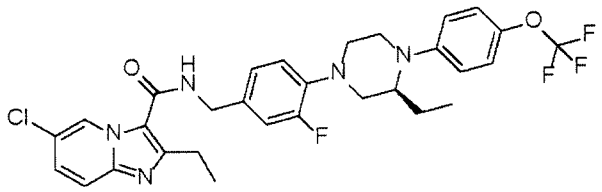
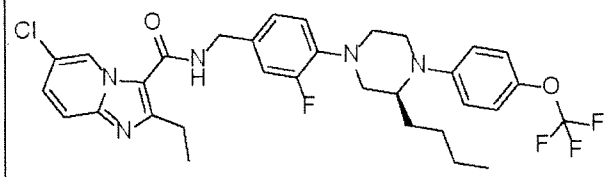
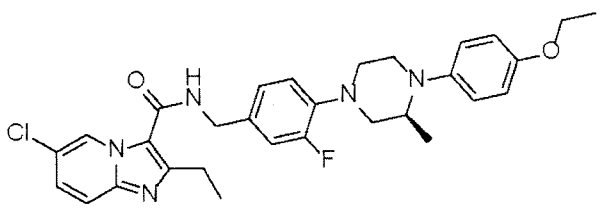
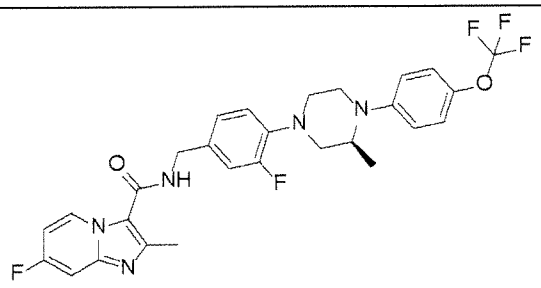
[0213]
[Table 5]

I-1-28		B	3.26	578.3
I-1-29		A	3.19	576.2
I-1-30		A	3.14	560.25
I-1-31		B	2.95	570.25
I-1-32		B	3.3	604.2
I-1-33		B	3.06	574.25

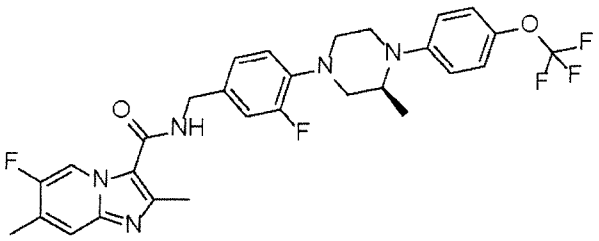
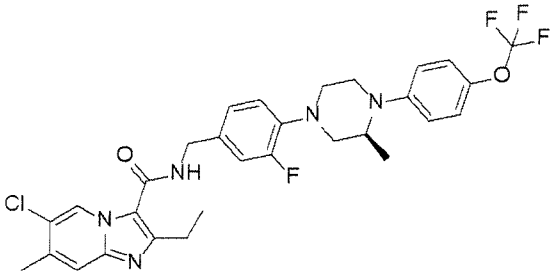
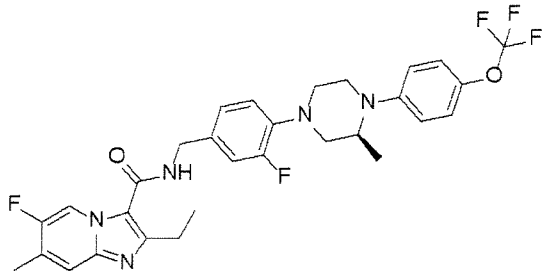
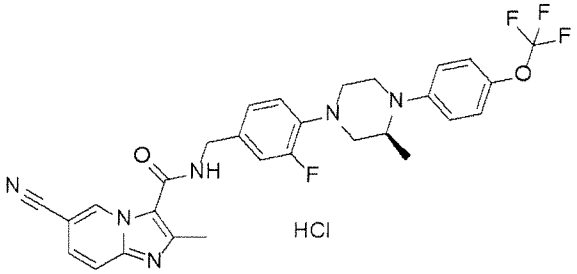
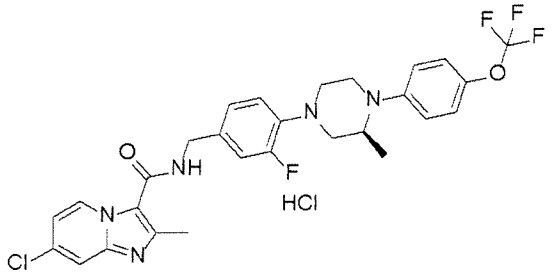
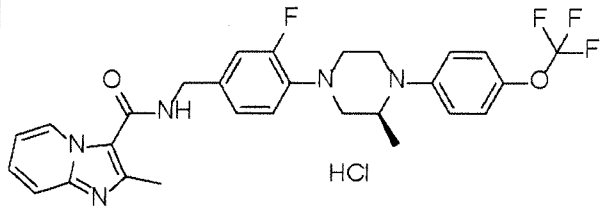
[0214]
[Table 6]

I-1-34		A	2.77	574.28
I-1-35		A	2.91	590.2
I-1-36		A	2.95	581.25
I-1-37		A	3.24	576.2
I-1-38		B	2.99	574.25
I-1-39		A	3.65	604.2

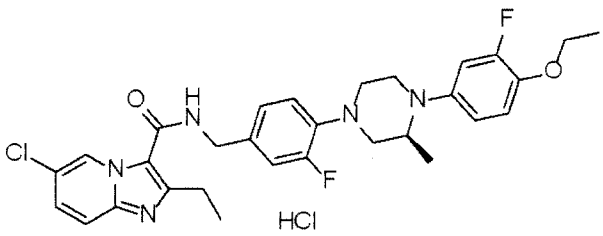
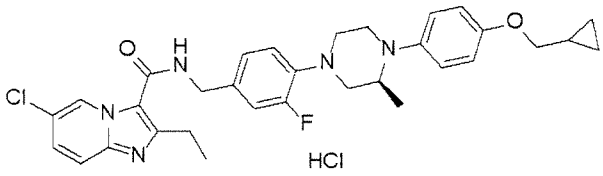
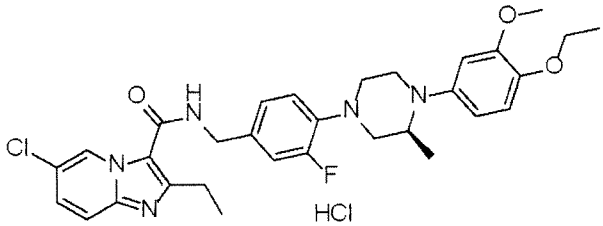
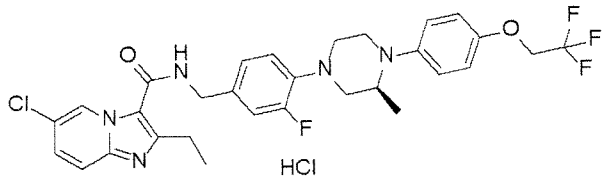
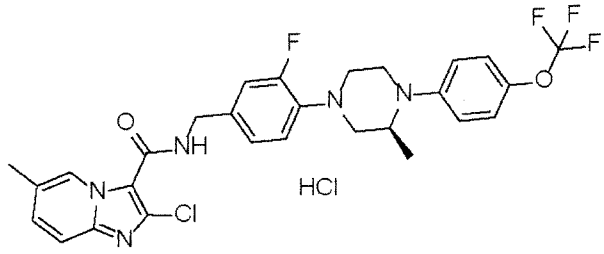
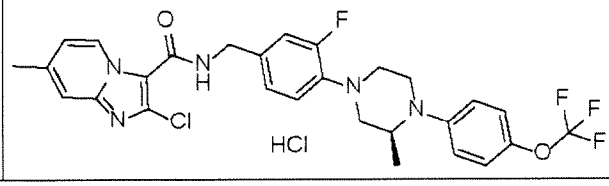
[0215]
[Table 7]

I-1-40		A	3.36	590.2
I-1-41		A	3.32	570.2
I-1-42		A	3.09	604.2
I-1-43		A	3.36	632.2
I-1-44		A	1.75	550.2
I-1-46		A	2.42	560.25

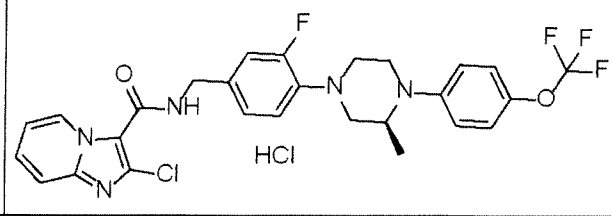
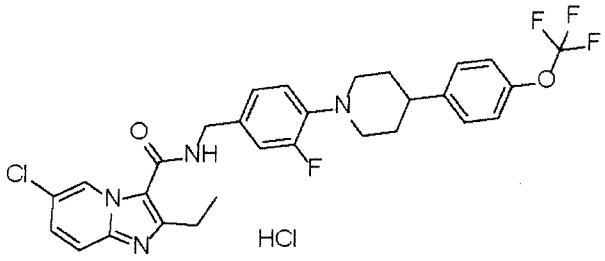
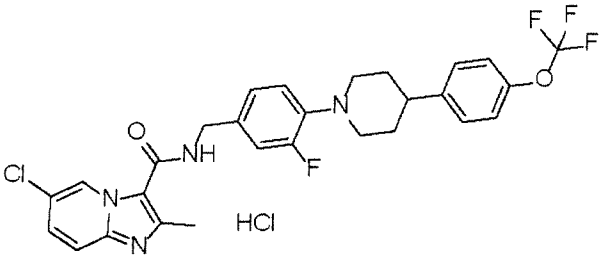
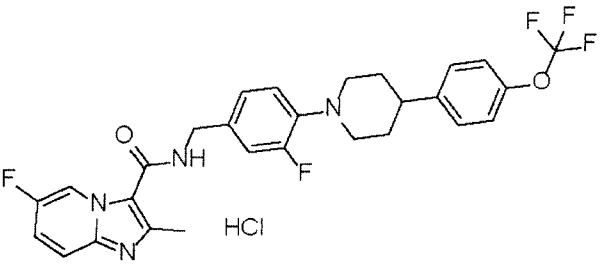
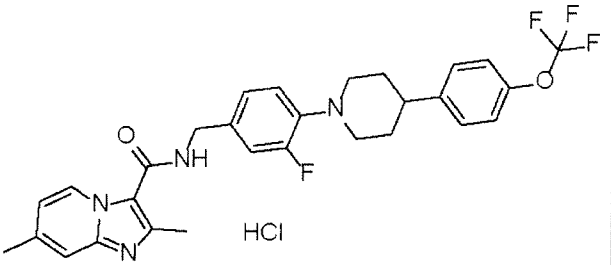
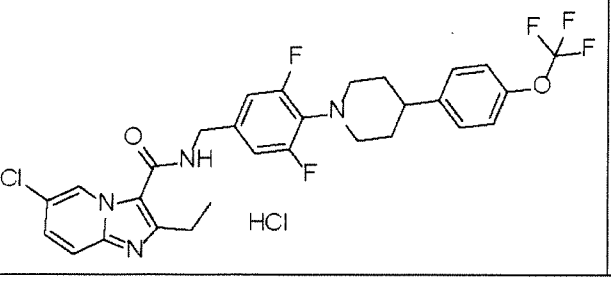
[0216]
[Table 8]

I-1-47		A	2.41	574.25
I-1-48		A	2.74	604.2
I-1-49		A	2.5	588.25
I-1-50		A	2.78	567.2
I-1-51		B	3.27	610.15
I-1-52		B	2.855	542.2

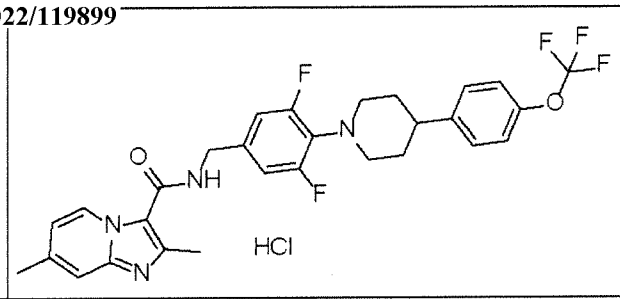
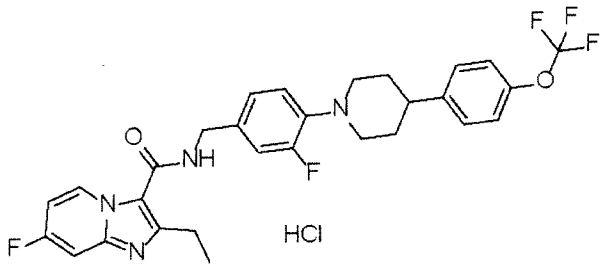
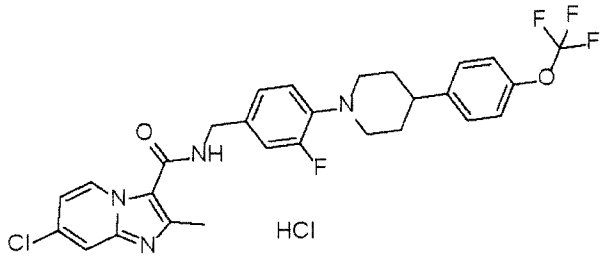
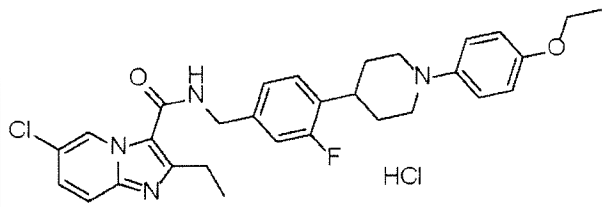
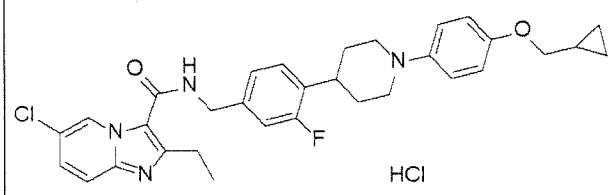
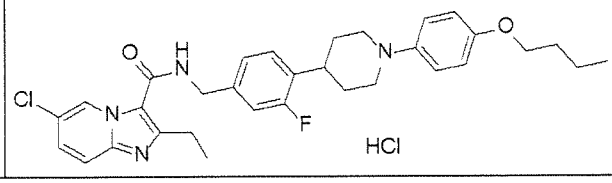
[0217]
[Table 9]

I-1-53		A	2.371	568.3
I-1-54		A	1.898	576.3
I-1-55		A	1.678	580.3
I-1-56		A	2.159	604.2
I-1-57		A	3.23	576
I-1-58		A	3.2	576

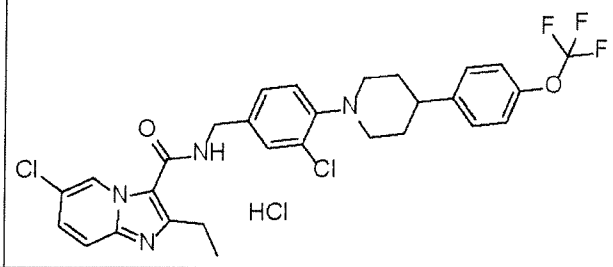
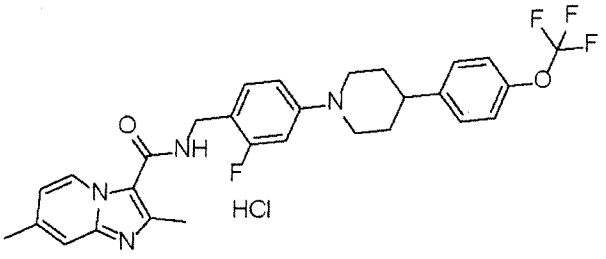
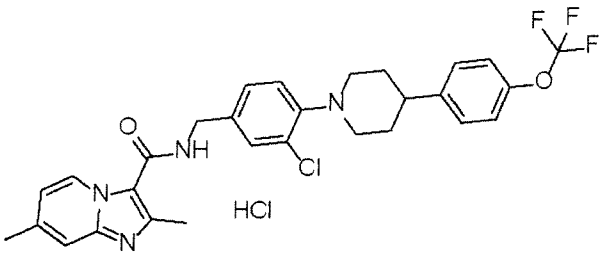
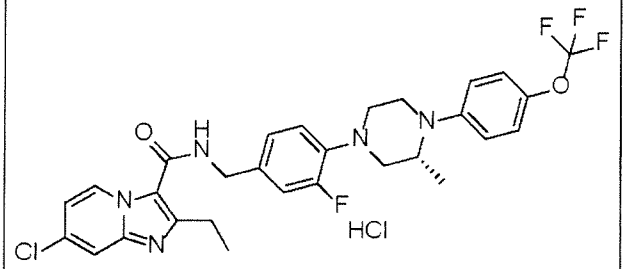
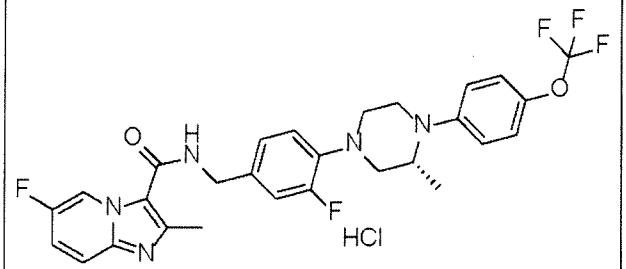
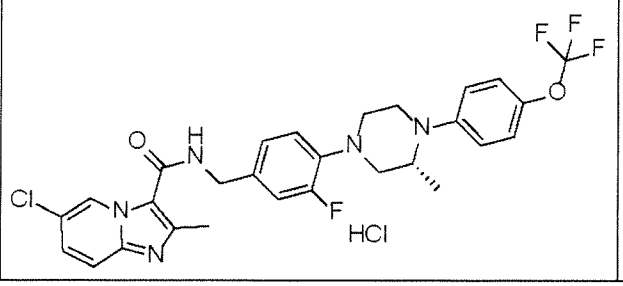
[0218]
[Table 10]

I-1-59		A	3.09	562
I-1-62		A	2.931	575.2
I-1-63		A	2.825	561.1
I-1-64		A	2.574	545.2
I-1-65		A	2.174	541.3
I-1-66		A	3.19	593.2

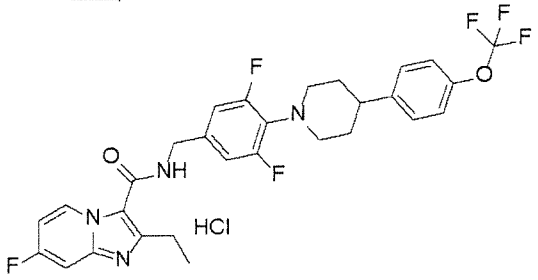
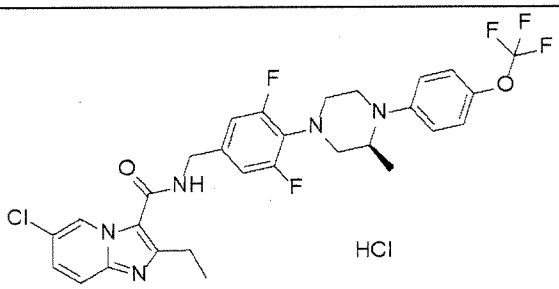
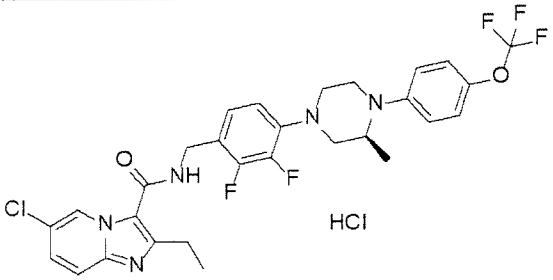
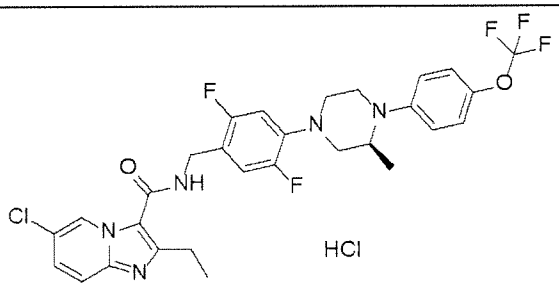
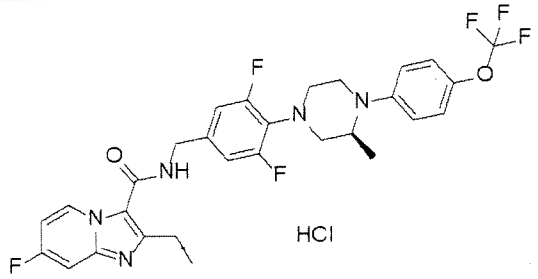
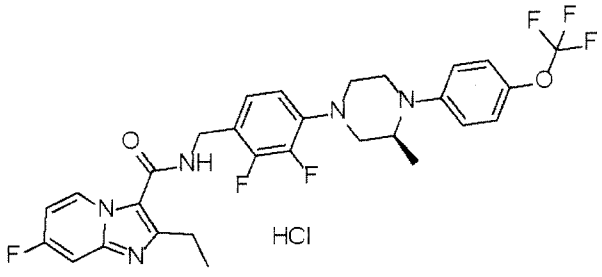
[0219]
[Table 11]

I-1-67		A	2.32	559.2
I-1-68		A	2.55	559.2
I-1-69		A	2.743	561.2
I-1-73		A	1.676	535.3
I-1-75		A	1.809	561.3
I-1-78		A	1.976	563.3

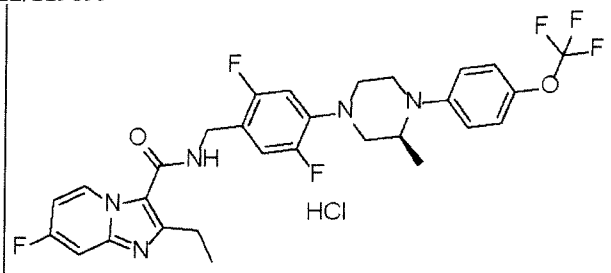
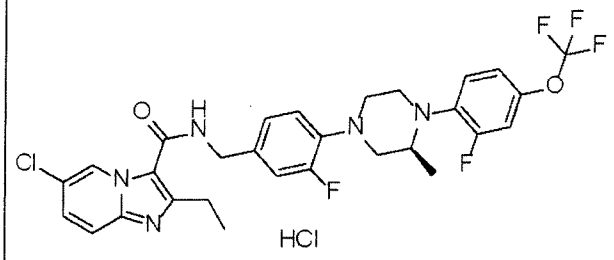
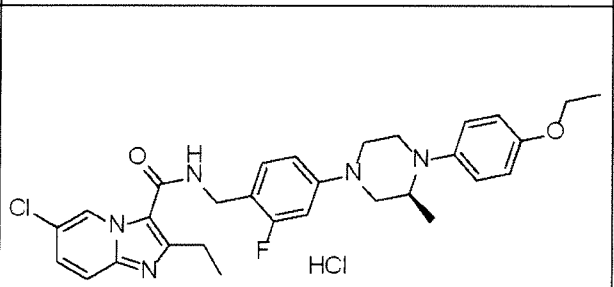
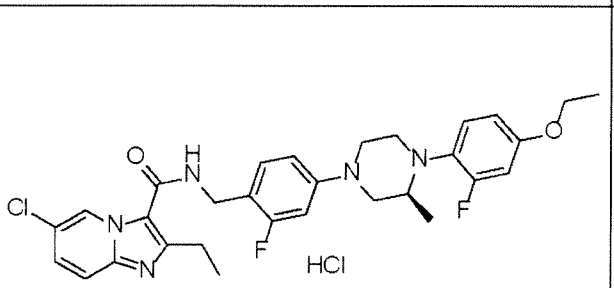
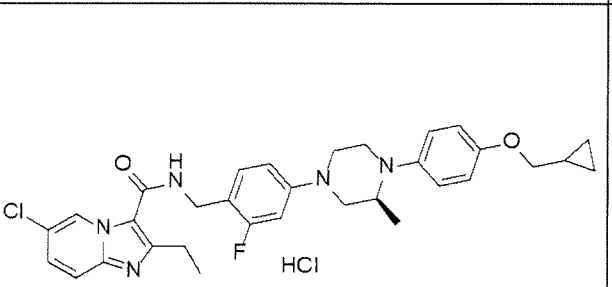
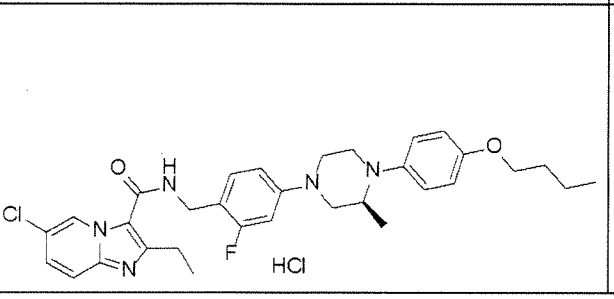
[0220]
[Table 12]

I-1-80		A	3.208	591.1
I-1-81		A	2.245	541.1
I-1-82		A	2.418	557.1
I-1-83		A	2.887	590.1
I-1-84		A	2.604	560.2
I-1-85		A	2.852	576.2

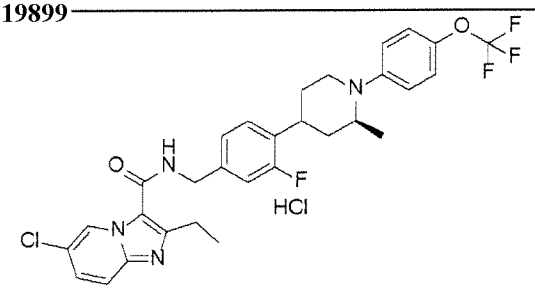
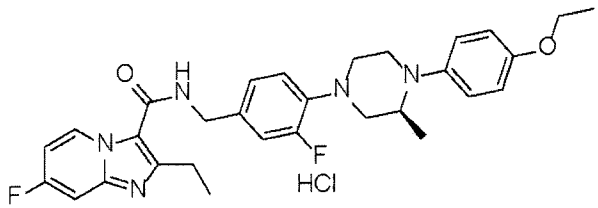
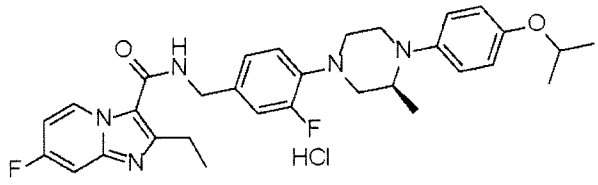
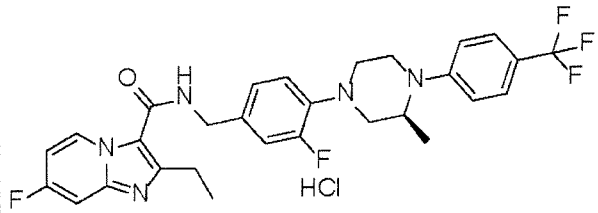
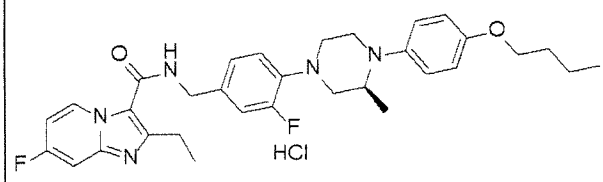
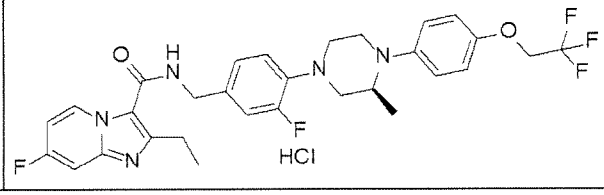
[0221]
[Table 13]

I-1-88		A	2.819	577.2
I-1-92		A	3.113	608.1
I-1-93		A	3.041	608.1
I-1-94		A	3.048	608.1
I-1-95		A	2.741	592.2
I-1-96		A	2.677	592.2

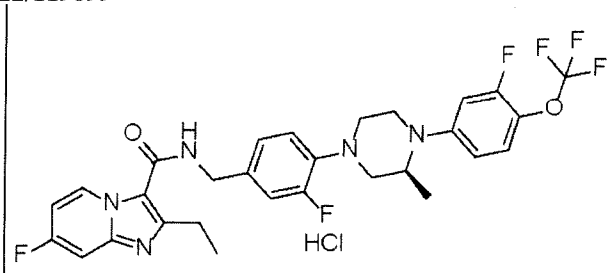
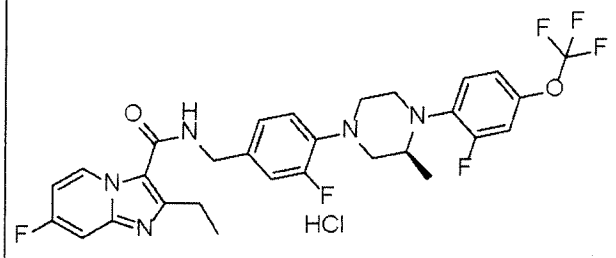
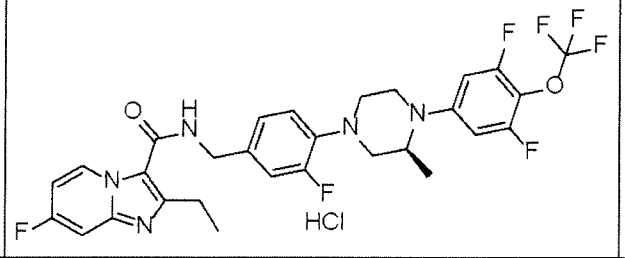
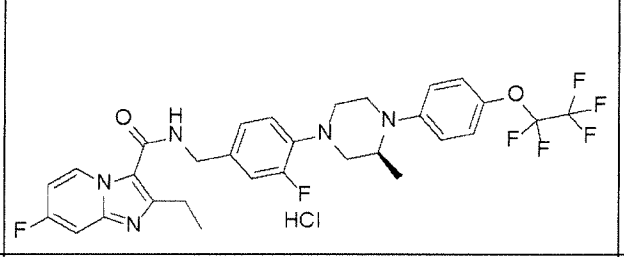
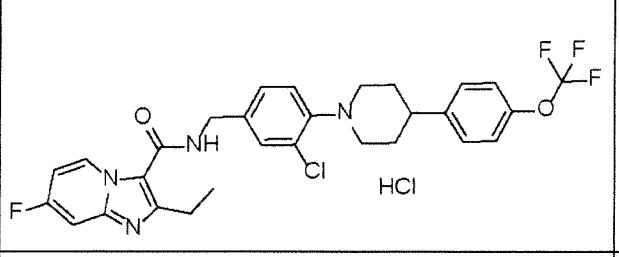
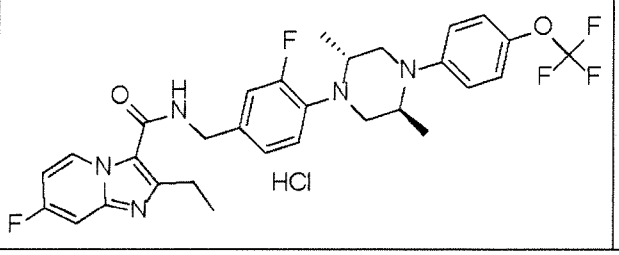
[0222]
[Table 14]

I-1-97		A	2.682	592.2
I-1-98		B	3.276	608.2
I-1-100		B	2.95	550
I-1-101		B	3.08	568
I-1-102		B	3.06	576
I-1-103		B	3.33	578

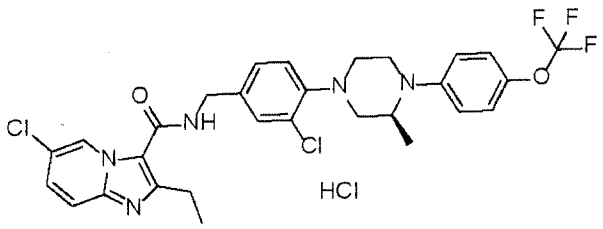
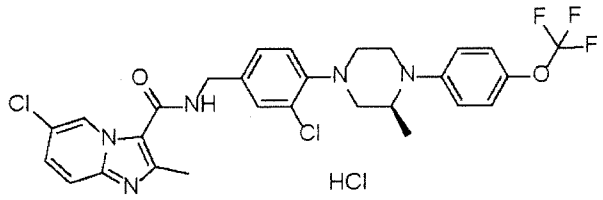
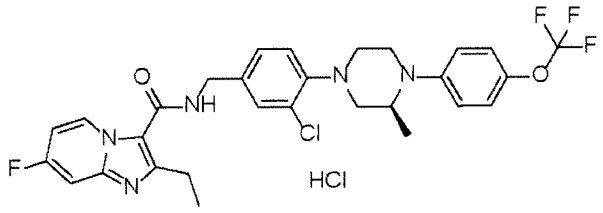
[0223]
[Table 15]

I-1-106		A	2.77	589.15
I-1-109		A	1.57	534
I-1-111		A	1.67	548
I-1-112		A	2.61	558
I-1-114		A	1.89	562
I-1-115		A	1.89	588

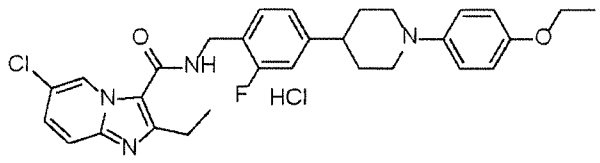
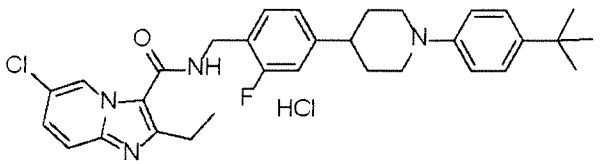
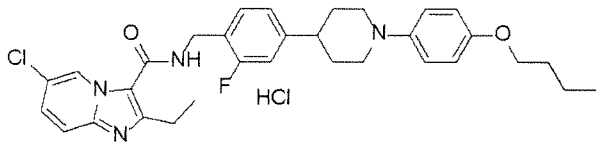
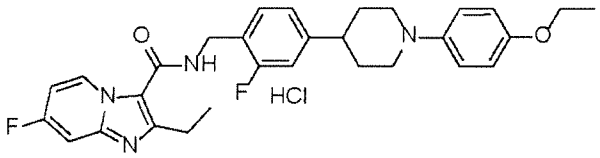
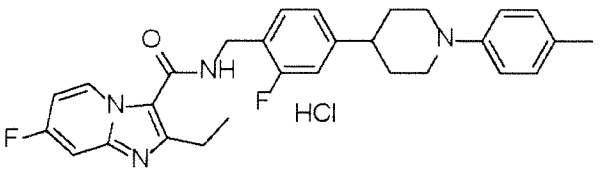
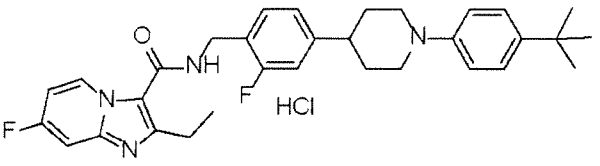
[0224]
[Table 16]

I-1-117		A	2.69	592
I-1-118		A	2.68	592
I-1-119		A	2.78	610
I-1-121		A	2.8	624
I-1-127		A	2.842	575.2
I-1-136		B	3.13	588.2

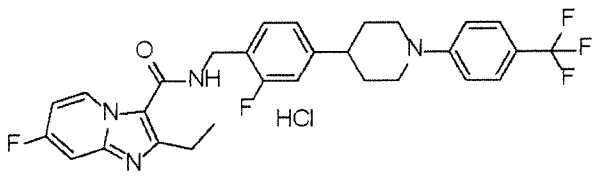
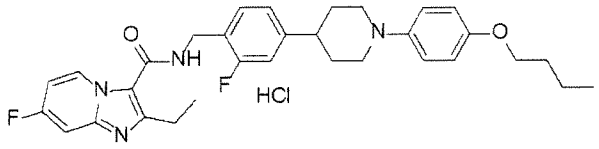
[0225]
[Table 17]

I-1-139		A	3.09	606.1
I-1-140		A	3	592.1
I-1-141		A	2.7	590.1

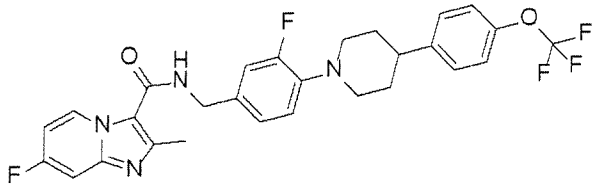
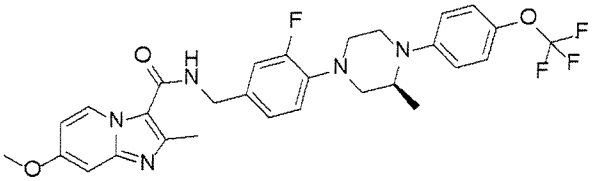
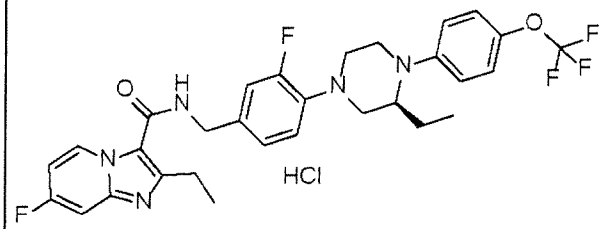
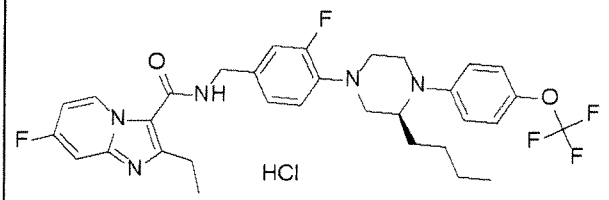
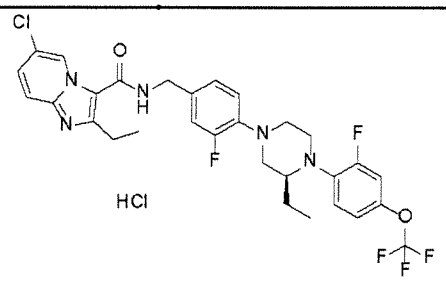
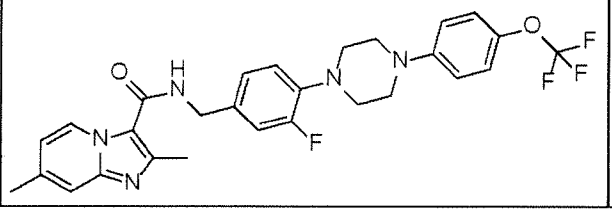
[0226]
[Table 18]

No.	Structure	LCMS method	RT	MS (M+H)
I-1-143		B	3	535
I-1-144		B	3.48	547
I-1-145		B	3.36	563
I-1-147		B	2.79	519
I-1-148		B	2.92	489
I-1-149		B	3.28	531

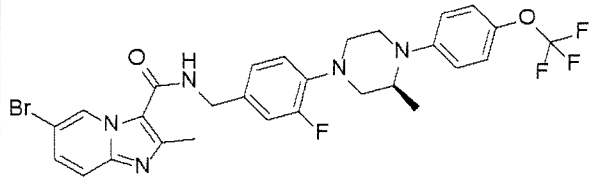
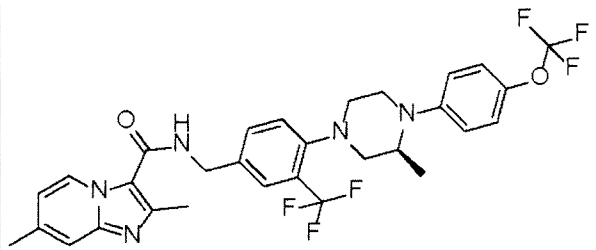
[0227]
[Table 19]

I-1-150		B	3	543
I-1-151		B	3.16	547

[0228]
[Table 20]

No.	Structure	LCMS method	RT	MS (M+H)
I-2-1		A	2.61	545.15
I-2-2		A	2.47	572.2
I-2-4		A	2.87	588.2
I-2-6		A	3.15	616.2
I-2-10		A	3.25	622.15
I-2-12		B	2.86	542.2

[0229]
[Table 21]

I-2-14		A	2.92	622.1
I-2-15		B	3.23	606.25

[0230]
Pharmacological examples
(Test Example 1)
Determination of IC85 for testing compounds against M. avium.

Preparation

One μL of DMSO stock solutions (200 x final concentration) of experimental compounds were added to round-bottom, sterile 96 well microtiter plates. Serial 4-fold dilutions (from 8 to 0.0000076 μM) were made directly in the microtiter plates from column 1 to 11. Untreated control samples with and without inoculum were included in column 12 in each plate.

A sample of *Mycobacterium avium* ATCC700898 was taken from 7H9 (5% OADC) agar plate. This was first diluted by CAMHB medium to obtain an optical density of 0.1 at 600 nm wavelength and then diluted 1/20, resulting in an inoculum of approximately 5x10 exp6 colony forming units per mL. Microtiter plates were filled with 200 μL of inoculum solution.

Plates were incubated at 37°C in a stainless-steel bat to prevent evaporation. After 3 days of incubation, resazurin was added to all wells. One day later, fluorescence was measured on EnVision Microplate Reader with 543 excitation and 590 nm emission wavelengths and calculated IC85 values.

[0231]

The results of Test Example 1 are shown below.

[0232]
[Table 22]

No.	IC85 (uM)	No.	IC85 (uM)	No.	IC85 (uM)
I-1-1	0.017	I-1-44	0.011	I-1-100	0.046
I-1-2	0.021	I-1-46	0.0026	I-1-101	0.47
I-1-3	0.003	I-1-47	0.11	I-1-102	0.024
I-1-4	0.1	I-1-48	0.035	I-1-103	0.019
I-1-5	0.048	I-1-49	0.068	I-1-106	0.0062
I-1-8	0.58	I-1-50	0.5	I-1-109	0.0071
I-1-9	0.94	I-1-51	0.11	I-1-111	0.0071
I-1-10	0.0031	I-1-52	0.0054	I-1-112	0.0014
I-1-12	0.07	I-1-53	0.037	I-1-114	0.0074
I-1-13	0.057	I-1-54	0.034	I-1-115	0.0046
I-1-14	0.76	I-1-55	0.69	I-1-117	0.0025
I-1-15	0.057	I-1-56	0.022	I-1-118	0.0076
I-1-16	0.0016	I-1-57	0.0036	I-1-119	0.0065
I-1-17	0.013	I-1-58	0.077	I-1-121	0.003
I-1-18	0.011	I-1-59	0.011	I-1-127	0.0077
I-1-19	0.13	I-1-62	0.0072	I-1-136	0.016
I-1-20	0.033	I-1-63	0.012	I-1-139	0.009
I-1-21	0.038	I-1-64	0.079	I-1-140	0.0057
I-1-22	0.028	I-1-65	0.12	I-1-141	0.002
I-1-23	0.045	I-1-66	0.011	I-1-143	0.023
I-1-24	0.032	I-1-67	0.068	I-1-144	0.017
I-1-25	0.0022	I-1-68	0.013	I-1-145	0.016
I-1-26	0.015	I-1-69	0.51	I-1-147	0.0083
I-1-27	0.033	I-1-73	0.019	I-1-148	0.0054
I-1-28	0.012	I-1-75	0.016	I-1-149	0.015
I-1-29	0.0027	I-1-78	0.037	I-1-150	0.0024
I-1-30	0.0031	I-1-80	0.06	I-1-151	0.01
I-1-31	0.14	I-1-81	0.33	I-2-1	0.016
I-1-32	0.0091	I-1-82	0.5	I-2-2	0.37
I-1-33	0.068	I-1-83	0.62	I-2-4	0.0065
I-1-34	0.008	I-1-84	0.038	I-2-6	0.0044
I-1-35	0.026	I-1-85	0.0069	I-2-10	0.023
I-1-36	0.11	I-1-88	0.0061	I-2-12	0.023
I-1-37	0.036	I-1-92	0.0055	I-2-14	0.0045
I-1-38	0.0013	I-1-93	0.011	I-2-15	0.25
I-1-39	0.011	I-1-94	0.014		
I-1-40	0.022	I-1-95	0.0022		
I-1-41	0.18	I-1-96	0.011		
I-1-42	0.009	I-1-97	0.0072		
I-1-43	0.015	I-1-98	0.0088		

[0233]
(Test Example 2)
Metabolic stability test

Using a commercially available pooled human liver microsomes, a compound of the present invention was reacted for a constant time, a remaining rate was calculated by comparing a reacted sample and an unreacted sample, thereby, a degree of metabolism in liver was assessed.

A reaction was performed (oxidative reaction) at 37 °C for 0 minute or 30 minutes in the presence of 1 mmol/L NADPH in 0.2 mL of a buffer (50 mmol/L Tris-HCl pH 7.4, 150 mmol/L potassium chloride, 10 mmol/L magnesium chloride) containing 0.5 mg protein/mL of human liver microsomes. After the reaction, 50 µL of the reaction solution was added to 100 µL of a methanol/acetonitrile = 1/1 (v/v), mixed and centrifuged at 3000 rpm for 15 minutes. The compound of the present invention in the supernatant was quantified by LC/MS/MS or solid phase extraction (SPE)/MS, and a remaining amount of the compound of the present invention after the reaction was calculated, letting a compound amount at 0 minute reaction time to be 100%.

[0234]

The results of Test Example 2 are shown below.

[0235]
[Table 23]

No.	MS_h_%	No.	MS_h_%	No.	MS_h_%
I-1-1	75	I-1-44	69	I-1-100	65
I-1-2	86	I-1-46	96	I-1-101	90
I-1-3	66	I-1-47	85	I-1-102	75
I-1-4	88	I-1-48	69	I-1-103	64
I-1-5	70	I-1-49	59	I-1-106	59
I-1-8	86	I-1-50	94	I-1-109	80
I-1-9	82	I-1-51	90	I-1-111	88
I-1-10	60	I-1-52	84	I-1-112	69
I-1-12	64	I-1-53	65	I-1-114	87
I-1-13	82	I-1-54	79	I-1-115	69
I-1-14	79	I-1-55	84	I-1-117	83
I-1-15	71	I-1-56	60	I-1-118	97
I-1-16	67	I-1-57	84	I-1-119	63
I-1-17	63	I-1-58	89	I-1-121	95
I-1-18	85	I-1-59	87	I-1-127	93
I-1-19	87	I-1-62	82	I-1-136	86
I-1-20	83	I-1-63	95	I-1-139	61
I-1-21	89	I-1-64	94	I-1-140	89
I-1-22	87	I-1-65	96	I-1-141	93
I-1-23	85	I-1-66	83	I-1-143	77
I-1-24	62	I-1-67	93	I-1-144	67
I-1-25	72	I-1-68	91	I-1-145	80
I-1-26	93	I-1-69	89	I-1-147	91
I-1-27	80	I-1-73	90	I-1-148	73
I-1-28	94	I-1-75	71	I-1-149	63
I-1-29	89	I-1-78	69	I-1-150	65
I-1-30	89	I-1-80	74	I-1-151	88
I-1-31	82	I-1-81	94	I-2-1	106
I-1-32	62	I-1-82	98	I-2-2	97.7
I-1-33	85	I-1-83	85	I-2-4	90.1
I-1-34	65	I-1-84	86	I-2-6	80.8
I-1-35	91	I-1-85	91	I-2-10	72.2
I-1-36	79	I-1-88	89	I-2-12	71.4
I-1-37	76	I-1-92	66	I-2-14	67
I-1-38	90	I-1-93	67	I-2-15	59.2
I-1-39	75	I-1-94	67		
I-1-40	89	I-1-95	91		
I-1-41	86	I-1-96	90		
I-1-42	59	I-1-97	86		
I-1-43	75	I-1-98	76		

[0236]

Biological Example - COMBINATIONS

Protocol

The compounds employed were as follows:

- Clarithromycin - "CAM"
- Azithromycin - "AZM"
- Rifampicin - "RFP"
- Ethambutol - "ETB"
- Clofazimine - "CFZ"
- The following "bc1 inhibitors":
  - ✓ I-1-3
  - ✓ I-1-149
  - ✓ I-1-144
  - ✓ I-2-6
  - ✓ I-1-25
  - ✓ I-1-42
  - ✓ I-1-29
  - ✓ I-1-39
  - ✓ I-1-43

[0237]

Design of the study

(Test Example 3)

There were 15 study groups and 4 mice per group

[Table 24]

Study Group	Treatment (compound / dose in mg/kg)	Formulation concentration
1	CAM 200 mg/kg + CFZ loading	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL
2	CAM 200 mg/kg + CFZ loading + I-1-3 0.2 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-3 0.02 mg/mL
3	CAM 200 mg/kg + CFZ loading + I-1-3 1 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-3 0.1 mg/mL
4	CAM 200 mg/kg + CFZ loading + I-1-3 5 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-3 0.5 mg/mL
5	CAM 200 mg/kg + CFZ loading + I-1-149 0.2 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-149 0.02 mg/mL
6	CAM 200 mg/kg + CFZ loading + I-1-149 1 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-149 0.1 mg/mL
7	CAM 200 mg/kg + CFZ loading + I-1-149 5 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-149 0.5 mg/mL
8	CAM 200 mg/kg + CFZ loading + I-1-144 0.2 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-144 0.02 mg/mL
9	CAM 200 mg/kg + CFZ loading + I-1-144 1 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-144 0.1 mg/mL
10	CAM 200 mg/kg + CFZ loading + I-1-144 5 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-144 0.5 mg/mL
11	CAM 200 mg/kg + CFZ loading + I-1-43 0.2 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-43 0.02 mg/mL
12	CAM 200 mg/kg + CFZ loading + I-1-43 1 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-43 0.1 mg/mL
13	CAM 200 mg/kg + CFZ loading + I-1-43 5 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-1-43 0.5 mg/mL
14	Control 1 (day 1)	
15	Control 2 (day 8)	

Generally, as can be seen from the table above, the following doses of the relevant compounds and formulation concentrations were given:

- Clarithromycin (CAM) - administered at a dose of 200 mg/kg in mice as a clinical dose of 600 mg in human; the formulation concentration being 20 mg/mL
- Clofazimine (CFZ) loading – On the first day, administration dose was 40 mg/kg. after the second day, administration dose was 6 mg/kg. At the beginning of second week, administered at a dose of 15 mg/kg, after this day, administration dose was 6 mg/kg. This dosing mimics the AUC of repetitive administration of 50 mg in human.

[0238]

Methods

All treatments were evaluated on Mycobacterium avium ATCC700898.

All formulations prepared in 0.5% (w/v) Methylcellulose.

All formulations were solutions and prepared once in a week.

Time Schedule, after mice were infected.

Necropsy Control 1	Day 1
Start Treatment	Day 1
Last treatment	Day 7
Necropsy Control 2	Day 8
Necropsy Treatment Groups	Day 8

The mice were infected with Mycobacterium avium strain.

The clarithromycin sensitive ATCC700898 was thawed at ambient temperature and diluted in saline for mouse inoculation. When 0.07 mL of this dilution is inoculated, each mouse receives 10^7 bacteria.

48 female 8-weeks old BALB/c mice, Charles River, were inoculated intranasally with 0.07 mL of a bacterial suspension containing ± 10^7 colony forming units (CFU).

[0239]

Dosing

The start of dosing was at Day 1.

- Body weight of all mice were regarded as around 20 g.
- All mice were dosed orally with 0.2 mL of the appropriate formulation, except the control groups, which were not treated.
- All groups were treated once daily on working days for a week (5 doses/treatments in total).
- The last doses/treatments were given on Day 7.

[0240]

Necropsy

At day 1 after the infection, 4 control mice were sacrificed, and the lung was collected in homogenization tubes.

At day 8 after the infection, 4 control mice and 40 treated mice were sacrificed, and the lung was collected in homogenization tubes.

[0241]

Assessment of infection and treatment

The effectiveness of treatments was assessed by counting the numbers of colony-forming-units (CFU) in the lungs.

- 1.8 mL Mueller Hinton Broth (MHB) was added to each homogenization tube containing lung.
- Lungs were homogenized, and four 10-fold serial dilutions were made in MHB.
- From each individual lung, 100 µL of the undiluted suspension and four serial 10-fold dilutions, were plated on 7H10 agar plates.
- CFU's were counted after incubation at 35°C for 3 weeks.
- The bactericidal effect of the treatment was defined as a significant decrease of the mean number of CFU in the treated group compared to pre-treatment value.

[0242]

Preparation of Media

7H10 agar + 5% OADC

- dissolve 19 g Middlebrook 7H10 agar (BD 262710) in 950 mL distilled water.
- add 5 mL glycerol
- autoclave at 121°C for 10 min and cool to 55°C
- add 50 mL Middlebrook OADC Enrichment (BD 212240)
- keep at 55°C
- pipette 20 mL agar solution/dish
- store at 4°C until ready to use after coagulation

[0243]

Results

[Table 25]

Study Group	Treatment (compound / dose in mg/kg)	Mean Log10	Standard deviation
1	CAM 200 mg/kg + CFZ loading	5.49	0.04
2	CAM 200 mg/kg + CFZ loading + I-1-3 0.2 mg/kg	5.09	0.17
3	CAM 200 mg/kg + CFZ loading + I-1-3 1 mg/kg	4.71	0.08
4	CAM 200 mg/kg + CFZ loading + I-1-3 5 mg/kg	4.3	0.42
5	CAM 200 mg/kg + CFZ loading + I-1-149 0.2 mg/kg	5.31	0.12
6	CAM 200 mg/kg + CFZ loading + I-1-149 1 mg/kg	5.09	0.12
7	CAM 200 mg/kg + CFZ loading + I-1-149 5 mg/kg	4.6	0.18
8	CAM 200 mg/kg + CFZ loading + I-1-144 0.2 mg/kg	5.15	0.09
9	CAM 200 mg/kg + CFZ loading + I-1-144 1 mg/kg	4.88	0.24
10	CAM 200 mg/kg + CFZ loading + I-1-144 5 mg/kg	4.37	0.15
11	CAM 200 mg/kg + CFZ loading + I-1-43 0.2 mg/kg	5.09	0.14
12	CAM 200 mg/kg + CFZ loading + I-1-43 1 mg/kg	4.76	0.10
13	CAM 200 mg/kg + CFZ loading + I-1-43 5 mg/kg	4.39	0.13
14	Control 1 (day 1)	6.83	0.13
15	Control 2 (day 8)	6.23	0.06

The results above can be seen with reference to Figure 1, which shows each the mean log10 value for CFUs of each of the 15 study groups. It also shows a "cut off' value of 2.00, which is essentially the value at which the CFUs (or the bacterial infection) is so low that it cannot accurately be measured, or the CFUs are below the detectable level.

- double combinations of clarithromycin + clofazimine resulted the effect causing drop to the mean log10 of 5.49
- triple combinations of clarithromycin + clofazimine + I-1-3 showed potent efficacy by I-1-3 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-149 showed potent efficacy by I-1-149 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-144 showed potent efficacy by I-1-144 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-43 showed potent efficacy by I-1-43 dose dependent manner

[0244]
(Test Example 4)
There were 6 study groups and 4 mice per group
[Table 26]

Study Group	Treatment (compound / dose in mg/kg)	Formulation concentration
1	CAM 200 mg/kg + CFZ loading	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL
2	CAM 200 mg/kg + CFZ loading + I-2-6 0.2 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-2-6 0.02 mg/mL
3	CAM 200 mg/kg + CFZ loading + I-2-6 1 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-2-6 0.1 mg/mL
4	CAM 200 mg/kg + CFZ loading + I-2-6 5 mg/kg	CAM 20 mg/mL + CFZ 4 mg/mL or 0.6 mg/mL or 1.5 mg/mL + I-2-6 0.5 mg/mL
5	Control 1 (day 1)	
6	Control 2 (day 8)	

Almost protocol was the same as the protocol described in the above Test Example 3.

[0245]
Results
[Table 27]

Study Group	Treatment (compound / dose in mg/kg)	Mean Log10	Standard deviation
1	CAM 200 mg/kg + CFZ loading	5.69	0.09
2	CAM 200 mg/kg + CFZ loading + I-2-6 0.2 mg/kg	5.43	0.07
3	CAM 200 mg/kg + CFZ loading + I-2-6 1 mg/kg	5.14	0.13
4	CAM 200 mg/kg + CFZ loading + I-2-6 5 mg/kg	4.41	0.16
5	Control 1 (day 1)	6.8	0.17
6	Control 2 (day 8)	6.27	0.08

The results above can be seen with reference to Figure 2, which shows each the mean log10 value for CFUs of each of the 6 study groups. It also shows a "cut off" value of 2.00, which is essentially the value at which the CFUs (or the bacterial infection) is so low that it cannot accurately be measured, or the CFUs are below the detectable level.

It can be seen that, compared to the control groups:

- double combinations of clarithromycin + clofazimine resulted the effect causing drop to the mean log10 of 5.69
- triple combinations of clarithromycin + clofazimine + I-2-6 showed potent efficacy by I-2-6 dose dependent manner

[0246]
(Test Example 5)
There were 15 study groups and 4 mice per group
[Table 28]

Study Group	Treatment (compound / dose in mg/kg)	Formulation concentration
1	CAM 200 mg/kg + CFZ 20 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL
2	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 0.2 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-25 0.02 mg/mL
3	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 1 mg/kg	CAM 20 mg/mL +CFZ 2 mg/mL + I-1-25 0.1 mg/mL
4	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 5 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-25 0.5 mg/mL
5	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 0.2 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-42 0.02 mg/mL
6	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 1 mg/kg	CAM 20 mg/mL +CFZ 2 mg/mL + I-1-42 0.1 mg/mL
7	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 5 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-42 0.5 mg/mL
8	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 0.2 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-29 0.02 mg/mL
9	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 1 mg/kg	CAM 20 mg/mL +CFZ 2 mg/mL + I-1-29 0.1 mg/mL
10	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 5 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-29 0.5 mg/mL
11	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 0.2 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-39 0.02 mg/mL
12	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 1 mg/kg	CAM 20 mg/mL +CFZ 2 mg/mL + I-1-39 0.1 mg/mL
13	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 5 mg/kg	CAM 20 mg/mL + CFZ 2 mg/mL + I-1-39 0.5 mg/mL
14	Control 1 (day 1)	
15	Control 2 (day 8)	

Almost protocol was the same as the protocol described in the above Test Example 3.

[0247]
Results
[Table 29]

Study Group	Treatment (compound / dose in mg/kg)	Mean Log10	Standard deviation
1	CAM 200 mg/kg + CFZ 20 mg/kg	4.97	0.17
2	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 0.2 mg/kg	4.77	0.06
3	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 1 mg/kg	4.33	0.25
4	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-25 5 mg/kg	3.86	0.12
5	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 0.2 mg/kg	4.52	0.09
6	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 1 mg/kg	4.34	0.19
7	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-42 5 mg/kg	3.82	0.13
8	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 0.2 mg/kg	4.49	0.37
9	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 1 mg/kg	4.30	0.24
10	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-29 5 mg/kg	3.84	0.16
11	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 0.2 mg/kg	4.86	0.10
12	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 1 mg/kg	4.64	0.13
13	CAM 200 mg/kg + CFZ 20 mg/kg + I-1-39 5 mg/kg	4.18	0.13
14	Control 1 (day 1)	6.11	0.16
15	Control 2 (day 8)	6.00	0.06

The results above can be seen with reference to Figure 3, which shows each the mean log10 value for CFUs of each of the 15 study groups. It also shows a "cut off" value of 2.00, which is essentially the value at which the CFUs (or the bacterial infection) is so low that it cannot accurately be measured, or the CFUs are below the detectable level.

It can be seen that, compared to the control groups:

- double combinations of clarithromycin + clofazimine resulted the effect causing drop to the mean log10 of 4.97
- triple combinations of clarithromycin + clofazimine + I-1-25 showed potent efficacy by I-1-25 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-42 showed potent efficacy by I-1-42 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-29 showed potent efficacy by I-1-29 dose dependent manner
- triple combinations of clarithromycin + clofazimine + I-1-39 showed potent efficacy by I-1-39 dose dependent manner

[0248]
(Test Example 6)

There were 6 study groups and 4 mice per group

[Table 30]

Study Group	Treatment (compound / dose in mg/kg)	Formulation concentration
1	AZM 10 mg/kg	1 mg/mL
2	AZM 10 mg/kg + RFP 10 mg/kg + ETB 100 mg/kg	1 mg/mL + 1 mg/mL + 10 mg/mL
3	AZM 10 mg/kg + CFZ 20 mg/kg	1 mg/mL + 2 mg/mL
4	AZM 10 mg/kg + CFZ 20 mg/kg + I-1-3 1 mg/kg	1 mg/mL + 2 mg/mL + 0.1 mg/mL
5	Control 1 (day 1)	
6	Control 2 (day 15)	

Almost protocol was the same as the protocol described in the above Test Example 3 except for the bacterial load and the period of treatment.

- 24 female 8-weeks old BALB/c mice, Charles River, were inoculated intranasally with 0.07 mL of a bacterial suspension containing ± 10^6 colony forming units (CFU).
- All groups were treated once daily on working days for 2 consecutive weeks (5 times/week, 10 doses/treatments in total).
- The last doses/treatments were given on Day 14.

[0249]

Results

[Table 31]

Study Group	Treatment (compound / dose in mg/kg)	Mean Log10	Standard deviation
1	AZM 10 mg/kg	6.19	0.06
2	AZM 10 mg/kg + RFP 10 mg/kg + ETB 100 mg/kg	5.93	0.09
3	AZM 10 mg/kg + CFZ 20 mg/kg	5.47	0.11
4	AZM 10 mg/kg + CFZ 20 mg/kg + I-1-3 1 mg/kg	3.71	0.35
5	Control 1 (day 1)	6.40	0.14
6	Control 2 (day 15)	6.02	0.13

The results above can be seen with reference to Figure 4, which shows each the mean log10 value for CFUs of each of the 6 study groups. It also shows a "cut off' value of 2.00, which is essentially the value at which the CFUs (or the bacterial infection) is so low that it cannot accurately be measured, or the CFUs are below the detectable level.

It can be seen that, compared to the control groups:

- Clinical standard therapy of azithromycin + rifampicin + ethambutol resulted the effect causing drop to a mean log10 of 0.1 CFU from control 2 (mean log10 of 5.93)
- double combinations of azithromycin + clofazimine resulted the effect causing

drop to the mean log10 of 5.47

- triple combinations of clarithromycin + clofazimine + I-1-3 showed surprising reduction in CFU (mean log10 of 3.71)

[0250]

Biological Example - COMBINATIONS

Protocol

The compounds employed were as follows:

- Clarithromycin - "CAM"
- The following "bc1 inhibitors":
  - ✓ I-1-3
  - ✓ I-1-144
  - ✓ I-1-149
  - ✓ I-2-6
  - ✓ I-1-29
  - ✓ I-1-39
  - ✓ I-1-25
  - ✓ I-1-42
  - ✓ I-1-43

[0251]

Design of the study

(Test Example 7)

There were 12 study groups.

[Table 32]

Study Group	Treatment (compound / concentration in μg/ml)
1	CAM 1 μg/ml
2	I-1-3 1 μg/ml
3	I-1-144 1 μg/ml
4	I-1-149 1 μg/ml
5	I-2-6 1 μg/ml
6	I-1-29 1 μg/ml
7	I-1-39 1 μg/ml
8	I-1-25 1 μg/ml
9	I-1-42 1 μg/ml
10	I-1-43 1 μg/ml
11	Control (day 0)
12	Control (day 3)

[0252]

Methods

All treatments were evaluated on Mycobacterium avium ATCC700898.

All compound solutions were prepared in 7H9 medium containing 5% OADC.

The assay buffer was also used 7H9 medium containing 5% OADC.

The clarithromycin sensitive ATCC700898 was cultured 7 days at 37°C in 7H9 medium containing 5% OADC. And then, glycerol was mixed with

the culture solution to a final concentration of 20% glycerol and stored at -80°C.

Determination of colony forming units (CFU) of the stock solution was performed by counting the numbers of colonies grown in 7H10 agar plates containing 5 % OADC. The bactericidal studies were performed using the medium in 96 well plate (final volume was 200 µl/well). The stock solution was diluted by the medium to a final concentration of approximately 1.0 x 10^5 CFU/ml. All CAM and bc1 inhibitors were dissolved in DMSO to make a 1 mg/mL solution. And then, the solutions were diluted with the medium to a final concentration as shown in Table 32. The assay plates were incubated at 37°C for 3 days.

[0253]

Sampling point

At day 0 after starting the assay, determination of CFU was conducted only in the control group for calculating initial number of CFU.

At day 3 after starting the assay, determination of CFU was conducted in all tested groups.

[0254]

Assessment of infection and treatment

The effectiveness of treatments was assessed by counting the numbers of colony-forming-units (CFU) in the lungs.

- The cultures of each groups were serially diluted 10-fold with saline.
- From each individual group, 100 µL of these diluents were applied to the 7H10 agar containing 5% OADC.
- CFU's were counted after incubation at 35°C for 2 weeks.
- The bacteriostatic and bactericidal effect of the treatment was defined as comparing with Control CFU at day0 and/or day3.
- When the number of CFU in maximum diluent were exceeded 3000 CFU, 3000 CFU was adopted as the upper limit of detection.

[0255]

Preparation of Media

7H9 medium + 5% OADC

- dissolve 2.35 g Middlebrook 7H9 medium (BD 262710) in 475 mL distilled water
- add 2.5 mL glycerol
- autoclave at 121°C for 10 min and cool to around room temperature
- add 25 mL Middlebrook OADC Enrichment (BD 212240)
- store at 4°C until ready to use

7H10 agar + 5% OADC

- dissolve 19 g Middlebrook 7H10 agar (BD 262710) in 950 mL distilled water.
- add 5 mL glycerol
- autoclave at 121°C for 10 min and cool to 55°C
- add 50 mL Middlebrook OADC Enrichment (BD 212240)
- keep at 55°C
- pipette 20 mL agar solution/dish
- store at 4°C until ready to use after coagulation

[0256]

Results

[Table 33]

Study Group	Treatment (compound / concentration in μg/ml)	Log10
1	CAM 1 μg/ml	4.96
2	I-1-3 1 μg/ml	5.68
3	I-1-144 1 μg/ml	5.50
4	I-1-149 1 μg/ml	5.69
5	I-2-6 1 μg/ml	5.38
6	I-1-29 1 μg/ml	5.75
7	I-1-39 1 μg/ml	5.59
8	I-1-25 1 μg/ml	5.76
9	I-1-42 1 μg/ml	5.75
10	I-1-43 1 μg/ml	5.68
11	Control (day 0)	5.23
12	Control (day 3)	>7.48

The results above can be seen with reference to Figure 5, which shows each the log10 value for CFUs of each of the 12 study groups. It also shows a "upper limit' value of 7.48, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

- All bc1 inhibitors revealed bacteriostatic effect as the log10 CFU of 5.38 to 5.76.

[0257]

(Test Example 8)

There were 30 study groups.

[Table 34]

Study Group	Treatment (compound / concentration in μg/ml)
1	CAM 1 μg/ml
2	CAM 1 μg/ml + I-1-3 0.1 μg/ml
3	CAM 1 μg/ml + I-1-3 1 μg/ml
4	CAM 1 μg/ml + I-1-3 10 μg/ml
5	CAM 1 μg/ml + I-1-144 0.1 μg/ml
6	CAM 1 μg/ml + I-1-144 1 μg/ml
7	CAM 1 μg/ml + I-1-144 10 μg/ml
8	CAM 1 μg/ml + I-1-149 0.1 μg/ml
9	CAM 1 μg/ml + I-1-149 1 μg/ml
10	CAM 1 μg/ml + I-1-149 10 μg/ml
11	CAM 1 μg/ml + I-2-6 0.1 μg/ml
12	CAM 1 μg/ml + I-2-6 1 μg/ml
13	CAM 1 μg/ml + I-2-6 10 μg/ml
14	CAM 1 μg/ml + I-1-29 0.1 μg/ml
15	CAM 1 μg/ml + I-1-29 1 μg/ml
16	CAM 1 μg/ml + I-1-29 10 μg/ml
17	CAM 1 μg/ml + I-1-39 0.1 μg/ml
18	CAM 1 μg/ml + I-1-39 1 μg/ml
19	CAM 1 μg/ml + I-1-39 10 μg/ml
20	CAM 1 μg/ml + I-1-25 0.1 μg/ml
21	CAM 1 μg/ml + I-1-25 1 μg/ml
22	CAM 1 μg/ml + I-1-25 10 μg/ml
23	CAM 1 μg/ml + I-1-42 0.1 μg/ml
24	CAM 1 μg/ml + I-1-42 1 μg/ml
25	CAM 1 μg/ml + I-1-42 10 μg/ml
26	CAM 1 μg/ml + I-1-43 0.1 μg/ml
27	CAM 1 μg/ml + I-1-43 1 μg/ml
28	CAM 1 μg/ml + I-1-43 10 μg/ml
29	Control (day 0)
30	Control (day 3)

Almost protocol was the same as the protocol described in the above Test Example 7.

[0258]
Results
[Table 35]

Study Group	Treatment (compound / concentration in μg/ml)	Log10
1	CAM 1 μg/ml	4.69
2	CAM 1 μg/ml + I-1-3 0.1 μg/ml	4.67
3	CAM 1 μg/ml + I-1-3 1 μg/ml	4.60
4	CAM 1 μg/ml + I-1-3 10 μg/ml	4.08
5	CAM 1 μg/ml + I-1-144 0.1 μg/ml	4.43
6	CAM 1 μg/ml + I-1-144 1 μg/ml	4.04
7	CAM 1 μg/ml + I-1-144 10 μg/ml	3.90
8	CAM 1 μg/ml + I-1-149 0.1 μg/ml	4.71
9	CAM 1 μg/ml + I-1-149 1 μg/ml	4.45
10	CAM 1 μg/ml + I-1-149 10 μg/ml	4.15
11	CAM 1 μg/ml + I-2-6 0.1 μg/ml	4.88
12	CAM 1 μg/ml + I-2-6 1 μg/ml	4.54
13	CAM 1 μg/ml + I-2-6 10 μg/ml	4.26
14	CAM 1 μg/ml + I-1-29 0.1 μg/ml	4.88
15	CAM 1 μg/ml + I-1-29 1 μg/ml	4.79
16	CAM 1 μg/ml + I-1-29 10 μg/ml	4.15
17	CAM 1 μg/ml + I-1-39 0.1 μg/ml	4.80
18	CAM 1 μg/ml + I-1-39 1 μg/ml	4.82
19	CAM 1 μg/ml + I-1-39 10 μg/ml	4.20
20	CAM 1 μg/ml + I-1-25 0.1 μg/ml	4.81
21	CAM 1 μg/ml + I-1-25 1 μg/ml	4.85
22	CAM 1 μg/ml + I-1-25 10 μg/ml	4.20
23	CAM 1 μg/ml + I-1-42 0.1 μg/ml	4.88
24	CAM 1 μg/ml + I-1-42 1 μg/ml	4.74
25	CAM 1 μg/ml + I-1-42 10 μg/ml	4.20
26	CAM 1 μg/ml + I-1-43 0.1 μg/ml	4.77
27	CAM 1 μg/ml + I-1-43 1 μg/ml	4.71
28	CAM 1 μg/ml + I-1-43 10 μg/ml	3.95
29	Control (day 0)	5.01
30	Control (day 3)	7.95

The results above can be seen with reference to Figure 6, which shows each the log10 value for CFUs of each of the 30 study groups. It also shows a "upper limit' value of 8.48, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

It can be seen that, compared to the control groups:

- double combinations of clarithromycin 1 μg/ml + bc1 inhibitors 10 μg/ml resulted the effect causing drop to the log10 of 3.90 to 4.26.
- double combinations of clarithromycin 1 μg/ml + several bc1 inhibitors (I-1-144, I-1-149 and I-2-6) revealed concentration correlation.

[0259]
(Test Example 9)
There were 11 study groups and 4 mice per group
[Table 36]

Study Group	Treatment (compound / concentration in μg/ml)
1	CAM 1 μg/ml
2	CAM 1 μg/ml + I-1-3 1 μg/ml
3	CAM 1 μg/ml + I-1-3 10 μg/ml
4	CAM 1 μg/ml + I-1-144 1 μg/ml
5	CAM 1 μg/ml + I-1-144 10 μg/ml
6	CAM 1 μg/ml + I-1-149 1 μg/ml
7	CAM 1 μg/ml + I-1-149 10 μg/ml
8	CAM 1 μg/ml + I-2-6 1 μg/ml
9	CAM 1 μg/ml + I-2-6 10 μg/ml
10	Control (day 0)
11	Control (day 3)

Methods

All treatments were evaluated on *Mycobacterium avium* ATCC7008 97.

The clarithromycin resistant ATCC700897 was cultured 7 days at 37°C in 7H9 medium containing 5% OADC. And then, glycerol was mixed with the culture solution to a final concentration of 20% glycerol and stored at -80°C. Determination of colony forming units (CFU) of the stock solution was perform ed by counting the numbers of colonies grown in 7H10 agar plates containing 5 % OADC.

Almost protocol was the same as the protocol described in the above Test Example 7 except for using strain.

[0260]

Results

[Table 37]

Study Group	Treatment (compound / concentration in μg/ml)	Log10
1	CAM 1 μg/ml	>6.48
2	CAM 1 μg/ml + I-1-3 1 μg/ml	4.95
3	CAM 1 μg/ml + I-1-3 10 μg/ml	4.80
4	CAM 1 μg/ml + I-1-144 1 μg/ml	4.98
5	CAM 1 μg/ml + I-1-144 10 μg/ml	4.71
6	CAM 1 μg/ml + I-1-149 1 μg/ml	4.92
7	CAM 1 μg/ml + I-1-149 10 μg/ml	4.82
8	CAM 1 μg/ml + I-2-6 1 μg/ml	4.97
9	CAM 1 μg/ml + I-2-6 10 μg/ml	4.75
10	Control (day 0)	4.47
11	Control (day 3)	>6.48

The results above can be seen with reference to Figure 7, which shows each the log10 value for CFUs of each of the 11 study groups. It also shows a "upper limit' value of 6.48, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

It can be seen that, compared to the control groups:

- double combinations of clarithromycin + bc1 inhibitors revealed bacteriostatic effect as the log10 CFU of 4.71 to 4.98, despite no bacteriostatic effect with clarithromycin alone.

[0261]
(Test Example 10)
There were 26 study groups.
[Table 38]

Study Group	Treatment (compound / concentration in μg/ml)
1	I-1-3 0.3 μg/ml
2	I-1-3 1 μg/ml
3	I-1-3 3 μg/ml
4	I-1-3 10 μg/ml
5	CAM 1 μg/ml
6	CAM 1 μg/ml + I-1-3 0.3 μg/ml
7	CAM 1 μg/ml + I-1-3 1 μg/ml
8	CAM 1 μg/ml + I-1-3 3 μg/ml
9	CAM 1 μg/ml + I-1-3 10 μg/ml
10	CAM 3 μg/ml
11	CAM 3 μg/ml + I-1-3 0.3 μg/ml
12	CAM 3 μg/ml + I-1-3 1 μg/ml
13	CAM 3 μg/ml + I-1-3 3 μg/ml
14	CAM 3 μg/ml + I-1-3 10 μg/ml
15	CAM 10 μg/ml
16	CAM 10 μg/ml + I-1-3 0.3 μg/ml
17	CAM 10 μg/ml + I-1-3 1 μg/ml
18	CAM 10 μg/ml + I-1-3 3 μg/ml
19	CAM 10 μg/ml + I-1-3 10 μg/ml
20	CAM 30 μg/ml
21	CAM 30 μg/ml + I-1-3 0.3 μg/ml
22	CAM 30 μg/ml + I-1-3 1 μg/ml
23	CAM 30 μg/ml + I-1-3 3 μg/ml
24	CAM 30 μg/ml + I-1-3 10 μg/ml
25	Control (day 0)
26	Control (day 3)

Almost protocol was the same as the protocol described in the above Test Example 9.

[0262]
Results
[Table 39]

Study Group	Treatment (compound / concentration in µg/ml)	Log10
1	I-1-3 0.3 µg/ml	>6.48
2	I-1-3 1 µg/ml	6.05
3	I-1-3 3 µg/ml	5.77
4	I-1-3 10 µg/ml	5.78
5	CAM 1 µg/ml	>6.48
6	CAM 1 µg/ml + I-1-3 0.3 µg/ml	>6.48
7	CAM 1 µg/ml + I-1-3 1 µg/ml	5.98
8	CAM 1 µg/ml + I-1-3 3 µg/ml	5.54
9	CAM 1 µg/ml + I-1-3 10 µg/ml	5.58
10	CAM 3 µg/ml	>6.48
11	CAM 3 µg/ml + I-1-3 0.3 µg/ml	6.32
12	CAM 3 µg/ml + I-1-3 1 µg/ml	5.97
13	CAM 3 µg/ml + I-1-3 3 µg/ml	5.56
14	CAM 3 µg/ml + I-1-3 10 µg/ml	5.54
15	CAM 10 µg/ml	>6.48
16	CAM 10 µg/ml + I-1-3 0.3 µg/ml	6.16
17	CAM 10 µg/ml + I-1-3 1 µg/ml	5.86
18	CAM 10 µg/ml + I-1-3 3 µg/ml	5.51
19	CAM 10 µg/ml + I-1-3 10 µg/ml	5.49
20	CAM 30 µg/ml	>6.48
21	CAM 30 µg/ml + I-1-3 0.3 µg/ml	6.13
22	CAM 30 µg/ml + I-1-3 1 µg/ml	5.86
23	CAM 30 µg/ml + I-1-3 3 µg/ml	5.59
24	CAM 30 µg/ml + I-1-3 10 µg/ml	5.58
25	Control (day 0)	5.45
26	Control (day 3)	>6.48

The results above can be seen with reference to Figure 8, which shows each the log10 value for CFUs of each of the 26 study groups. It also shows a "upper limit' value of 6.48, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

It can be seen that, compared to the control groups:

- Regardless of the concentration of clarithromycin, and even in the absence of clarithromycin, I-1-3 revealed a clear bacteriostatic effect at a concentration of 3 µg/ml or more as the log10 CFU of 5.49 to 5.78.
- I-1-3 at a concentration of 1 µg/ml also revealed bacteriostatic effect as t he log10 CFU of 5.86 to 6.05.

[0263]
Biological Example - COMBINATIONS
Protocol
The compounds employed were as follows:

- Clarithromycin - "CAM"
- Clofazimine - CFZ
- The following "bc1 inhibitor":
  - ✓ I-1-3

[0264]
Design of the study
(Test Example 11)
There were 6 study groups.
[Table 40]

Study Group	Treatment (compound / concentration in μg/ml)
1	CAM 1 μg/ml
2	I-1-3 1 μg/ml
3	CAM 1 μg/ml + CFZ 1 μg/ml
4	CAM 1 μg/ml + CFZ 1 μg/ml + I-1-3 1 μg/ml
5	Control (day 0)
6	Control (day 1)

[0265]
Methods

All treatments were evaluated on Mycobacterium intracellulare ATCC13950.

All compound solutions were prepared in 7H9 medium containing 5% OADC.

The assay buffer was also used 7H9 medium containing 5% OADC.

The clarithromycin susceptable ATCC13950 was cultured 7 days at 37°C in 7H9 medium containing 5% OADC. And then, glycerol was mixed with the culture solution to a final concentration of 20% glycerol and stored at -80°C. Determination of colony forming units (CFU) of the stock solution was performed by counting the numbers of colonies grown in 7H10 agar plates containing 5% OADC. The bactericidal studies were performed using the medium in 96 well plate (final volume was 200 μl/well). The stock solution was diluted by the medium to a final concentration of approximately 2.0 x 10^5 CFU/ml. All CAM, CFZ and bc1 inhibitor were dissolved in DMSO to make a 1 mg/mL solution. And then, the solutions were diluted with the medium to a final concentration as shown in Table 40. The assay plates were incubated at 37°C for 1 day.

[0266]
Sampling point

At day 0 after starting the assay, determination of CFU was conducted only in the control group for calculating initial number of CFU.

At day 1 after starting the assay, determination of CFU was conducted in all tested groups.

[0267]
Assessment of infection and treatment

The effectiveness of treatments was assessed by counting the numbers of colony-forming-units (CFU) in the lungs.

- The cultures of each groups were serially diluted 10-fold with saline.
- From each individual group, 100 μL of these diluents were applied to the 7H10

agar containing 5% OADC.

- CFU's were counted after incubation at 35°C for 2 weeks.
- The bacteriostatic and bactericidal effect of the treatment was defined as comparing with Control CFU at day 0 and/or day 1.
- When the number of CFU in maximum diluent were exceeded 500 CFU, 500 CFU was adopted as the upper limit of detection.

[0268]
Preparation of Media
7H9 medium + 5% OADC

- dissolve 2.35 g Middlebrook 7H9 medium (BD 262710) in 475 mL distilled water
- add 2.5 mL glycerol
- autoclave at 121°C for 10 min and cool to around room temperature
- add 25 mL Middlebrook OADC Enrichment (BD 212240)
- store at 4°C until ready to use

7H10 agar + 5% OADC

- dissolve 19 g Middlebrook 7H10 agar (BD 262710) in 950 mL distilled water.
- add 5 mL glycerol
- autoclave at 121°C for 10 min and cool to 55°C
- add 50 mL Middlebrook OADC Enrichment (BD 212240)
- keep at 55°C
- pipette 20 mL agar solution/dish
- store at 4°C until ready to use after coagulation

[0269]
Results
[Table 41]

Study Group	Treatment (compound / concentration in μg/ml)	Log10
1	CAM 1 μg/ml	5.61
2	I-1-3 1 μg/ml	>5.70
3	CAM 1 μg/ml + CFZ 1 μg/ml	5.61
4	CAM 1 μg/ml + CFZ 1 μg/ml + I-1-3 1 μg/ml	4.54
5	Control (day 0)	5.64
6	Control (day 1)	>5.70

The results above can be seen with reference to Figure 9, which shows each the log10 value for CFUs of each of the 6 study groups. It also shows a "upper limit' value of 5.70, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

- Only group 4 revealed clearly bactericidal effect as the log10 CFU of 4.54 at day 1.

[0270]
(Test Example 12)
There were 6 study groups and 4 mice per group

[Table 42]

Study Group	Treatment (compound / dose in mg/kg)	Formulation concentration
1	CAM 200 mg/kg + RFP 10 mg/kg + ETB 100 mg/kg	CAM 20 mg/mL + RFP 1 mg/mL + ETB 10 mg/mL
2	CAM 200 mg/kg + CFZ loading	CAM 20 mg/mL + CFZ 6 mg/mL or 2 mg/mL or 0.9 mg/mL
3	CAM 200 mg/kg + CFZ loading + I-1-3 1 mg/kg	CAM 20 mg/mL + CFZ 6 mg/mL or 2 mg/mL or 0.9 mg/mL + I-1-3 0.1 mg/mL
4	CAM 200 mg/kg + CFZ loading + I-1-3 5 mg/kg	CAM 20 mg/mL + CFZ 6 mg/mL or 2 mg/mL or 0.9 mg/mL + I-1-3 0.5 mg/mL
5	Control 1 (day 22)	
6	Control 2 (day 46)	

Generally, as can be seen from the table above, the following doses of the relevant compounds and formulation concentrations were given:

- CFZ loading – On the first day, administration dose was 60 mg/kg. after the second day, administration dose was 9 mg/kg. At the beginning of second week, administered at a dose of 20 mg/kg, after this day, administration dose was 9 mg/kg. This dosing mimics the Cmax of repetitive administration of 50 mg in human.

[0271]

Methods

All treatments were evaluated on Mycobacterium avium ATCC13950.

All formulations prepared in 20% Tween20, 80% aq. (20% 2-Hydroxypropyl-beta-cyclodextrin and 0.6% Hydroxypropyl Methylcellulose, pH3).

All formulations were solutions and prepared once in a week.

Time Schedule, after mice were infected.

Necropsy Control 1	Day 22
Start Treatment	Day 22
Last treatment	Day 45
Necropsy Control 2	Day 46
Necropsy Treatment Groups	Day 46

The mice were infected with Mycobacterium intracellulare strain.

The clarithromycin sensitive ATCC13950 was thawed at ambient temperature and diluted in saline for mouse inoculation. When 0.07 mL of this dilution is inoculated, each mouse receives 10^7 bacteria.

48 female 8-weeks old BALB/c mice, Charles River, were inoculated intranasally with 0.07 mL of a bacterial suspension containing ± 10^7 colony forming units (CFU).

[0272]

Dosing

The start of dosing was at Day 22.

- Body weight of all mice were regarded as around 20 g.
- All mice were dosed orally with 0.2 mL of the appropriate formulation, except the control groups, which were not treated.

- All groups were treated once daily on working days for a week (5 doses/treatments in total).
- The last doses/treatments were given on Day 45.

[0273]
Necropsy

At day 22 after the infection, 4 control mice were sacrificed, and the lung was collected in homogenization tubes.

At day 46 after the infection, 4 control mice and 40 treated mice were sacrificed, and the lung was collected in homogenization tubes.

[0274]
Assessment of infection and treatment

The effectiveness of treatments was assessed by counting the numbers of colony-forming-units (CFU) in the lungs.

- 1.8 mL Mueller Hinton Broth (MHB) was added to each homogenization tube containing lung.
- Lungs were homogenized, and four 10-fold serial dilutions were made in MHB.
- From each individual lung, 100 µL of the undiluted suspension and four serial 10-fold dilutions, were plated on 7H10 agar plates.
- CFU's were counted after incubation at 35°C for 3 weeks.
- The bactericidal effect of the treatment was defined as a significant decrease of the mean number of CFU in the treated group compared to pre-treatment value.

[0275]
Preparation of Media
7H10 agar + 5% OADC

- dissolve 19 g Middlebrook 7H10 agar (BD 262710) in 950 mL distilled water.
- add 5 mL glycerol
- autoclave at 121°C for 10 min and cool to 55°C
- add 50 mL Middlebrook OADC Enrichment (BD 212240)
- keep at 55°C
- pipette 20 mL agar solution/dish
- store at 4°C until ready to use after coagulation

[0276]
Results
[Table 43]

Study Group	Treatment (compound / dose in mg/kg)	Mean Log10	Standard deviation
1	CAM 200 mg/kg + RFP 10 mg/kg + ETB 100 mg/kg	5.23	0.12
2	CAM 200 mg/kg + CFZ loading	4.96	0.04
3	CAM 200 mg/kg + CFZ loading + I-1-3 1 mg/kg	2.05	0.10
4	CAM 200 mg/kg + CFZ loading + I-1-3 5 mg/kg	<2.00	-
5	Control 1 (day 22)	6.49	0.06
6	Control 2 (day 46)	5.85	0.03

The results above can be seen with reference to Figure 10, which shows each the mean log10 value for CFUs of each of the 6 study groups. It also shows a "cut off" value of 2.00, which is essentially the value at which the CFUs (or the bacterial infection) is so low that it cannot accurately be measured, or the CFUs are below the detectable level.

It can be seen that, compared to the control groups:

- triple combinations of clarithromycin + Rifampicin + Ethambutol resulted the effect causing drop to the mean log10 of 5.23.
- double combinations of clarithromycin + clofazimine showed the effect causing drop to the mean log10 of 4.96
- triple combinations of clarithromycin + clofazimine + I-1-3 showed surprising reduction in CFU (mean log10 of 2.05 in Study Group 3, under the cut off value in Study Group 4)

[0277]
Biological Example - COMBINATIONS
Protocol
The compounds employed were as follows:

- Clarithromycin - "CAM"
- Clofazimine - CFZ
- The following "bc1 inhibitor":
  - ✓ I-1-3

[0278]
Design of the study
(Test Example 13)
There were 7 study groups.
[Table 44]

Study Group	Treatment (compound / concentration in μg/ml)
1	CAM 1 μg/ml
2	CFZ 1 μg/ml
3	I-1-3 1 μg/ml
4	CAM 1 μg/ml + CFZ 1 μg/ml
5	CAM 1 μg/ml + CFZ 1 μg/ml + I-1-3 1 μg/ml
6	Control (day 0)
7	Control (day 2)

[0279]
Methods

All treatments were evaluated on Mycobacterium avium ATCC700897. All compound solutions were prepared in 7H9 medium containing 5% OADC.

The assay buffer was also used 7H9 medium containing 5% OADC.

The clarithromycin resistant ATCC700897 was cultured 7 days at 37°C in 7H9 medium containing 5% OADC. And then, glycerol was mixed with the culture solution to a final concentration of 20% glycerol and stored at -80°C. Determination of colony forming units (CFU) of the stock solution was performed by counting the numbers of colonies grown in 7H10 agar plates containing 5% OADC. The bactericidal studies were performed using the medium in 96 well plate (final volume was 200 μl/well). The stock solution was diluted by the medium to a final concentration of approximately 2.0 x 10^5 CFU/ml. All CAM, CFZ and bc1 inhibitor were dissolved in DMSO to make a 1 mg/mL solution. And then, the solutions were diluted with the medium to a final concentration as shown in Table 44. The assay plates were incubated at 37°C for 2 days.

[0280]
Sampling point

At day 0 after starting the assay, determination of CFU was conducted only in the control group for calculating initial number of CFU.

At day 2 after starting the assay, determination of CFU was conducted in all tested groups.

[0281]
Assessment of infection and treatment

The effectiveness of treatments was assessed by counting the numbers of colony-forming-units (CFU) in the lungs.

- The cultures of each groups were serially diluted 10-fold with saline.
- From each individual group, 100 μL of these diluents were applied to the 7H10 agar containing 5% OADC.
- CFU's were counted after incubation at 35°C for 2 weeks.
- The bacteriostatic and bactericidal effect of the treatment was defined as comparing with Control CFU at day0 and/or day2.
- When the number of CFU in maximum diluent were exceeded 500 CFU, 500 CFU was adopted as the upper limit of detection.

[0282]

Preparation of Media

7H9 medium + 5% OADC

- dissolve 2.35 g Middlebrook 7H9 medium (BD 262710) in 475 mL distilled water
- add 2.5 mL glycerol
- autoclave at 121°C for 10 min and cool to around room temperature
- add 25 mL Middlebrook OADC Enrichment (BD 212240)
- store at 4°C until ready to use

7H10 agar + 5% OADC

- dissolve 19 g Middlebrook 7H10 agar (BD 262710) in 950 mL distilled water.
- add 5 mL glycerol
- autoclave at 121°C for 10 min and cool to 55°C
- add 50 mL Middlebrook OADC Enrichment (BD 212240)
- keep at 55°C
- pipette 20 mL agar solution/dish
- store at 4°C until ready to use after coagulation

[0283]

Results

[Table 45]

Study Group	Treatment (compound / concentration in μg/ml)	Log10
1	CAM 1 μg/ml	>5.70
2	CFZ 1 μg/ml	>5.70
3	I-1-3 1 μg/ml	>5.70
4	CAM 1 μg/ml + CFZ 1 μg/ml	>5.70
5	CAM 1 μg/ml + CFZ 1 μg/ml + I-1-3 1 μg/ml	4.90
6	Control (day 0)	5.93
7	Control (day 2)	>5.70

The results above can be seen with reference to Figure 11, which shows each the log10 value for CFUs of each of the 7 study groups. It also shows a "upper limit' value of 5.70, which is essentially the value at which the CFUs is so high that it cannot accurately be measured.

- Only group 5 revealed bactericidal effect as the log10 CFU of 4.90.

[0284]

Based on the above test results, the medicament of the present invention can be a useful agent for treatment and/or prevention of symptom and/or disease induced by infection with mycobacteria.

[0285]

Usefulness as a medicament can be examined by the following tests, etc.

[0286]

Test Example 14: CYP inhibition test

Using commercially available pooled human liver microsomes, an

inhibitory degree of each metabolite production amount by the compound of the present invention was assessed as marker reactions of human main five CYP isoforms (CYP1A2, 2C9, 2C19, 2D6, and 3A4), 7-ethoxyresorufin O-deethylation (CYP1A2), tolbutamide methyl-hydroxylation (CYP2C9), mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), and terfenedine hydroxylation (CYP3A4).

[0287]

The reaction conditions were as follows: substrate, 0.5 μmol/L ethoxyresorufin (CYP1A2), 100 μmol/L tolbutamide (CYP2C9), 50 μmol/L S-mephenytoin (CYP2C19), 5 μmol/L dextromethorphan (CYP2D6), 1 μmol/L terfenedine (CYP3A4); reaction time, 15 minutes; reaction temperature, 37°C; enzyme, pooled human liver microsomes 0.2 mg protein/mL; concentration of the compound of the present invention, 1.0, 5.0, 10, 20 μmol/L (four points).

[0288]

Each of five kinds of substrates, human liver microsomes, or the compound of the present invention in 50 mmol/L Hepes buffer were added to a 96-well plate at the composition as described above, and NADPH, as a cofactor was added to initiate metabolism reactions. After the incubation at 37°C for 15 minutes, a methanol/acetonitrile = 1/1 (V/V) solution was added to stop the reaction. After the centrifugation at 3000 rpm for 15 minutes, resorufin (CYP1A2 metabolite) in the supernatant was quantified by a fluorescent multilabel counter or LC/MS/MS and hydroxytolbutamide (CYP2C9 metabolite), 4' hydroxymephenytoin (CYP2C19 metabolite), dextrorphan(CYP2D6 metabolite), and terfenadine alcohol metabolite (CYP3A4 metabolite) were quantified by LC/MS/MS.

[0289]

The sample obtained by adding only DMSO that was a solvent dissolving a compound instead of the compound of the present invention to a reaction mixture was adopted as a control (100%). Remaining activity (%) was calculated at each concentration of the compound of the present invention compared to control, and IC_{50} was calculated by reverse presumption by a logistic model using a concentration and an inhibition rate.

[0290]

Test Example 15: CYP3A4 (MDZ) MBI test

The CYP3A4(MDZ) MBI test is a test of investigating Mechanism based inhibition (MBI) potential on CYP3A4 inhibition of the compound of the present invention by the enhancement of the inhibitory effect caused by a metabolic reaction of the compound of the present invention. CYP3A4 inhibition was evaluated using pooled human liver microsomes by 1-hydroxylation reaction of midazolam (MDZ) as a marker reaction.

[0291]

The reaction conditions were as follows: substrate, 10 μmol/L MDZ; pre-reaction time, 0 or 30 minutes; substrate metabolic reaction time, 2 minutes; reaction temperature, 37°C; protein content of pooled human liver microsomes, at pre-reaction 0.5 mg/mL, at reaction 0.05 mg/mL (at 10-fold dilution); concentrations of the compound of the present invention, 1, 5, 10, 20 μmol/L or 0.83, 5, 10, and 20 μmol/L (four points).

[0292]

Pooled human liver microsomes and a solution of the compound of the present invention in K-Pi buffer (pH 7.4) as a pre-reaction solution were added to a

96-well plate at the composition of the pre-reaction. A part of pre-reaction solution was transferred to another 96-well plate, and 1/10 diluted by K-Pi buffer containing a substrate. NADPH as a cofactor was added to initiate a reaction as a marker reaction (Preincubation 0 min). After a predetermined time of a marker reaction, a solution of methanol/acetonitrile = 1/1 (V/V) was added to stop the reaction. In addition, NADPH was added to a remaining pre-reaction solution to initiate a pre-reaction (Preincubation 30 min). After a predetermined time of a pre-reaction, a part was transferred to another 96-well plate, and 1/10 diluted by K-Pi buffer containing a substrate to initiate a reaction as a marker reaction. After a predetermined time of a marker reaction, a solution of methanol/acetonitrile = 1/1 (V/V) was added to stop the reaction. After centrifuged at 3000 rpm for 15 minutes, 1-hydroxymidazolam in the supernatant was quantified by LC/MS/MS.

[0293]

The sample obtained by adding only DMSO that was a solvent dissolving a compound instead of the compound of the present invention to a reaction mixture was adopted as a control (100%). Remaining activity (%) was calculated at each concentration of the compound of the present invention compared to control, and IC value was calculated by reverse-presumption by a logistic model using a concentration and an inhibition rate. Shifted IC value was calculated as "IC of preincubation 0 min/ IC of preincubation 30 min". When a shifted IC was 1.5 or more, this was defined as positive. When a shifted IC was 1.0 or less, this was defined as negative.

[0294]

Test Example 16: BA test

Materials and Methods for experiments to evaluate oral absorption

(1) Animals: rats were used

(2) Breeding conditions: The mice or rats were allowed to freely take solid food and sterilized tap water.

(3) Dose and grouping: orally or intravenously administered at a predetermined dose; grouping was as follows (Dose depends on the compound)

Oral administration: 2 to 60 μmol/kg or 1 to 30 mg/kg (n = 2 to 3)

Intravenous administration: 1 to 30 μmol/kg or 0.5 to 10 mg/kg (n = 2 to 3)

(4) Preparation of dosing solution: for oral administration, in a solution or a suspension state; for intravenous administration, in a solubilized state

(5) Administration method: in oral administration, forcedly administered into ventriculus with oral probe; in intravenous administration, administer from caudal vein with a needle-equipped syringe

(6) Evaluation items: blood was collected over time, and the plasma concentration of drug was measured by LC/MS/MS

(7) Statistical analysis: regarding the transition of the plasma concentration of the compound of the present invention, the area under the plasma concentration-time curve (AUC) was calculated by non-linear least squares program WinNonlin (Registered trade name), and the bioavailability (BA) was calculated from the AUCs of the oral administration group and intravenous administration group.

[0295]

Test Example 17: Fluctuation Ames Test

Mutagenicity of the compound of the present invention was evaluated.

A 20 μL of freezing-stored *Salmonella typhimurium* (TA98 strain, TA100 strain) was inoculated on 10 mL of a liquid nutrient medium (2.5% Oxoid

nutrient broth No.2), and this was incubated at 37°C for 10 hours under shaking. The 7.70 to 8.00 mL of TA98 culture medium was centrifuged (2000 × g, 10 minutes). Bacteria were suspended in a Micro F buffer (K_2HPO_4: 3.5 g/L, KH_2PO_4: 1 g/L, $(NH_4)_2SO_4$: 1 g/L, trisodium citrate dihydrate: 0.25 g/L, and $MgSO_4 \cdot 7H_2O$: 0.1 g/L) with the same volume as that of the culture medium used for centrifugation. The suspension was added to 120 mL of Exposure medium (Micro F buffer containing biotin: 8 µg/mL, histidine: 0.2 µg/mL, and glucose: 8 mg/mL). The 3.10 to 3.42 mL of TA100 culture medium strain was mixed with 120 to 130 mL Exposure medium. Each 12 µL of DMSO solution of the compound of the present invention (several stage dilution from maximum dose 50 mg/mL at 2 to 3 fold ratio), DMSO as a negative control, and 50 µg/mL of 4-nitroquinoline 1-oxide DMSO solution for the TA98 strain and 0.25 µg/mL of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide DMSO solution for the TA100 strain in the assay without metabolic activation, 40 µg/mL of 2-aminoanthracene DMSO solution for the TA98 strain and 20 µg/mL of 2-aminoanthracene DMSO solution for the TA100 strain in the assay with metabolic activation as a positive control, and 588 µL of the test bacterial suspension (498 µL and 90 µL of S9 mixture in the case of metabolic activation assay) was mixed, and this was incubated at 37°C for 90 minutes under shaking. 460 µL of the mixture was mixed with 2300 µL of Indicator medium (Micro F buffer containing 8 µg/mL biotin, 0.2 µg/mL histidine, 8 mg/mL glucose, 37.5 µg/mL bromocresol purple), each 50 µL was dispensed to microplate 48 wells/dose, and this was incubated at 37°C for 3 days. Since the wells containing the bacteria which gained growth ability by point mutation in amino acid (histidine) synthesizing enzyme gene turns from purple to yellow due to a pH change, the number of yellow wells in 48 wells was counted per dose, and was compared with the negative control group. (-) and (+) means negative and positive in mutagenicity respectively.

[0296]

Test Example 18: hERG Test

For the purpose of assessing risk of an electrocardiogram QT interval prolongation of the compound of the present invention, effects of the compound of the present invention on delayed rectifier K+ current (I_{Kr}), which plays an important role in the ventricular repolarization process, was studied using CHO cells expressing human ether-a-go-go related gene (hERG) channel.

After a cell was retained at a membrane potential of -80 mV by whole cell patch clamp method using an automated patch clamp system (QPatch; Sophion Bioscience A/S) and gave a leak potential of -50 mV, I_{Kr} induced by depolarization pulse stimulation at +20 mV for 2 seconds and, further, repolarization pulse stimulation at -50 mV for 2 seconds, was recorded. Extracellular solution (NaCl: 145 mmol/L, KCl: 4 mmol/L, $CaCl_2$: 2 mmol/L, $MgCl_2$: 1 mmol/L, glucose: 10 mmol/L, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid): 10 mmol/L, pH = 7.4) adjusted to contain 0.1% dimethylsulfoxide was used as a medium. The extracellular solution in which the medium and the compound of the present invention had been dissolved at each objective concentration was applied to the cell for 7 minutes or more at room temperature. From the recording I_{Kr}, an absolute value of the tail peak current was measured based on the current value at the resting membrane potential using analysis software (QPatch Assay software; Sophion Bioscience A/S). Further, the tail peak current after application of the compound of the present invention relative to the tail peak current after application of the medium was calculated as a %

inhibition to assess the influence of the compound of the present invention on I_{Kr}.

[0297]

Test Example 19: Solubility test

The solubility of the compound of the present invention was determined under 1% DMSO addition conditions. 10 mmol/L solution of the compound was prepared with DMSO. 2 μL of the solution of the compound of the present invention was respectively added to 198 μL of JP-1 fluid or JP-2 fluid. The mixture was left shaking at room temperature for 1 hour, and the mixture was vacuum-filtered. The filtrate was 10- or 100-fold diluted with methanol/water = 1/1 (v/v) or acetonitrile/methanol/water = 1/1/2 (v/v/v), and the compound concentration in the filtrate was measured with LC/MS or Solid-Phase Extraction (SPE) /MS by the absolute calibration method.

[0298]

The composition of the JP-1 fluid was as below.

Water was added to 2.0 g of sodium chloride and 7.0 mL of hydrochloric acid to reach 1000 mL.

The composition of the JP-2 fluid was as below.

1 volume of water was added to 1 volume of the solution in which 3.40 g of potassium dihydrogen phosphate and 3.55 g of anhydrous disodium hydrogen phosphate were dissolved in water to reach 1000 mL.

[0299]

Test Example 20: Powder solubility test

Appropriate quantity of the compound of the present invention was put in suitable containers. 200 μL of JP-1 fluid (water was added to 2.0 g of sodium chloride and 7.0 mL of hydrochloric acid to reach 1000 mL), 200 μL of JP-2 fluid (1 volume of water was added to 1 volume of the solution which 3.40 g of potassium dihydrogen phosphate and 3.55 g of anhydrous disodium hydrogen phosphate dissolve in water to reach 1000 mL) or 20 mmol/L sodium taurocholate (TCA)/JP-2 fluid (JP-2 fluid was added to 1.08 g of TCA to reach 100 mL) was independently added to each container. When total amount was dissolved after adding the test reagent, the compound of the present invention was added appropriately. After sealing and shaking at 37°C for 1 hour, the solution was filtered and 100μL of methanol was added to 100 μL of each filtrate to dilute two-fold. The dilution rate was changed as necessary. After checking that there is no bubble and precipitate, the container was sealed and shaken. The compound of the present invention was measured using HPLC by absolute calibration curve method.

[0300]

Test Example 21: P-gp substrate test

The compound of the present invention is added to one side of Transwell (registered trademark, CORNING) where human MDR1-expressing cells or parent cells have been monolayer-cultured. The cells are reacted for a constant time. The membrane permeability coefficients from the apical side toward the basolateral side (A → B) and from the basolateral side toward the apical side (B → A) are calculated for the MDR1-expressing cells or the parent cells, and the efflux ratio (ER; ratio of the membrane permeability coefficients of B → A and A → B) values of the MDR1-expressing cells and the parent cells are calculated. The efflux ratio (ER) values of the MDR1-expressing cells and the parent cells are compared to confirm whether or not the compound of the present invention would be a P-gp substrate.

[0301]
Formulation Example

The following Formulation Examples are only exemplified and not intended to limit the scope of the invention.

[0302]
Formulation Example 1: Tablets

The compounds used in the present invention, lactose, and calcium stearate were mixed. The mixture was crushed, granulated and dried to give a suitable size of granules. Next, calcium stearate was added to the granules, and the mixture was compressed and molded to give tablets.

[0303]
Formulation Example 2: Capsules

The compounds used in the present invention, lactose, and calcium stearate were mixed uniformly to obtain powder medicines in the form of powders or fine granules. The powder medicines were filled into capsule containers to give capsules.

[0304]
Formulation Example 3: Granules

The compounds used in the present invention, lactose and calcium stearate are mixed uniformly and the mixture is compressed and molded. Then, it is crushed, granulated and sieved to give suitable sizes of granules.

[0305]
Formulation Example 4: Orally disintegrated tablets

The compounds used in the present invention and crystalline cellulose are mixed, granulated and tablets are made to give orally disintegrated tablets.

[0306]
Formulation Example 5: Dry syrups

The compounds used in the present invention and lactose are mixed, crushed, granulated and sieved to give suitable sizes of dry syrups.

[0307]
Formulation Example 6: Injections

The compounds used in the present invention and phosphate buffer are mixed to give injection.

[0308]
Formulation Example 7: Infusions

The compounds used in the present invention and phosphate buffer are mixed to give injection.

[0309]
Formulation Example 8: Inhalations

The compounds used in the present invention and lactose are mixed and crushed finely to give inhalations.

[0310]
Formulation Example 9: Ointments

The compounds used in the present invention and petrolatum are mixed to give ointments.

[0311]
Formulation Example 10: Patches

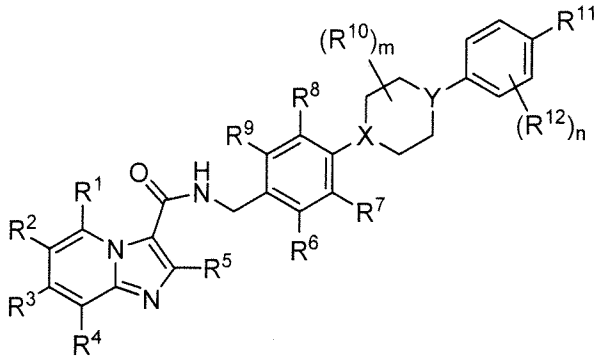
The compounds used in the present invention and base such as adhesive plaster or the like are mixed to give patches.

[Industrial Applicability]

[0312] The medicament of the present invention can be a medicine useful as a therapeutic and/or prophylactic agent for symptoms and/or diseases induced by infection with mycobacteria.

Claims

1. A medicament characterized in that (A) a compound represented by formula (I):



(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
is combined with
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

2. The medicament according to claim 1, wherein R^1 and R^4 are hydrogen atom.

3. The medicament according to claim 1, wherein R^2 is hydrogen atom, halogen or substituted or unsubstituted alkyl.

4. The medicament according to claim 1, wherein R^3 is hydrogen atom or halogen.

5. The medicament according to claim 1, wherein R^5 is substituted or unsubstituted alkyl.

6. The medicament according to claim 1, wherein R^6, R^8 and R^9 are hydrogen atom, and R^7 is halogen.

7. The medicament according to claim 1, wherein X is N.

8. The medicament according to claim 1, wherein Y is N.

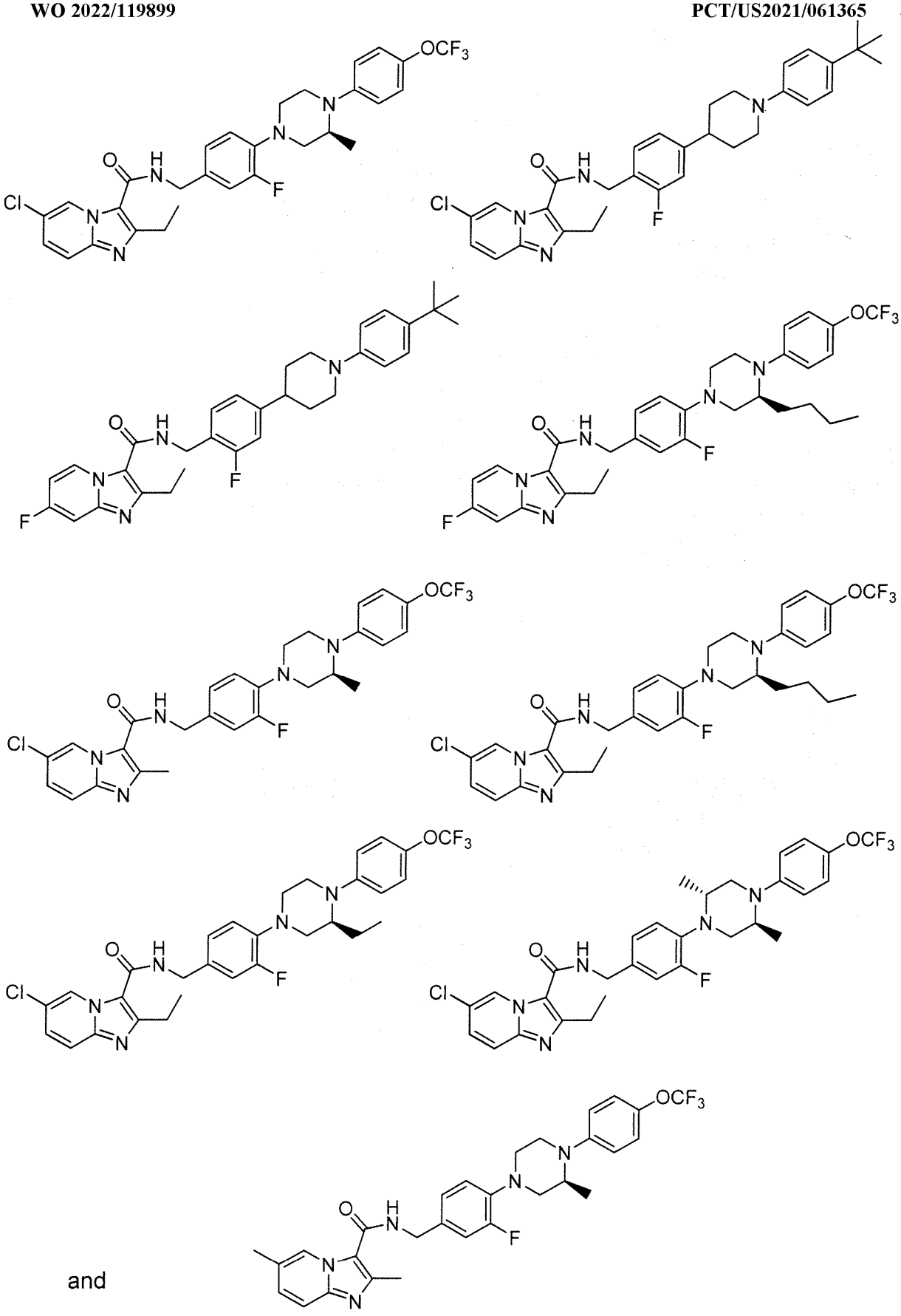
9. The medicament according to claim 1, wherein m is 1.

10. The medicament according to claim 9, wherein R^{10} is substituted or unsubstituted alkyl.

11. The medicament according to claim 1, wherein R^{11} is substituted or unsubstituted alkyloxy.

12. The medicament according to claim 1, wherein n is 0.

13. The medicament according to claim 1, wherein (A) is the compound selected from the group consisting of



and

, or its pharmaceutically acceptable salt.

14. The medicament according to claim 1, wherein (B) is clarithromycin or its pharmaceutically acceptable salt.

15. The medicament according to claim 1, wherein (A), (B) and (C) are simultaneously, sequentially or at intervals administered.

16. The medicament according to claim 1, wherein the medicament is combination drugs.

17. The medicament according to claim 1, wherein the medicament is used for the treatment or prevention of mycobacterial infection.

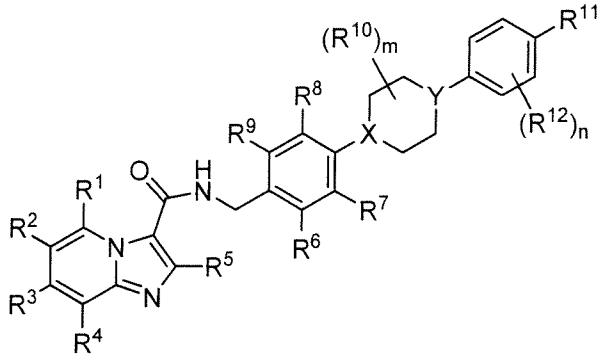
18. A method of enhancing the anti-bacterial activity of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt, comprising administering the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt with a compound represented by formula (I) in claim 1, or its pharmaceutically acceptable salt.

19. A method of enhancing the anti-bacterial activity of a compound represented by formula (I) in claim 1, or its pharmaceutically acceptable salt, comprising administering the compound represented by formula (I) in claim 1, or its pharmaceutically acceptable salt with (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt.

20. The method according to claim 18, wherein the (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt is/are administered simultaneously, sequentially or at intervals with a therapeutically effective amount of the compound represented by formula (I) in claim 1, or its pharmaceutically acceptable salt.

21. The method according to claim 19, wherein the compound represented by formula (I) in claim 1, or its pharmaceutically acceptable salt, is administered simultaneously, sequentially or at intervals with a therapeutically effective amount of (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and/or (C) clofazimine, or its pharmaceutically acceptable salt.

22. A method of treating mycobacterial infection comprising administering a combination of
(A) a compound represented by formula (I):

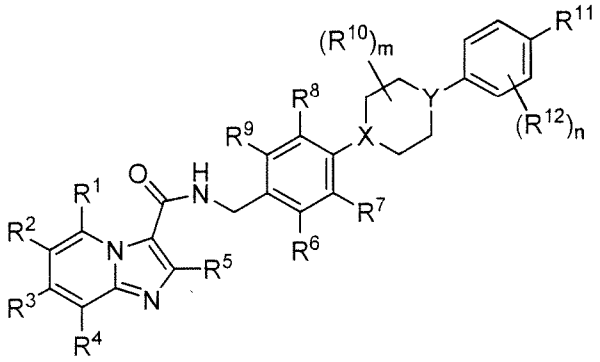


(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and
(C) clofazimine, or its pharmaceutically acceptable salt, in a therapeutically effective amount thereof to an individual in need of treatment for mycobacterial infection.

23. The method according to claim 22, wherein (A) a compound represented by formula (I), or its pharmaceutically acceptable salt, (B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt and (C) clofazimine, or its pharmaceutically acceptable salt, are administered simultaneously, sequentially or at intervals.

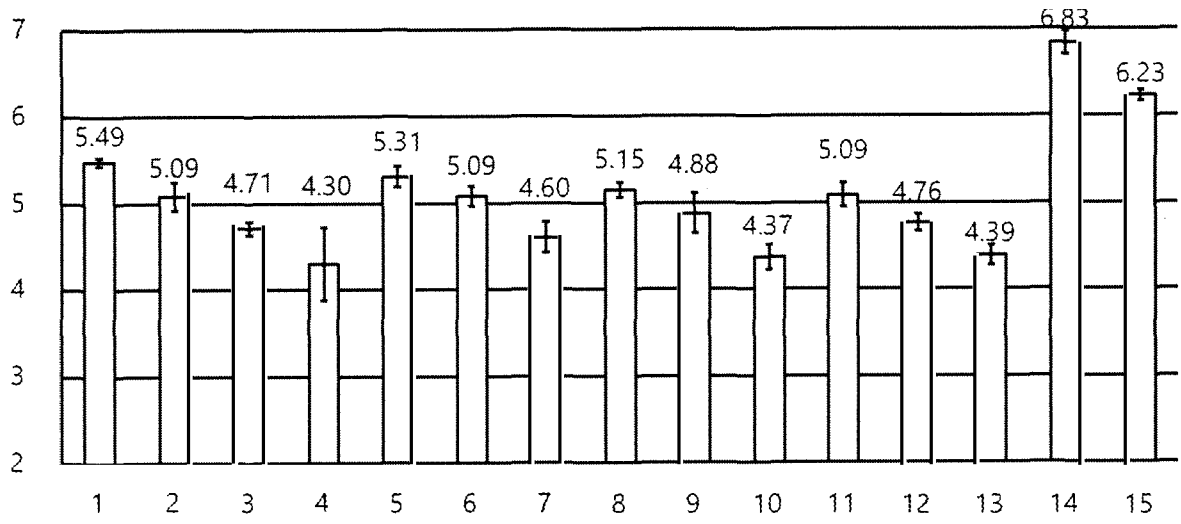
24. A pharmaceutical composition or kit, comprising:
(A) a compound represented by formula (I):



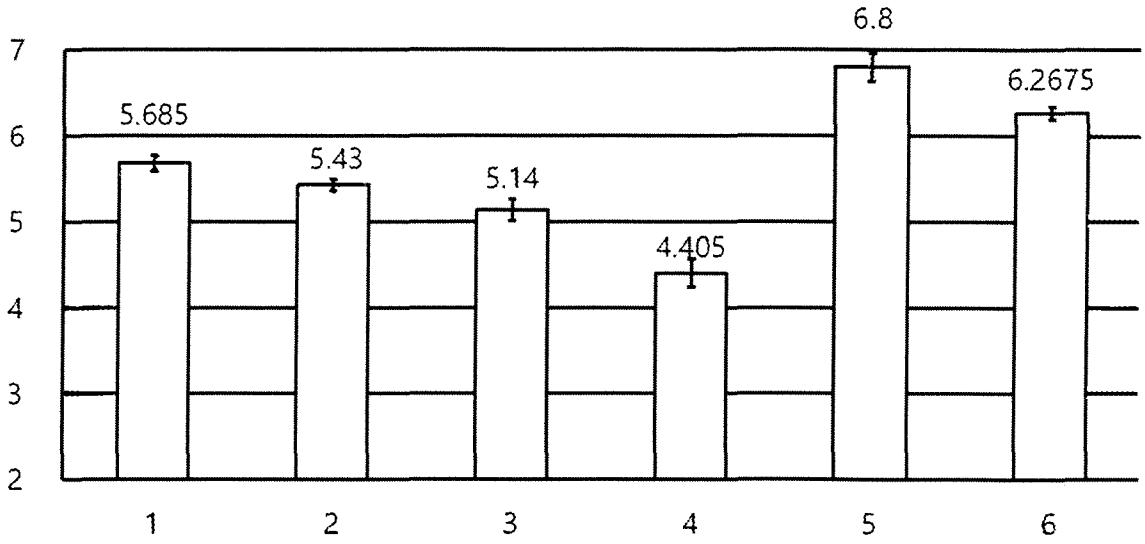
(I)

, or its pharmaceutically acceptable salt,
wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
R^5 is a hydrogen atom, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
R^6, R^7, R^8 and R^9 are each independently hydrogen atom, halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that R^6, R^7, R^8 and R^9 are not simultaneously hydrogen atom;
X is CH or N;
Y is CH or N;
R^{10} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;
m is 0, 1, 2, 3 or 4;
R^{11} is halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy or pentafluorothio;
R^{12} is each independently halogen, hydroxy, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy or substituted or unsubstituted alkynyloxy;
n is 0, 1, 2, 3 or 4;
(B) clarithromycin or its pharmaceutically acceptable salt, or azithromycin or its pharmaceutically acceptable salt; and
(C) clofazimine, or its pharmaceutically acceptable salt.

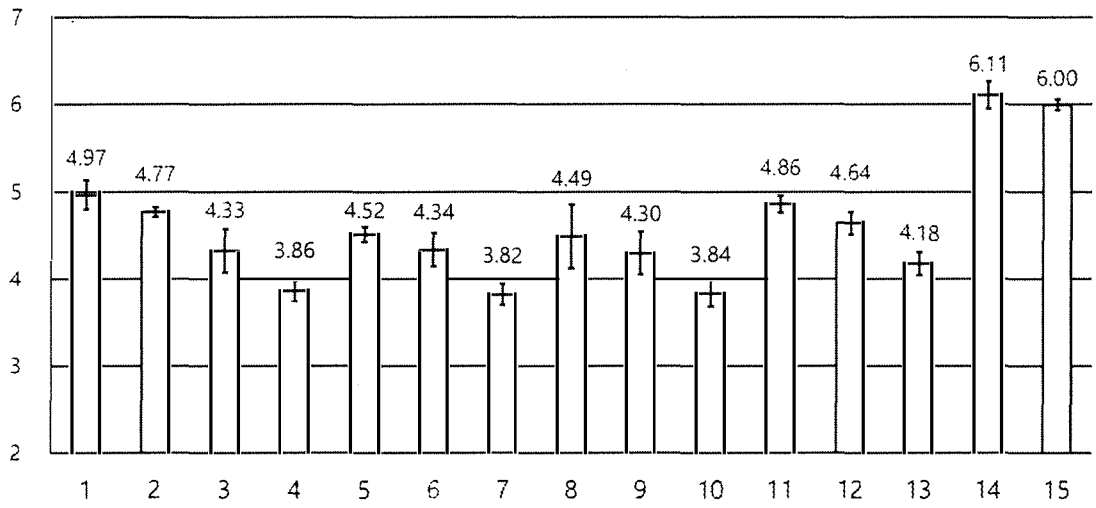
[Figure 1]


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5.09
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5.09
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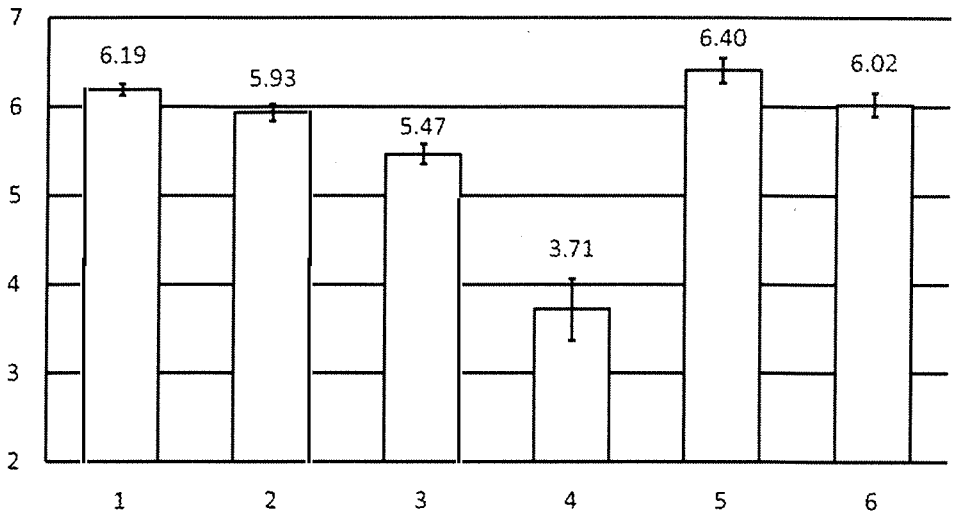
[Figure 2]



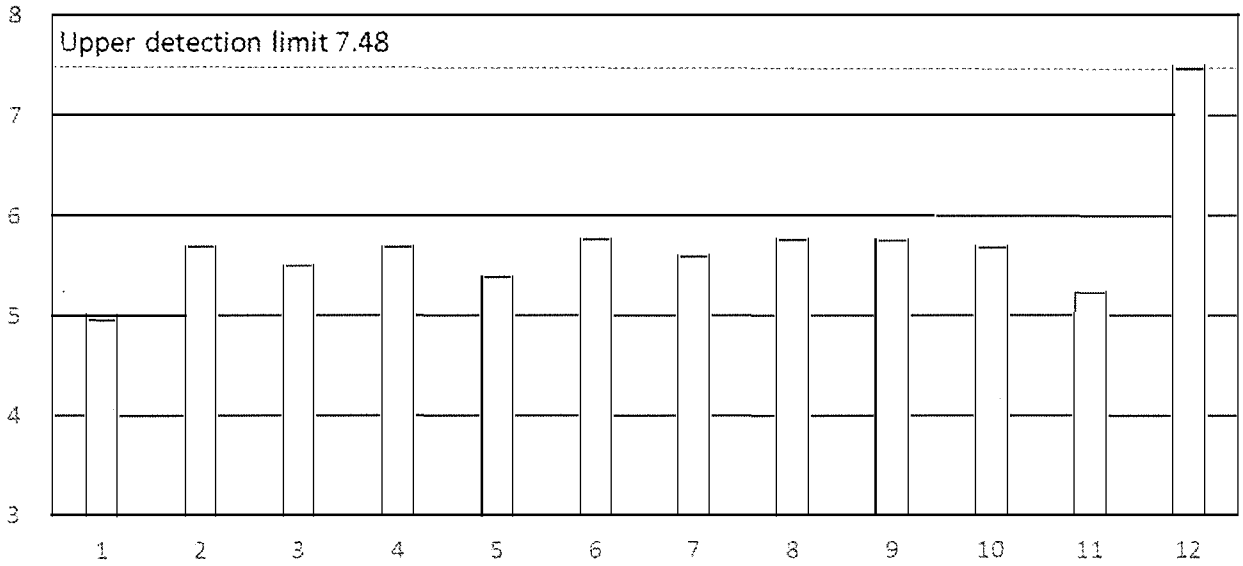
[Figure 3]


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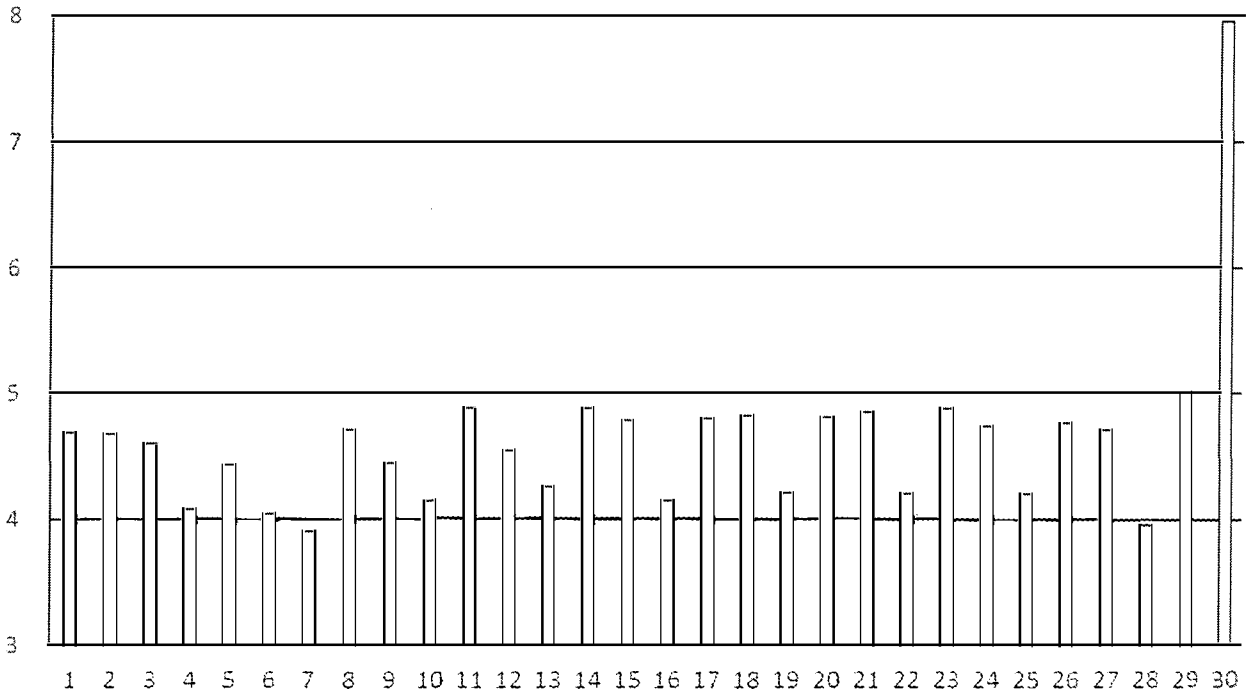
[Figure 4]



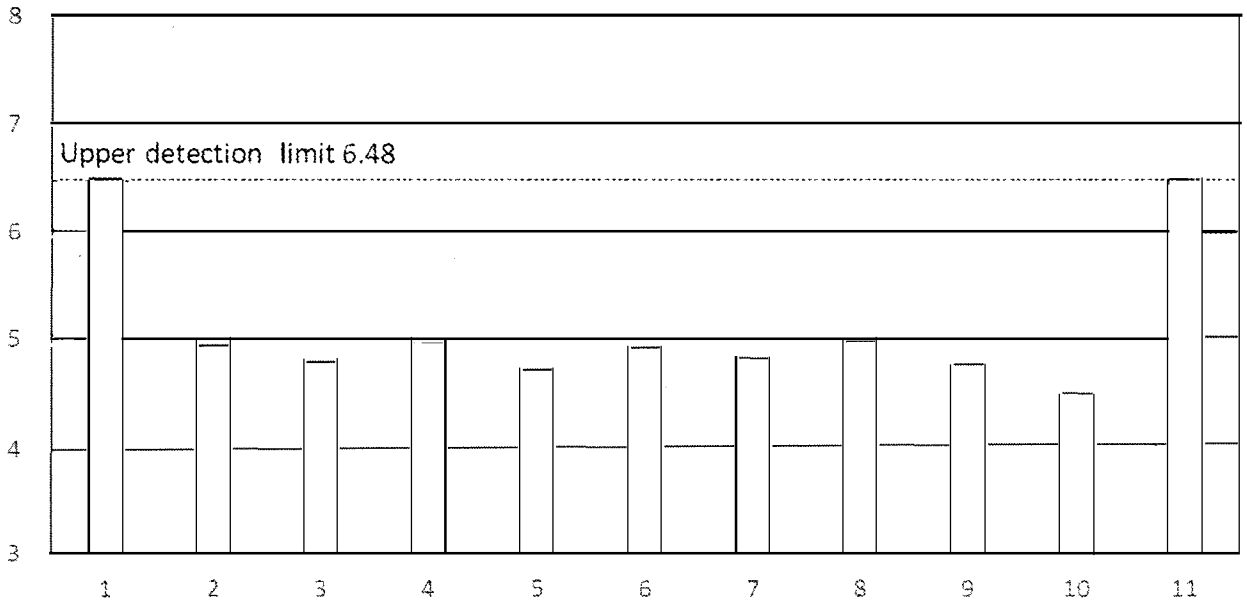
[Figure 5]



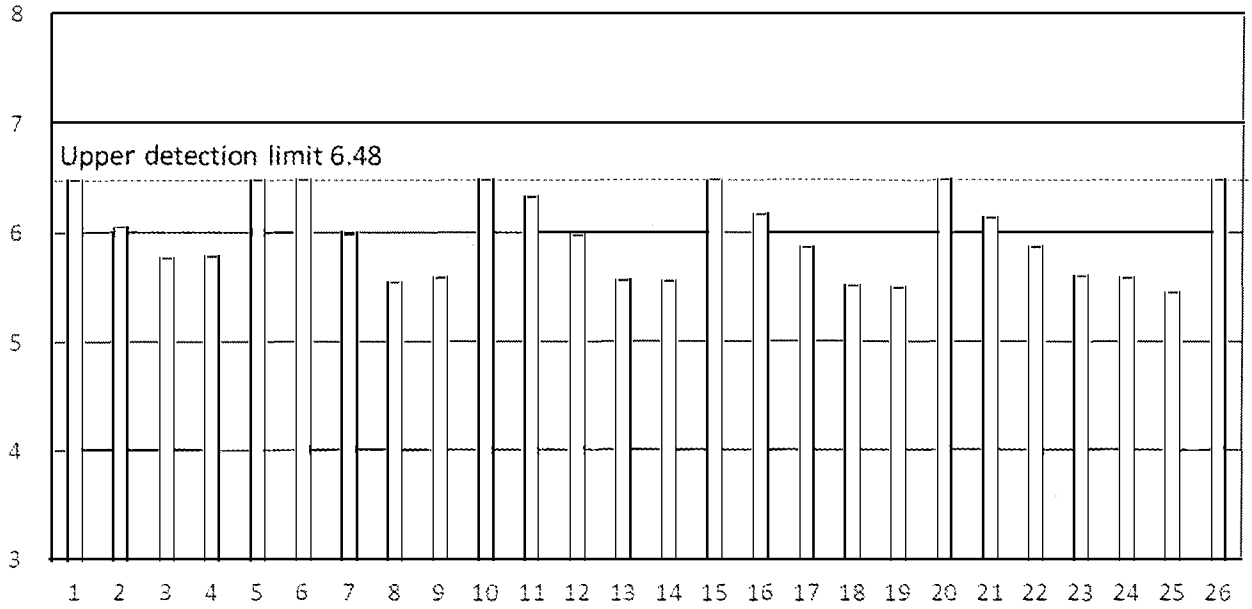
[Figure 6]


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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

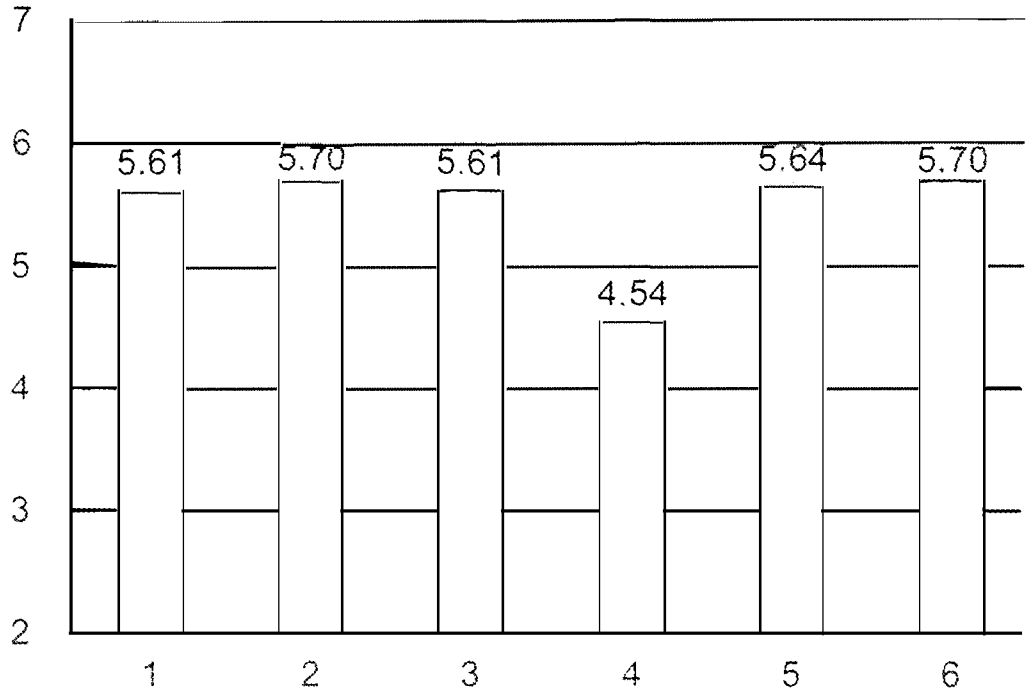
[Figure 7]



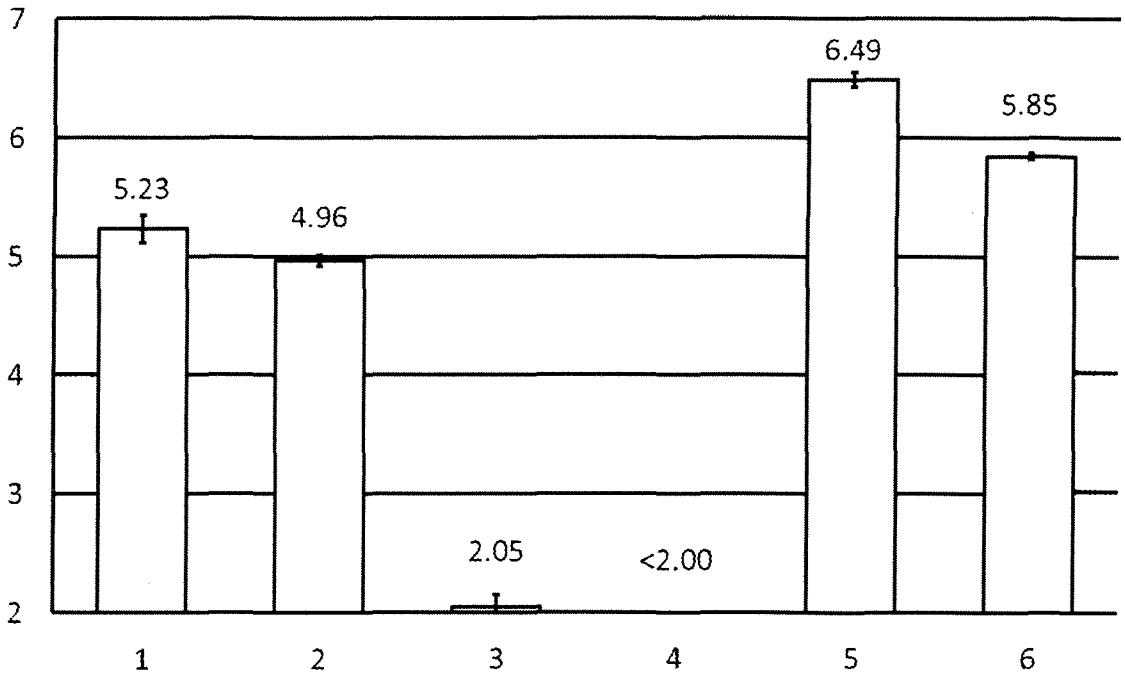
[Figure 8]


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Upper detection limit 6.48
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

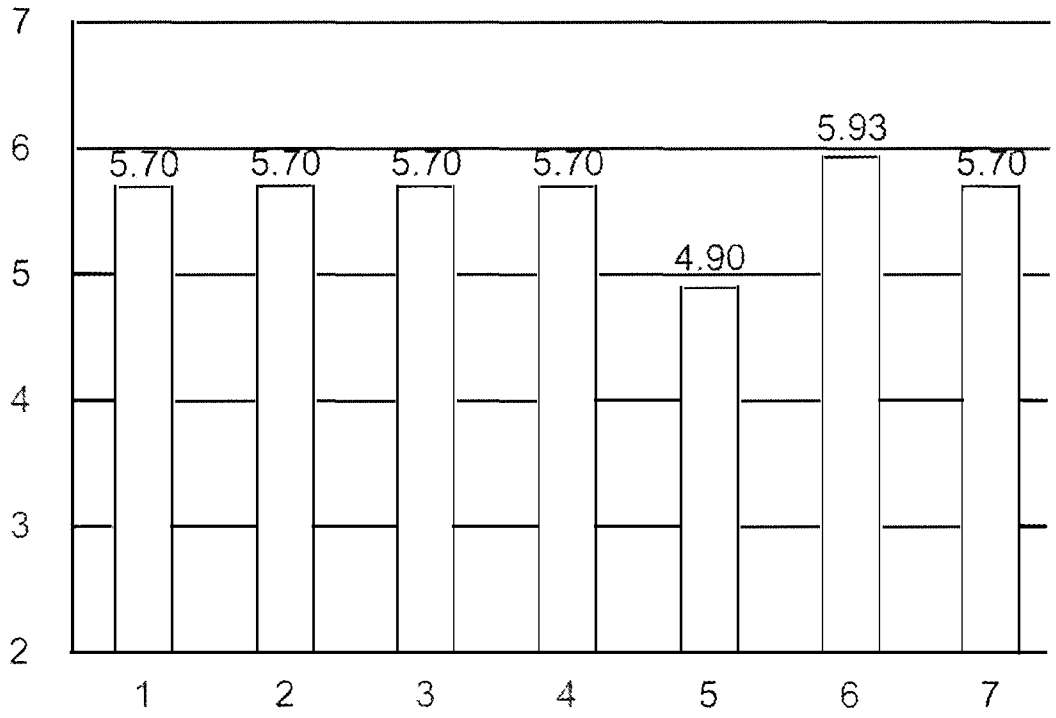
[Figure 9]



[Figure 10]



[Figure 11]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/061365

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/497(2006.01)i; ***A61K 31/4545***(2006.01)i; ***A61K 31/498***(2006.01)i; ***A61K 31/7048***(2006.01)i; ***A61K 31/7052***(2006.01)i; ***A61P 31/06***(2006.01)i
FI: A61K31/497; A61K31/4545; A61K31/7048; A61K31/7052; A61K31/498; A61P31/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/00-33/44; A61P31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2022
Registered utility model specifications of Japan 1996-2022
Published registered utility model applications of Japan 1994-2022

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

JSTPlus/JMEDPlus/JST7580 (JDreamIII); CAplus/REGISTRY/MEDLINE/EMBASE/BIOSIS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/0265506 A1 (MILLER, Marvin J.) 20 September 2018 (2018-09-20) claims 1, 15-17, Figures 7, 8, compounds ND-011454, 011457, 011458, 011461, 011496, 011543, 11870, 11874, 11869, 12000-12002, 12007-12010, Paragraphs [0003]-[0004], [0012], [0223], [0228]-[0235], [0283]	1-24
Y		1-24
Y	US 2013/0065884 A1 (NO, Zaesung) 14 March 2013 (2013-03-14) claims 1, 7, 10-13, Figure 3, compounds 111-115, 176-182, 283-290, 304-312, Example 3, Paragraph [0047]	1-24
Y	US 2020/0016154 A1 (JANSSEN SCIENCES IRELAND UNLIMITED COMPANY) 16 January 2020 (2020-01-16) Claims 2-5, 8, 13, Paragraphs [0019], [0037], [0039], [0178]	1-24
Y	WO 2020/051151 A1 (PARATEK PHARMACEUTICALS, INC.) 12 March 2020 (2020-03-12) Page 1 Line 27 - Page 2 Line 14	1-24

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 February 2022	**08 March 2022**
Name and mailing address of the ISA/JP **Japan Patent Office** **3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo** **100-8915, Japan**	Authorized officer **SHINKUMA, Tadanobu 4C 6113** Telephone No. **+81-3-3581-1101 Ext. 3452**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/061365

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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