Appeal decision

Appeal No. 2018-4573

U.S.A.
Appellant ViiV Healthcare Company

Patent Attorney HIRAKI & ASSOCIATES

The case of appeal against the examiner's decision of refusal for Japanese Patent application No. 2016-15242, titled "ANTIVIRAL THERAPY" [published on August 12, 2016, Japanese Unexamined Patent Application Publication No. 2016-145204] has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

The present application is a divisional application filed on January 29, 2016, which is a part of Japanese Patent Application No. 2012-551213 with an international filing date of January 24, 2011 (claiming priority benefit under Paris Convention for the Protection of Industrial Property with a receipt date of January 27, 2010 in the United States). The history of the procedures after the filing is summarized as below:

February 26, 2016 : Written amendment
March 4 of the same year : Written statement
November 28 of the same year : Notice of reasons for refusal
April 4, 2017 : Written opinion and written amendment
April 26 of the same year : Notice of reasons for refusal
July 31 of the same year : Written opinion
November 21 of the same year : Decision of Rejection
Prepared on December 7 of the same year: Response record
April 5, 2018 : Notice of appeal
November 27 of the same year : Notice of reasons for refusal
Prepared on January 9, 2019 : Response record

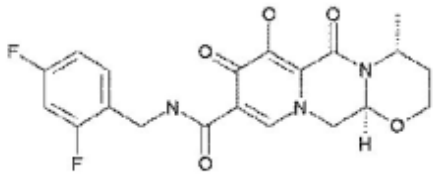
January 16 of the same year : Written opinion

(For your information, the response record prepared on December 7, 2017 records a response to an inquiry of typographical errors of cited documents, and the response record prepared on January 9, 2019 records a response to an inquiry of typographical errors of Claims subject to the notice of reasons for refusal.)

No. 2 The Invention

The inventions according to Claims 1 to 15 of the present application should be specified by the matters recited in Claims 1 to 15 of the Claims to which an amendment was made by the written amendment on April 4, 2017. Of these, the invention according to Claim 1 (hereinafter referred to as "the Invention") is set forth as below:

"[Claim 1]
A pharmaceutical composition comprising a compound of formula (I):
[Chemical formula 1]



(I)

or a pharmaceutically acceptable salt thereof and rilpivirine or a pharmaceutically acceptable salt thereof."

No. 3 Reasons for refusal notified by the body

The reason for refusal notified for the Invention by the body on November 27, 2018 is that the Invention does not fall within a scope that allows a person skilled in the art to recognize that the problem to be solved by the invention may be solved, and thus the recitation of the scope of claims of the present application does not conform to the requirement of Article 36(6)(i) of the Patent Act.

No. 4 The Detailed Descriptions of the Invention of the specification

The Detailed Description of the Invention of the specification has the following description (Note that the underline of "rilpivirine (TMC-278)" of [0025] is added by the body.):

"[Technical field]
[0001]

The present invention relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents."

"[Background Art]
[0002]

The human immunodeficiency virus ('HIV') is the causative agent for acquired immunodeficiency syndrome ('AIDS'), a disease characterized by destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ('ARC'), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever, and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.
[0003]

In addition to CD4, HIV requires a co-receptor for entry into target cells. The chemokine receptors function together with CD4 as co-receptors for HIV. The chemokine receptors CXCR4 and CCR5 have been identified as the main co-receptors for HIV-1. CCR5 acts as a major co-receptor for fusion and entry of macrophage-tropic HIV into host cells. These chemokine receptors are thought to play an essential role in the establishment and dissemination of an HIV infection. Therefore, CCR5 antagonists are thought to be useful as therapeutic agents active against HIV.
[0004]

As in the case of several other retroviruses, HIV encodes the production of a protease which carries out post-translational cleavage of precursor polypeptides in a process necessary for the formation of infectious virions. These gene products include pol, which encodes the virion RNA-dependent DNA polymerase (reverse transcriptase), an endonuclease, HIV protease, and gag, which encodes the core-proteins of the virion.
[0005]

One focus of anti-viral drug design has been to create compounds which inhibit the formation of infectious virions by interfering with the processing of viral polyprotein precursors. Processing of these precursor proteins requires the action of virus-encoded

proteases which are essential for replication. The anti-viral potential of HIV protease inhibition has been demonstrated using peptidyl inhibitors.
[0006]

A required step in HIV replication in human T-cells is the insertion by virally-encoded integrase of proviral DNA into the host cell genome. Integration is believed to be mediated by integrase in a process involving assembly of a stable nucleoprotein complex with viral DNA sequences, cleavage of two nucleotides from the 3' termini of the linear proviral DNA, and covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The repair synthesis of the resultant gap may be accomplished by cellular enzymes. Inhibitors of HIV integrase can be effective in treating AIDS and inhibiting viral replication.
[0007]

Administration of combinations of therapeutic compounds in the treatment of HIV infection and related conditions can result in potentiated antiviral activity, reduced toxicity, delayed progression to resistance, and increased drug efficacy. Combinations administered in a single dosage unit can result in increased patient compliance as the pill burden is reduced and dosing schedules are simplified. However, not all compounds are suitable for administration in combination. Factors that influence the feasibility of combinations include the chemical instability of the compounds, size of the dosage unit, potential for antagonistic or merely additive activities of the combined compounds, and difficulties in achieving a suitable formulation.
[0008]

There is continued need to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to treat HIV infection. Due to their high potency and pharmacokinetic profile, certain HIV integrase inhibitors are attractive as components in combination therapy."

"[Means for solving the problem]
[0009]

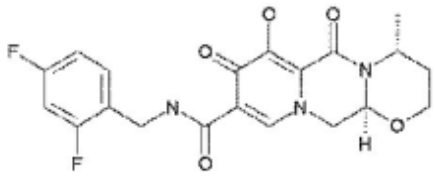
The present invention relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents. Such combinations are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in treatment of AIDS and/or ARC. The present invention also features pharmaceutical compositions containing HIV integrase inhibitors."

"[Description of Embodiments]

[0011]

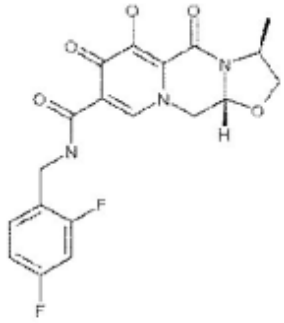
The present invention relates to combinations comprising a compound of the following formula (I), (II), or (III):

[Chemical formula 1]



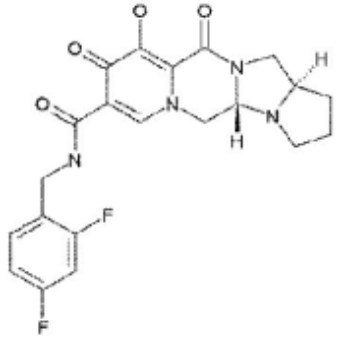
(I)

[Chemical formula 2]



(II)

[Chemical formula 3]



(III)

[0012]

or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of nucleotide reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, CCR5 antagonists, CXCR4 antagonists, fusion inhibitors, maturation inhibitors, and integrase inhibitors.

[0013]

The present invention relates to methods of treatment of HIV infection, AIDS, and AIDS related conditions by administering to a subject a compound of formula (I), (II), or (III) and one or more therapeutic agents selected from the group consisting of nucleotide reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, CCR5 antagonists, CXCR4 antagonists, fusion inhibitors, maturation inhibitors, and integrase inhibitors.

[0014]

A compound of formula (I) is also known as GSK1349572. A chemical name of the compound of formula (I) is (4R, 12aS)-N-[2,4-flurophenyl)methyl]-3,4,6,8,12, 12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-2H-pyrido [1',2':4,5]pyrazino [2,1-b] [1,3] oxazine-9-carboxamide.

[0015]

A chemical name of the compound of formula (II) is (3S, 11aR)-N-[(2,4-difluorophenyl)methyl]-2,3,5,7,11,11a-hexahydro-6-hydroxy-3-methyl-5,7-dioxo-oxazolo [3,2-a] pyrido [1,2-d]pyrazine-8-carboxamide.

[0016]

A chemical name of the compound of formula (III) is (4aS, 13aR)-N-[2,4-difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1H-pyrido[1,2-a]pyrrolo[1',2':3,4,]imidazo[1,2-d]pyrazine-8-carboxamide."

"[0022]

The present invention relates to methods of treating or preventing viral infection, for example an HIV infection, in a human comprising administering to the human a therapeutically effective amount of a compound of formula (I), (II), or (III) or a pharmaceutically acceptable salt thereof in combination with one or more therapeutic agents selected from the group consisting of nucleotide reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, CCR5 antagonists, CXCR4 antagonists, fusion inhibitors, maturation inhibitors, and integrase inhibitors. The combination may be administered simultaneously or sequentially.

[0023]

The compounds of formula (I), (II), and (III) are particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment may extend to prophylaxis as well as the treatment of established infections,

symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

[0024]

Combination therapies comprise the administration of a compound of the present invention or a pharmaceutically acceptable salt thereof and another pharmaceutically active agent. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[0025]

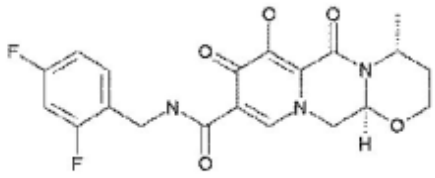
Examples of such therapeutic agents include, but are not limited to, agents that are effective for the treatment of viral infections or associated conditions. Among these agents are nucleotide reverse transcriptase inhibitors, acyclic nucleoside phosphonates, such as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl) cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy] methyl]phosphinylidene] bis(oxymethylene)-2,2-dimethyl propanoic acid (bis-POM PMEA, adefovir dipivoxil), adefovir, [[(1R)-2-(6-amino-9H-purin- 9-yl)-1-methylethoxy]methyl] phosphonic acid (tenofovir), tenofovir disoproxil fumarate, and (R)-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA); nucleoside reverse transcriptase inhibitors, such as 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2', 3'- didehydrothymidine (d4T, stavudine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)- cytosine (lamivudine), cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC, emtricitabine), (-)-cis-4-[2-amino-6-(cyclo-propylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), fozivudine tidoxil, alovudine, amdoxovir, elvucitabine, apricitabine, and festinavir (OBP-601); protease inhibitors, such as indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, lopinavir, atazanavir, tipranavir, darunavir, brecanavir, palinavir, lasinavir, TMC-31091 1, DG-17, PPL-100, and SPI-256; non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine, delavirdine, efavirenz, GSK2248761 (IDX-12899), lersivirine (UK-453,061), rilpivirine (TMC-278), etravirine, loviride, immunocal, oltipraz, capravirine, and RDEA-806; integrase inhibitors, such as raltegravir, elvitegravir, and JTK-656; CCR5 and/or CXCR4 antagonists, such as, maraviroc, vicriviroc (Sch-D), TBR-652 (TAK-779), TAK-449, PRO-140, GSK706769, and SCH-532706; fusion inhibitors, such as enfuvirtide (T-20), T-1249, PRO-542, ibalizumab (TNX-355), BMS-378806 (BMS-

806), BMS-488043, KD-247, 5- Helix inhibitors, and HIV attachment inhibitors; and maturation inhibitors, such as bevirimat (PA-344 and PA-457).

[0026]

The present invention features a combination comprising a compound of formula (I):

[Chemical formula 4]



(I)

[0027]

or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of lamivudine, abacavir, tenofovir, efavirenz, GSK2248761, lersivirine, lopinavir, fosamprenavir, and atazanavir.

[0028]

The present invention also features a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from abacavir, efavirenz, and lopinavir. The present invention features a combination comprising of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and abacavir.

[0029]

The present invention features a method of treatment of HIV infection comprising administering to a subject a compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of lamivudine, abacavir, tenofovir, efavirenz, GSK2248761, lersivirine, lopinavir, fosamprenavir, and atazanavir.

[0030]

The present invention features a method of treatment of HIV infection comprising administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir. The present invention features a method of treatment of HIV infection comprising administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt thereof, and abacavir.

[0031]

The present invention features a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of: lamivudine, abacavir, efavirenz, tenofovir, GSK2248761 , lersivirine, lopinavir, fosamprenavir, and atazanavir together with a pharmaceutically acceptable carrier therefor.

[0032]

The present invention features a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents selected from the group consisting of: abacavir, efavirenz, and lopinavir, together with a pharmaceutically acceptable carrier therefor. The present invention features a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and abacavir together with a pharmaceutically acceptable carrier therefor."

"[0047]

The present invention features combinations, methods of treatment, and pharmaceutical compositions as described above, wherein a pharmaceutically acceptable salt of a compound of formula (I), (II), or (III) is a sodium salt.

[0048]

The present invention features combinations, methods of treatment, and pharmaceutical compositions as described above wherein one or more therapeutic agents are a pharmaceutically acceptable salt of said therapeutic agents, such as abacavir hemisulfate, fosamprenavir calcium, atazanavir sulfate, tenofovir disoproxil sulfate, vicriviroc maleate, or bevirimat dimeglumine.

[0049]

The present invention features methods of treatment as described above, wherein the subject is a human.

[0050]

The present invention features combinations, methods of treatment, and pharmaceutical compositions as described above, wherein the combination is administered sequentially.

[0051]

The present invention features combinations, methods of treatment, and pharmaceutical compositions as described above, wherein the combination is administered simultaneously or concurrently.

[0052]

Compounds of formula (I), (II), and (III) may be made by methods disclosed in WO2006/116764, U.S. 61/193,634 (WO2010/068253), or U.S. 61/193,636 (WO2010/068262), incorporated herein by reference hereto.

[0053]

Abacavir may be made by methods disclosed in U.S. Patent Nos. 5,034,394; ... and 6,646,125.

[0054]

Lamivudine may be made by methods disclosed in U.S. Patent Nos. 5,047,407; ... and 6,329,522.

[0055]

Tenofovir may be made by methods disclosed in U.S. Patent Nos. 5,922,695; ...6,069,249.

[0056]

Efavirenz may be made by may be made by methods disclosed in U.S. Patent Nos. 5,519.021; ... and 6,939,964.

[0057]

GSK2248761 may be made by methods disclosed in U.S. Patent No. 7,534,809.

[0058]

Lersivirine may be made by methods disclosed in U.S. Patent No. 7,109,228.

[0059]

Lopinavir may be made by methods disclosed in U.S. Patent No. 5,914,332.

[0060]

Fosamprenavir may be made by methods disclosed in U.S. Patent Nos. 6,436,989; 6,514,953; and 6,281,367.

[0061]

Atazanavir may be made by methods disclosed in U.S. Patent Nos. 5,849,911 and 6,087,383.

[0062]

The therapeutic agents of the combinations may be made according to published methods or by any method known to those skilled in the art.

[0063]

In an aspect of the invention, a compound of formula (I), (II), or (III) or a pharmaceutically acceptable salt thereof may be formulated into compositions together with one or more therapeutic agents. The composition may be a pharmaceutical composition, which comprises a compound of formula (I), (II), or (III), one or more therapeutic agents, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In

one embodiment, the composition comprises an amount of a combination of the present invention effective to treat or prevent viral infection, such as an HIV infection, in a biological sample or in a patient. In another embodiment, combinations of the invention and pharmaceutical compositions thereof, comprising an amount of a combination of the present invention effective to inhibit viral replication or to treat or prevent a viral infection or disease or disorder, such as an HIV infection, and a pharmaceutically acceptable carrier, adjuvant, or vehicle, may be formulated for administration to a patient, such as for oral administration.

[0064]

The present invention features combinations according to the invention for use in medical therapy, such as for the treatment or prophylaxis of a viral infection, such as an HIV infection and associated conditions. The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thromobocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraperesis, anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients."

"[0069]

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day; more preferably in the range 1 to 30 mg per kilogram body weight per day; particularly preferably in the range 0.5 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredients are calculated as the parent compound of formula (I), (II), or (III) and other therapeutic agents. For salts thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six, or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternate days. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 2000 mg; preferably 5 to 500 mg; more preferably 10 to 400 mg, and particular preferably 20 to 300 mg of each active ingredient per unit dosage form.

[0070]

The combinations may be administered to achieve peak plasma concentrations of each active ingredient.

[0071]

While it is possible for the active ingredients to be administered alone, it is preferable to present as a pharmaceutical composition. The compositions of the present invention comprise an active ingredient, as defined above, together with one or more acceptable carriers thereof and one or more additional therapeutic agents. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

[0072]

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal, and sublingual), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product."

"[Examples]

[0084]

Example 1 Biological Activity

Assays

Methods

Antiviral HIV activity was measured by means of a tetrazolium-based colorimetric procedure in the human T-cell leukemia virus (HTLV-1) transformed cell line MT-4. Aliquots of test compound were diluted vertically across a deep-well master assay plate, in medium ..., at concentrations that were approximately 40-fold higher than the final assay concentration. Serial dilutions were made at either 1:2 or 1:3.16 ratios. HIV inhibitors were diluted horizontally across master assay plates, also in concentrations that were approximately 40-fold higher than the final assay concentration. Small aliquots of both the vertically-diluted and the horizontally-diluted compounds were combined in daughter plates using an automated 96-well pipetting system ... Checkerboard style dilutions were arranged so that every concentration of test compound was tested in the presence and absence of every concentration of the HIV inhibitors. Anti-HIV activity tests were performed in triplicate assays, or more, of each combination. Exponentially

growing MT-4 cells were harvested and centrifuged at 1,000 rpm for 10 minutes in a Jouan centrifuge (Model CR 412). Cell pellets were re-suspended in fresh medium ... to a density of 1.25 x 10^6 cells/mL. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection (MOI) of 73 pfU per 1 x 10^4 cells. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hour at 37°C in a tissue culture incubator with humidified 5% CO_2 atmosphere. After the 1-hour incubation the virus/cell suspension was added to each well of the plates containing pre-diluted compounds. Plates were then placed in a tissue culture incubator with humidified 5% CO_2 for 5 days. At the end of the incubation period, 40 µL of CellTiter 96 MTS reagent (Promega No. G3581) was added to each well of the incubation plate. Plates were incubated at 37°C for 2 to 3 hours to allow for color development. O.D. was measured at 492 nM using a microplate absorbance reader (Tecan no. 20-300).

[0085]

Virus used

HIV-1 strain IIIB, wild-type laboratory strain, virus titer = 6.896 E4 $TCID_{50}$/mL.

[0086]

Data Analysis

Although some assay formats might theoretically miss antagonism due to combination cytotoxicity, the approach described here should not miss an antagonistic effect. The readout in the MT-4 cell assay utilizes MTS, a tetrazolium-based staining reagent where changes in optical density (O.D.) of the reagent are used to estimate the total cell number remaining after treatment. Final MT-4 cell numbers may decrease due to two effects. First, an HIV-induced cytotoxicity may occur when HIV kills greater than 75% of the MT-4 cells during the 5 days following infection. Second, a compound-induced cytotoxicity may occur, where the compound either directly kills the MT-4 cells or prevents cell growth (stasis) over the 5 days in either infected or uninfected cells. In either of these situations the O.D. is low as compared with infected cells protected by anti-HIV-1 compounds or relative to untreated and uninfected control cells. Since both cytotoxic effects and antagonism of anti-HIV activity would lead to lower O.D., we should not miss an antagonistic effect due to combination cytotoxicity, but could underestimate synergistic combinations.

[0087]

Within assay combination cytotoxicity was evaluated by comparing wells containing the uninfected MT-4 cells from the assay plates that contained the highest concentration of test compound or the comparator compound, with wells containing HIV-

1 infected MT-4 cells under the corresponding highest combination concentrations. For each of these values there is one well per assay plate and thus at least 3 wells per combination assay. Although they do not comprise a formal combination cytotoxicity analysis, the ratio of compound in combinations to compound alone provides a measure of the compound combination cytotoxicity within the concentrations examined.

[0088]

The interaction of each pair of compound combinations was analyzed by the methods described by Selleseth, D.W. et al. (2003) Antimicrobial Agents and Chemotherapy 47:1468-71. Synergy and antagonism are defined as deviations from dosewise additivity, which results when two drugs interact as if they were the same drug. Values for average deviation from additivity in the range of - 0.1 to - 0.2 indicate weak synergy and values that approach -0.5 would indicate strong synergy of the interaction. Conversely, positive values of 0.1 to 0.2 would indicate that a weak antagonism exists between the treatments.

[0089]

Results

A compound of formula (I) was found to be additive with raltegravir, adefovir, and maraviroc and was not affected by the presence of ribavirin. A compound of formula (I) was found to be synergistic with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide."

No. 5 Judgment

1 The determination of whether or not the recitation of the Claims might comply with the support requirement should follow the steps of: comparing the recitation of the Claims and the descriptions of the Detailed Description of the invention; and considering whether or not the invention recited in the Claims might fall within the scope in which person ordinarily skilled in the art could recognize that a problem to be solved by the invention might be solved by the description of the Detailed Description of the Invention, or considering whether or not the invention recited in the Claims might fall within the scope in which person ordinarily skilled in the art could recognize without such description or suggestion in view of common technical knowledge as of the filing that the problem to be solved by the invention might be solved.

Accordingly, from the above viewpoint, a consideration is given hereinafter.

2 Problem to be solved by the Invention

According to the description of [0001], [0007], and [0008] of the specification of the present application, the combined administration of therapeutic compounds in the treatment of HIV infection may cause the promotion of antiviral activity, decreased toxicity, delayed progression to resistance, and increased drug efficacy. Not all the compounds are suitable for the combined administration, but there might be a problem of the combined compounds causing antagonist effects. It can be said that the present invention has a problem "to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to treat HIV infection in connection with combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents".

3 Common general knowledge of anti-HIV drug

Since the world's first anti-HIV drug of zidovudine (AZT) was approved by the FDA on 1987, novel anti-HIV drugs have been constantly developed, and HIV infection disease has come to be seen as chronic disease by the polypharmacy therapy that appeared in 1996.

As of the original filing date, anti-HIV drug such as nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and CCR5 antagonists had been known, and it was necessary to administer the respective agents in combination by well understanding action mechanism, properties, and side effects of the respective agents and taking into account the interaction thereof in order to maximize the outcome of anti-HIV therapy of polypharmacy.

Further, as of the original filing date, there was a report of the case where a combination of two agents was effective, including an example where a combination of darunavir and raltegravir made a success; however, combination therapy of two agents had not been common. A standard treatment of anti-HIV therapy was polypharmacy therapy of three or four agents.

(Regarding the common technical knowledge, see "Folia Pharmacol. Jpn.", 130, 152-156, 2007, "J. New Rem. & Clin.", Vol. 58, No. 7, p. 135 (1259) to 138 (1262), 2009, "Clinics and Viruses", Vol. 38, No. 4, pp. 260-269, 2010.10, "Treatment of HIV Infection Diseases and AIDS", Vol. 2, No. 1, pp. 14-17, "Introduction", lines 1 to 10, May 2011 [Note: May 2011 is after the filing date of the original application, but the corresponding part shows the recognition of a person ordinarily skilled in the art as of the original filing date.] etc.)

4 The scope in which a person ordinarily skilled in the art can recognize that a problem to be solved by the Invention may be solved

(1) The Detailed Description of the Invention of the specification discloses that "the present invention relates to methods of treating or preventing viral infection, such as an HIV infection, in a human comprising administering to the human a therapeutically effective amount of a compound of formula (I), (II), or (III) or a pharmaceutically acceptable salt thereof in combination with one or more therapeutic agents selected from the group consisting of nucleotide reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, CCR5 antagonists, CXCR4 antagonists, fusion inhibitors, maturation inhibitors, and integrase inhibitors. The combination may be administered simultaneously or sequentially." ([0022]), "Combination therapies comprise the administration of a compound of the present invention or a pharmaceutically acceptable salt thereof and another pharmaceutically active agent. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect." ([0024]). Non-limited examples of therapeutic agents in combination with the compounds of formula (I), (II), and (III) include a number of therapeutic agents ([0025]).

Of many therapeutic agents exemplified, what is specifically disclosed to combine with the compound of formula (I) to make a single pharmaceutical composition is only "one or more therapeutic agents selected from the group consisting of lamivudine, abacavir, tenofovir, efavirenz, GSK2248761, lersivirine, lopinavir, fosamprenavir, and atazanavir" ([0031][0032]).

Further, not all the compounds of compounds for treatment of HIV are necessarily suitable for the combined administration, but might possibly cause antagonist effects ([0007]). Examples of the specification of the present application describe a result of MT-4 cell assay for the confirmation of synergistic effects, additive effects, and antagonist effects, and describe that "a compound of formula (I)" was found to be "additive with raltegravir, adefovir, and maraviroc" and "synergistic with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, and enfuvirtide"
([0089]).

(2) As shown in the above 3, as of the original filing date there was common technical knowledge that it was necessary to administer the respective agents in combination by well understanding action mechanism, properties, and side effects of the respective agents and taking into account the interaction in order to maximize the outcome of anti-HIV therapy of polypharmacy. In view of this, a person skilled in the art who read the description of the specification of the present application (in particular the description that not all the therapeutic compounds of HIV are suitable for the combined administration, but possibly cause antagonist effects ([0007])) would not recognize without the support of any specific experimental results that all the exemplified therapeutic drugs in [0025] may be used as a single pharmaceutical composition in combination with the compound of formula (I).

Consequently, what a person skilled in the art can recognize as the invention solving a problem to be solved by the invention is at most only a pharmaceutical composition comprising "the compounds of formula (I)" and any of "raltegravir, adefovir, maraviroc, stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, and enfuvirtide" for which the experimental results of MT-4 cell assay are shown.

5 Supporting Requirement of the Invention

The specification of the present application does not disclose any experimental results using rilpivirine. Further, rilpivirine is described only in [0025] as one of many non-limited examples that can be combined with any of compounds of formula (I), (II), and (III). Rilpivirine is not described in [0031][0032] that describe a single pharmaceutical composition comprising specific therapy drugs and compound of formula (I). Thus there is not even a ground that makes us focus on a specific combination of the compound of formula (I) and rilpivirine from the description of the specification of the present application.

Further, as shown in the above 3, in view that there was common technical knowledge as of the original filing date that it was necessary to administer the respective agents in combination by well understanding action mechanism, properties, and side effects of the respective agents and taking into account the interaction in order to maximize the outcome of anti-HIV therapy of polypharmacy, it must be said that a person skilled in the art who read the description of the specification of the present application (in particular not all the compounds of therapeutic compounds of HIV are necessarily suitable for the combined administration, but might possibly cause antagonist effects ([0007])) could not recognize that it was suitable for the combined use and would become a feasible pharmaceutical composition if "a combination of the compound of formula (I)

and rilpivirine", on which there was neither experimental result nor even a ground that makes a person skilled in the art focus from the description of the specification of the present application, should be provided for a single pharmaceutical composition.

Therefore, it cannot be said that the Invention of a pharmaceutical composition comprising "a combination of the compound of formula (I) and rilpivirine" falls within a scope that allows a person skilled in the art to recognize from the description of the Detailed Description of the Invention of the specification of the present application in view of the common general knowledge as of the original filing date that a problem "to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to treat HIV infection in connection with combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents" may be solved.

2 Appellant's allegation

(1) The Appellant presents reference documents 1 to 4 and alleges in the written statement submitted on March 4, 2016 and the notice of appeal submitted on April 5, 2018 that (i) it is outstanding that a combination of two agents of the compound of formula (I) (DTG; dolutegravir) and rilpivirine (RPV) shows the best resistant profile compared to the combinations of the other reverse transcriptase inhibitors and integrase inhibitors, unexpectedly inhibits the HIV growth at a lower level compared to a single dose administration, and suppresses the expression of NNRTI or INSTI resistance, and (ii) the combination of the present invention is demonstrated to show a preferable or at least not inferior result compared to the standard combinations of three or four drugs, and a pharmaceutical product of the combinations of the Invention has already been approved in the United States.

However, the specification of the present application does not individually describe the combinations according to the Invention, nor does it describe pharmacological data for the Invention. Further, a person skilled in the art cannot recognize from the matters described in the specification of the present application in view of the common technical knowledge as of the original filing date that the Invention is suitable for the use in combination for the treatment of HIV infection and a feasible pharmaceutical composition.

Regardless of the fact that the disclosure of the specification is to such an extent as described above, it is impossible to use the results of experiments that have been conducted after the original filing date of reference documents 1 to 3 or articles in order to clarify the fact that a technical idea of the Invention being suitable for the combined

use in the treatment of HIV infection, and that being a feasible pharmaceutical composition was not simply a matter of speculation by the inventor.

Further, the approval of a pharmaceutical product according to the combination of the Invention in the United States (reference document 4) does not affect the determination about the support requirement of the Invention.

Therefore, considering the above allegation by the Appellant, it must be said that the determination about the support requirement is as per the above.

(2) The Appellant alleges in the written opinion dated January 16, 2019 that "The specification of the present application describes non-nucleoside reverse transcriptase inhibitors (NNRTIs) as a compound capable of being combined with a compound of formula (I), and further describes rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) (paragraphs 0022 and 0025 of the specification of the present application). It is thus submitted that a person skilled in the art could recognize from the description of the specification of the present application that a problem might be solved by the Invention. Therefore, it is submitted that the above reason for rejection has been overcome."

However, the Appellant only points out the description of [0022] and [0025] of the specification of the present application, and fails to explain any technical grounds for making a person skilled in the art believe that a problem to be solved by the Invention may be solved.

Therefore, the above allegation by the Appellant might not affect the determination as shown above.

No. 6 Closing

As seen above, the present application should be rejected, since the recitation of the Claims does not conform to the requirement of Article 36(6)(i) of the Patent Act.

Therefore, the appeal decision shall be made as described in the conclusion.

March 20, 2019

Chief administrative judge: TAKIGUCHI, Naoyoshi
Administrative judge: FUJIWARA, Hiroko
Administrative judge: MAEDA, Kayoko