ID 1

Court File No. T- 745 -24

FEDERAL COURT

B E T W E E N:

(Court Seal)

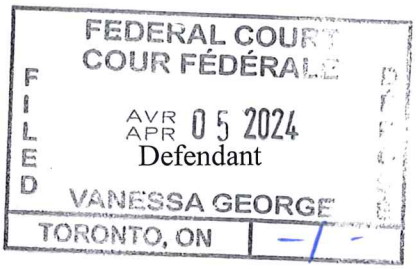
VIIV HEALTHCARE COMPANY and VIIV HEALTHCARE ULC

Plaintiffs

- and -

SANDOZ CANADA INC.

Defendant



STATEMENT OF CLAIM

TO THE DEFENDANT:

A LEGAL PROCEEDING HAS BEEN COMMENCED AGAINST YOU by the plaintiffs. The claim made against you is set out in the following pages.

IF YOU WISH TO DEFEND THIS PROCEEDING, you or a solicitor acting for you are required to prepare a statement of defence in Form 171B prescribed by the *Federal Courts Rules*, serve it on the plaintiffs' solicitor or, if the plaintiffs do not have a solicitor, serve it on the plaintiffs, and file it, with proof of service, at a local office of this Court

WITHIN 30 DAYS after the day on which this statement of claim is served on you, if you are served in Canada or the United States; or

WITHIN 60 DAYS after the day on which this statement of claim is served on you, if you are served outside Canada and the United States.

TEN ADDITIONAL DAYS are provided for the filing and service of the statement of defence if you or a solicitor acting for you serves and files a notice of intention to respond in Form 204.1 prescribed by the *Federal Courts Rules*.

Copies of the *Federal Courts Rules*, information concerning the local offices of the Court and other necessary information may be obtained on request to the Administrator of this Court at Ottawa (telephone 613-992-4238) or at any local office.

IF YOU FAIL TO DEFEND THIS PROCEEDING, judgment may be given against you in your absence and without further notice to you.

April 5, 2024

VANESSA GEORGE
REGISTRY OFFICER
AGENT DU GREFFE

Issued by: _____
(Registry Officer)

Address of local office: 180 Queen Street West, Suite 200
Toronto ON M5V 3L6

TO: Sandoz Canada Inc.
110 de Lauzon Street
Boucherville, Quebec
J4B 1E6

Attention: Jocelyn Binet, Vice President, Legal Affairs and General Counsel

AND TO: Neil Fineberg
Fineberg Ramamoorthy LLP
151 Bloor Street West, Suite 609
Toronto, Ontario
M5S 1S4

Tel.: 647.795.8633
Fax: 647.795.8634
Email: neil@fineberg.legal

CLAIM

1. The Plaintiffs ViiV Healthcare Company and ViiV Healthcare ULC claim:

   (a) a declaration pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, as amended (the "*Regulations*") and Rule 64 of the *Federal Courts Rules* that the making, constructing, using, offering for sale, selling, importing or exporting of the Sandoz Product (as described below) in accordance with the Abbreviated New Drug Submission ("ANDS"), Control No. 246452 filed with the Minister of Health by the Defendant and referenced in the Defendant's letter dated February 16, 2024 purporting to be a Notice of Allegation and Detailed Statement in respect of Canadian Patent No. 2,967,453 (the "453 Patent") and Canadian Patent No. 3,003,988 (the "988 Patent") would infringe, directly or indirectly, or induce the infringement of at least one of the following claims (the "Asserted Claims"):

      (i) Claims 1-12 of the 453 Patent;

      (ii) Claims 1-10 of the 988 Patent.

   (b) an injunction pursuant to subsection 57(1) of the *Patent Act*, R.S.C. 1985, c. P-4, as amended (the "*Patent Act*") and subsection 7(1) of the *Regulations,* restraining the Defendant and any person over whom the Defendant exercises control from directly or indirectly making, constructing, using, offering for sale, selling, importing to or exporting from Canada, the Sandoz Product, or inducing anyone else to do any of those things, until after the expiry of the 453 Patent and the 988 Patent and any applicable Certificates of Supplementary Protection setting out either of those patents that are included on the Patent Register for TRIUMEQ and are not the subject of an allegation pursuant to the *Regulations*;

(c) an order directing that the Defendant shall forthwith deliver up to the Plaintiffs or, at the Plaintiffs' option, destroy under oath, all goods in its possession or power used, made, imported or being made in infringement of the Asserted Claims of the 453 Patent and the 988 Patent;

(d) their costs of this action:

(i) on an appropriate scale according to section 6.12 of the *Regulations*; or

(ii) in the alternative, on a solicitor and client basis, including G.S.T./H.S.T.; and

(e) such further and other relief as counsel may advise, and this Honourable Court deems just.

I. THE NATURE OF THE ACTION

2. This is an action under section 6 of the *Regulations* in respect of a letter sent by Registered Mail on February 16, 2024 by Sandoz Canada Inc. to GlaxoSmithKline Inc. (the "Sandoz Letter") and purporting to be a Notice of Allegation and Detailed Statement in respect of the 453 Patent and the 988 Patent pursuant to subsections 5(2.1)(c) and 5(3)(a), (b), and (c) of the *Regulations*.

II. THE PARTIES

3. The Plaintiff, ViiV Healthcare Company ("ViiV USA"), is a private limited company incorporated under the laws of the United States, having its principal office or place of business at Five Moore Drive, Research Triangle Park, North Carolina, 27709-3398, United States of America.

4. ViiV USA is the owner of the 453 Patent and the 988 Patent and is a necessary party to this action under subsection 6(2) of the *Regulations*.

5. The Plaintiff, ViiV Healthcare ULC ("ViiV Canada"), is a corporation organized and existing under the laws of the province of Alberta, having a place of business at 245 Boulevard Armand-Frappier, Laval, Quebec, H7V 4A7, Canada.

ViiV Canada markets, sells and distributes various drugs in Canada, including dolutegravir, abacavir and lamivudine in tablet form for oral administration in a single medication under the brand name TRIUMEQ® (TRIUMEQ), among other drug products that contain dolutegravir, abacavir and/or lamivudine as active ingredients.

6. The Minister of Health has issued notices of compliance ("NOCs") to ViiV Canada enabling it to market and sell TRIUMEQ in Canada in a dosage strength comprising 50 mg dolutegravir (as dolutegravir sodium), 600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine in tablet form for oral administration. ViiV Canada is identified as the manufacturer for TRIUMEQ on Health Canada's Drug Product Database. The representative for service on ViiV Canada is listed as "General Counsel" at GlaxoSmithKline Inc. in Mississauga, Ontario. ViiV Canada is the "first person" in respect of TRIUMEQ as that term is used in subsections 4(1) and 6(1) of the *Regulations*. ViiV Canada has marketed and sold TRIUMEQ in Canada since October 2014.

7. The Defendant, Sandoz Canada Inc. ("Sandoz"), is a corporation organized and existing under the laws of Canada, having a place of business at 110 de Lauzon Street, Boucherville, Quebec, J4B 1E6, Canada.

III. TRIUMEQ

8. TRIUMEQ is indicated in Canada for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents aged 12 years and older and weighing at least 40 kg.

9. TRIUMEQ is sold in Canada in tablet form for oral administration. It contains the medicinal ingredients dolutegravir (as dolutegravir sodium), abacavir (as abacavir sulfate), and lamivudine at dosage strengths of 50 mg, 600 mg and 300 mg, respectively.

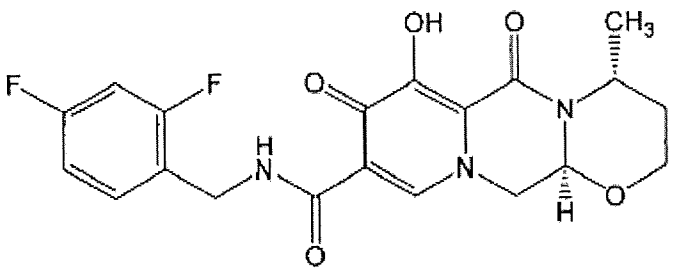
10. ***Dolutegravir.*** Dolutegravir is a chemical compound that can be described, without limitation, as:

(a) (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo·3,4,6,9,9a,10-hexahydro·2H-1-oxa-4a,8a-diaza- anthracene-7-carboxylic acid 2,4,-difluoro-benzylamide;

(b) (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate; and/or

(c) (4R,12aS)-N-[(2,4-difluorophenyl)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.

11. The chemical structure of dolutegravir may be depicted as:



12. Dolutegravir is a HIV integrase inhibitor or integrase strand transfer inhibitor ("INSTI"). It works by binding to and blocking the function of HIV integrase, an enzyme that plays a critical role in HIV replication.

13. Dolutegravir sodium is a pharmaceutically acceptable salt of dolutegravir, wherein the salt forming counterion is Na^+.

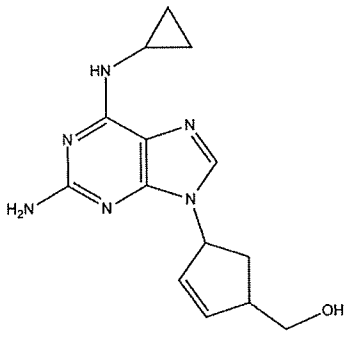
14. Dolutegravir (as dolutegravir sodium) is one of the active ingredients in TRIUMEQ. Dolutegravir (as dolutegravir sodium) is also the/an active ingredient in other drug products sold by ViiV Canada in Canada for the treatment of HIV infection, including TIVICAY ® (dolutegravir).

15. ***Abacavir.*** Abacavir is a chemical compound that can be described, without limitation, as:

(a) (-)-cis-4-[2-amino-6-(cyclo-propylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol; and/or

(b) (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol.

16. The chemical structure of abacavir may be depicted as:



17. Abacavir sulfate is a pharmaceutically acceptable salt of abacavir, wherein the salt forming counterion is SO_4^{2-}. Abacavir sulfate may also be referred to as abacavir hemisulfate due to the fact that the ratio between abacavir and the sulfate ion is 2:1.

18. Abacavir (as abacavir sulfate) is one of the active ingredients in TRIUMEQ.

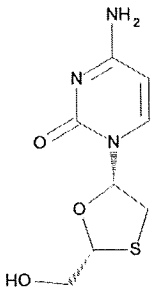
19. Abacavir is a nucleoside reverse transcriptase inhibitor ("NRTI"). Once metabolized by the body, it acts by blocking the function of the HIV reverse transcriptase enzyme, another enzyme that plays a critical role in HIV replication.

20. ***Lamivudine.*** Lamivudine is a chemical compound that can be described, without limitation, as:

(a) (-)-cis-1-(2-hydroxymethyl)-1 ,3-oxathiolane 5-yl)- cytosine; and/or

(b) 2(1H)-Pyrimidinone, 4-amino-1-[2- (hydroxymethyl)-1,3-oxathiolan-5-yl]-(2R-cis).

21. The chemical structure of lamivudine may be depicted as:



22. Lamivudine is one of the active ingredients in TRIUMEQ.

23. Like abacavir, lamivudine is a NRTI. Once metabolized by the body, it acts by blocking the function of the HIV reverse transcriptase enzyme, another enzyme that plays a critical role in HIV replication.

IV. THE 453 AND 988 PATENTS AND THE PLAINTIFFS' PATENT RIGHTS

24. The Plaintiffs plead and rely on the 453 Patent and the 988 Patent, certified copies of which are attached as Schedules "A" and "B" respectively to this Statement of Claim.

25. The 453 Patent is entitled "Combinations for Use in the Inhibition of HIV-1". It was granted to ViiV USA on July 17, 2018; ViiV USA is the owner of the 453 Patent. The inventor of the 453 Patent is Mark Richard Underwood.

26. The patent application from which the 453 Patent issued was filed in Canada on January 24, 2011, claiming priority from US Priority Application No. US61/298,589. The patent application from which the 453 Patent issued was opened to public inspection on August 4, 2011.

27. The 453 Patent has been in full force and effect since its date of issue. It will expire on January 24, 2031. The 453 Patent and each of its claims is presumed to be valid pursuant to section 43(2) of the *Patent Act*.

28. The 453 Patent describes combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents that may be useful in the inhibition

of HIV-1, the inhibition of HIV replication, and/or for the prevention or treatment of infection by HIV. The 453 Patent contains 12 claims.

29. The Asserted Claims of the 453 Patent relate more specifically to the following subject matter, as more fully particularized in the 453 Patent:

(a) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and abacavir, or a pharmaceutically acceptable salt thereof;

(b) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and abacavir, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt of abacavir is an hemisulfate salt;

(c) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and abacavir, or a pharmaceutically acceptable salt thereof, and further comprising lamivudine;

(d) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and abacavir, or a pharmaceutically acceptable salt thereof, with or without lamivudine, wherein the pharmaceutically acceptable salt of dolutegravir is the sodium salt;

(e) a pharmaceutical composition comprising any one of the combinations described above and a pharmaceutically acceptable carrier therefor;

(f) use of an effective amount of any one of the combinations described above for:

(i) inhibiting HIV-1; and/or

(ii) treating an HIV infection;

(g) use of an effective amount of any one of the combinations described above for inhibiting HIV-1 and/or treating an HIV infection wherein the combination is for:

(i) simultaneous administration; and/or

(ii) sequential administration;

(h) use of any of the pharmaceutical compositions described above in:

(i) the inhibition of HIV-1; and/or

(ii) the treatment of an HIV infection;

(i) a patient pack comprising any one of the combinations described above and instructions for use in the treatment of an HIV infection.

30. The construction of the 453 Patent and the Asserted Claims and/or the inventive concept thereof will the subject of expert opinion. The Plaintiffs reserve the right to respond to any construction or interpretation of the 453 Patent and/or its claims asserted by Sandoz or its expert witnesses in this action.

31. The 988 Patent is entitled "Combinations for Use in the Inhibition of HIV-1". It was granted to ViiV USA on January 7, 2020; ViiV USA is the owner of the 988 Patent. The inventor of the 988 Patent is Mark Richard Underwood.

32. The patent application from which the 988 Patent issued was filed in Canada on January 24, 2011, claiming priority from US Priority Application No. US61/298,589. The patent application from which the 988 Patent issued was opened to public inspection on August 4, 2011.

33. The 988 Patent has been in full force and effect since its date of issue. It will expire on January 24, 2031. The 988 Patent and each of its claims is presumed to be valid pursuant to section 43(2) of the *Patent Act*.

34. The 988 Patent describes combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents that may be useful in the inhibition of HIV-1, the inhibition of HIV replication, and/or for the prevention or treatment of infection by HIV. The 988 Patent contains 10 claims.

35. The Asserted Claims of the 988 Patent relate more specifically to the following subject matter, as more fully particularized in the 988 Patent:

(a) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and lamivudine, or a pharmaceutically acceptable salt thereof;

(b) a combination comprising dolutegravir, or a pharmaceutically acceptable salt thereof, and lamivudine, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt of dolutegravir is a sodium salt;

(c) a pharmaceutical composition comprising any one of the combinations described above and a pharmaceutically acceptable carrier thereof;

(d) use of an effective amount of any one of the combinations described above for:

(i) inhibiting HIV-1; and/or

(ii) treating an HIV infection;

(e) use of an effective amount of any one of the combinations described above for inhibiting HIV-1 and/or treating an HIV infection wherein the combination is for:

(i) simultaneous administration; and/or

(ii) sequential administration;

(f) use of any of the pharmaceutical compositions described above in:

(i) the inhibition of HIV-1; and/or

(ii) the treatment of an HIV infection;

(g) a patient pack comprising any one of the combinations described above and instructions for use in the treatment of an HIV infection.

36. The construction of the 988 Patent, the Asserted Claims and/or the inventive concept will the subject of expert opinion. The Plaintiffs reserve the right to respond to any construction or interpretation of the 988 Patent and/or its claims asserted by Sandoz or its expert witnesses.

37. Pursuant to the provisions of the *Patent Act* and, in particular, sections 42, 43 and 44 thereof, ViiV USA has, as the patentee of the 453 and 988 Patents, the exclusive right, privilege and liberty in Canada of making, constructing and using the inventions claimed by the 453 and 988 Patents, and licensing them to others to be used, for the full term of the 453 and 988 Patents.

38. ViiV Canada is licensed indirectly by ViiV USA under the 453 and 988 Patents and, as such, is a person claiming under the patentee by virtue of section 55 of the *Patent Act*. ViiV USA has authorized ViiV Canada to make, use and/or sell in Canada combinations of dolutegravir and abacavir and/or lamivudine, including TRIUMEQ.

39. ViiV USA has permitted ViiV Canada to list the 453 and 988 Patents on the Patent Register maintained by the Minister of Health under the *Regulations* in respect of TRIUMEQ.

40. The 453 Patent and the 988 Patent are and always have been eligible for listing on the Patent Register in respect of TRIUMEQ.

41. The 998 Patent is also the subject of Certificate of Supplementary Protection ("CSP") No. 900051 issued to ViiV Canada. CSP 900051 expires on January 24, 2033. CSP 900051 is also listed on the Patent Register maintained by the Minister of Health under the *Regulations* in respect of TRIUMEQ.

42. Canadian Patent No. 2,606,282, is also listed on the Patent Register for TRIUMEQ and expires on April 29, 2026.

V. INFRINGEMENT BY SANDOZ

The Sandoz Letter and the Sandoz Product

43. On February 16, 2024 Sandoz sent the Sandoz Letter by Registered Mail to GlaxoSmithKline Inc. The Sandoz Letter advised that Sandoz has filed an Abbreviated New Drug Submission ("ANDS") with Health Canada, under submission number 246452, for the issuance of a notice of compliance in respect of its proposed dolutegravir/abacavir/lamivudine product in tablet form for oral

administration containing 50 mg dolutegravir, 600 mg abacavir and 300 mg lamivudine as the medicinal ingredients (the "Sandoz Product" or "Sandoz Dolutegravir-Abacavir-Lamivudine").

44. Sandoz states that it has compared the proposed Sandoz Product to ViiV Canada's dolutegravir, abacavir, lamivudine product in tablet form for oral administration in the dosage strength of 50 mg dolutegravir, 600 mg abacavir and 300 mg lamivudine (i.e., TRIUMEQ).

45. Sandoz is seeking approval to sell the proposed Sandoz Product in Canada for the treatment of human immunodeficiency virus (HIV-1) infection in certain populations of adults and adolescents.

46. The Sandoz Letter addresses the 453 and 988 Patents and makes allegations of non-infringement and invalidity in respect of both. Pursuant to the *Regulations*, Sandoz is required to provide a statement of the legal and factual bases for its allegations that no claim of the 453 Patent or 988 Patent would be infringed by the proposed Sandoz Product, and a detailed statement of the legal and factual bases for its allegations that each of the claims of the 453 Patent and 988 Patent is invalid.

47. The Plaintiffs have relied upon the Sandoz Letter and the legal and factual bases for Sandoz's allegations that are contained therein.

48. The Plaintiffs do not bear the burden of disproving the allegations of non-infringement or invalidity of the claims of the 453 Patent and 988 Patent set out in the Sandoz Letter. However, and in any event, the Plaintiffs deny each and every one of those allegations.

49. The Sandoz Letter does not address or make any allegation in respect of CSP 90051 or the 282 Patent. Pursuant to section 5 of the *Regulations,* Sandoz is required to make a statement or allegation as provided by subsection 5(2.1) in respect of each patent and each certificate of supplementary protection in which the patent is set out and that is included on the Patent Register in respect of TRIUMEQ.

50. Pursuant to section 7 of the Regulations, if Sandoz does not make any allegation under subsection 5(2.1)(c) in respect of a particular patent or CSP that they are required to address pursuant to the *Regulations*, no NOC for the proposed Sandoz Product can issue until after the expiry of such patent or CSP..

51. The Plaintiffs have no knowledge of Sandoz having made any allegation under subsection 5(2.1)(c) to date in respect of the Sandoz ANDS and either the 282 Patent or CSP 90051. As such, the Plaintiffs currently have no reasonable basis to bring any action under the *Regulations* in respect of the 282 Patent or CSP 90051 and the proposed Sandoz Product.

52. In the event that Sandoz has or does make an allegation in respect of the 282 Patent and the proposed Sandoz Product, the Plaintiffs reserve their rights to amend this Statement of Claim or bring a fresh action to assert that the activities of Sandoz in respect of its proposed Sandoz Product will infringe one or more of the claims of the 282 Patent.

53. In the event that Sandoz has or does make an allegation in respect of CSP 90051 and the proposed Sandoz Product, the Plaintiffs reserve their rights to amend this Statement of Claim or commence a fresh action to assert that the activities of Sandoz in respect of its proposed Sandoz Product described below will infringe CSP 90051 for the same reasons that they will infringe the Asserted Claims of the 988 Patent.

Sandoz will infringe the Asserted Claims of the 453 Patent and/or the 988 Patent

54. Sandoz intends to either make in or import into Canada, offer for sale and sell in Canada, the proposed Sandoz Product.

55. The proposed Sandoz Product contains a combination of dolutegravir, abacavir and lamivudine (and/or pharmaceutically acceptable salts of these compounds) as claimed in the Asserted Claims of the 453 and 988 Patents, properly construed.

56. The proposed Sandoz Product is made by combining dolutegravir, abacavir and lamivudine (and/or the pharmaceutically acceptable salts of these compounds) as claimed in the Asserted Claims of the 453 and 988 Patents, properly construed.

57. The proposed Sandoz Product is a pharmaceutical composition that comprises the combination of dolutegravir, abacavir and lamivudine (and/or pharmaceutically acceptable salts of these compounds) together with one or more pharmaceutically acceptable carriers, as claimed in the Asserted Claims of the 453 and 988 Patents, properly construed.

58. Sandoz is seeking approval for, and will position, the proposed Sandoz Product to be prescribed, dispensed, sold and used in Canada instead of, and with comparable effect to, TRIUMEQ.

59. The proposed Sandoz Product is a pharmaceutical composition that comprises the combination of dolutegravir, abacavir and lamivudine (and/or pharmaceutically acceptable salts of these compounds) with one or more pharmaceutically acceptable carriers, which is intended by Sandoz to be used in:

(a) the inhibition of HIV-1; and/or

(b) the treatment of an HIV infection;

as claimed in the Asserted Claims of the 453 and 988 Patents, properly construed.

60. The proposed Sandoz Product will be available as a patient pack comprising a pharmaceutical composition containing dolutegravir, abacavir and lamivudine (and/or pharmaceutically acceptable salts of these compounds) and instructions for use in the treatment of an HIV infection, as claimed in the Asserted Claims of the 453 and 988 Patents, properly construed.

61. Sandoz intends that the proposed Sandoz Product will be prescribed, sold and/or dispensed to and used by patients in Canada for:

(a) inhibiting HIV-1; and

(b) treating an HIV infection.

62. Sandoz intends that the proposed Sandoz Product will be prescribed, sold, and/or dispensed to and used by patients in Canada for simultaneous administration of dolutegravir, abacavir and lamivudine (and/or pharmaceutically acceptable salts of these compounds).

63. If and when patients in Canada use the proposed Sandoz Product for the uses as stated in paragraphs 59 to 62 above, one or more of the Asserted Claims of the 453 and 988 Patents will be infringed.

64. If the proposed Sandoz Product is approved in accordance with its ANDS, one or more of the Asserted Claims of the 453 and 988 Patents will be infringed by the importing into Canada, making, constructing, using, offering to sell, and selling in Canada, or exporting from Canada, of the proposed Sandoz Product.

65. The infringing activities will be carried out by Sandoz directly or indirectly and/or by third parties induced by Sandoz to infringe. To the extent that any infringing activities set out above are carried out by third parties, Sandoz knows that its actions and/or influence in respect of the proposed Sandoz Product will result in such acts of infringement by those third parties. Without the influence of Sandoz, such infringing acts of third parties would not occur.

66. Sandoz intends to pursue the activities set out above in respect of the proposed Sandoz Product. Unless Sandoz is restrained by this Honourable Court, one or more of the Asserted Claims of the 453 and 988 Patents will be infringed.

67. Sandoz has not obtained any license, consent or permission from any of the Plaintiffs for any of its activities in respect of the proposed Sandoz Product.

68. The Plaintiffs are unaware of the full extent of Sandoz's infringing activities (direct or indirect; past, present and intended). Full particulars of all such activities are within the knowledge of Sandoz.

69. To the extent that Sandoz has provided additional particulars about the Sandoz ANDS, the proposed Sandoz Product or of its infringing activities in the Sandoz Letter and/or in documents provided pursuant to subsection 5(3)(c)(iii) of the *Regulations*, Sandoz has asserted that such particulars are subject to Confidentiality Rules imposed on the Plaintiffs under section 5(3.5) of the *Regulations*.

Plaintiffs' claimed relief

70. The Plaintiffs claim declaratory and injunctive relief in accordance with section 6 and subsection 7(1)(e) of the *Regulations*, section 57(1) of the *Patent Act* and Rule 64 of the *Federal Courts Rules*.

71. The Plaintiffs plead and rely on the *Regulations*; the *Patent Act*; the *Federal Courts Act,* RSC 1985, C. F-7, as amended; the *Federal Courts Rules*, SOR/98-106, as amended; the *Food and Drugs Act*, CRC 1978, c. 870, as amended, the *Canada Evidence Act*, RSC 1985, c. C-5, as amended; as well as such further and other grounds as counsel may advise and this Honorable Court may permit.

72. Unless Sandoz is restrained by this Honourable Court, its infringement of one or more of the Asserted Claims of the 453 and 988 Patents will cause damages to the Plaintiffs and/or will result in Sandoz earning unlawful profits.

73. In the event that Sandoz commits any act of infringement of any of the Asserted Claims prior to the determination of this action, the Plaintiffs reserve the right to amend this Statement of Claim to seek additional relief accordingly, including by adding any additional parties claiming under the patentees and to seek any and all relief available under the *Patent Act* or otherwise in respect of same, including without limitation an interlocutory injunction, or a claim for damages or an accounting of Sandoz's profits, at the Plaintiffs' election.

74. This is not a simplified action under the *Federal Courts Rules*, as the Plaintiffs' claim is not exclusively for monetary relief.

75. The Plaintiffs propose that this action be tried at Toronto, Ontario.

Dated at Toronto, Ontario this 5th day of April, 2024.

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Solicitors for the Plaintiffs

Schedule "A"

Innovation, Sciences et Développement économique Canada
Office de la propriété intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

Bureau Canadien des Brevets
CERTIFICATION

Canadian Patent Office
CERTIFICATION

La présente atteste que les documents ci-joints, dont la liste figure ci-dessous, sont des copies authentiques des documents déposés au Bureau des brevets.

This is to certify that the documents attached hereto and identified below are true copies of the documents on file in the Patent Office.

Canadian Patent Number: CA 2967453

Date/ Date
2024-01-24

Agent certificateur
Certifying officer

Canada

Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 2967453 C 2018/07/17

(11)(21) **2 967 453**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(22) **Date de dépôt/Filing Date:** 2011/01/24

(41) **Mise à la disp. pub./Open to Public Insp.:** 2011/08/04

(45) **Date de délivrance/Issue Date:** 2018/07/17

(62) **Demande originale/Original Application:** 2 787 691

(30) **Priorité/Priority:** 2010/01/27 (US61/298,589)

(51) **Cl.Int./Int.Cl.** ***A61K 31/5365*** (2006.01),
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(54) **Titre : COMBINAISONS A UTILISER POUR L'INHIBITION DE VIH-1**
(54) **Title: COMBINATIONS FOR USE IN THE INHIBITION OF HIV-1**

(57) **Abrégé/Abstract:**
The present disclosure relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents. Such combinations may be useful in the inhibition of HIV-1 or potentially the inhibition of HIV replication, or for the prevention and/or treatment of infection by HIV, or in the treatment of AIDS and/or ARC.

COMBINATIONS FOR USE IN THE INHIBITION OF HIV-1

This is a division of Canadian patent application no. 2,787,691 filed January 24, 2011.

BACKGROUND OF THE DISCLOSURE

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the 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 may inhibit replication of HIV in infected cells. Such compounds may be useful in the prevention or treatment of HIV infection in humans.

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.

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.

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.

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.

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 combinations. 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.

There is continued need to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to inhibit HIV-1 and potentially treat HIV infection. Due to their high potency and pharmacokinetic profile, certain HIV integrase inhibitors are attractive as components in combination therapy.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).

Figure 2: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with efavirenz (EFV).

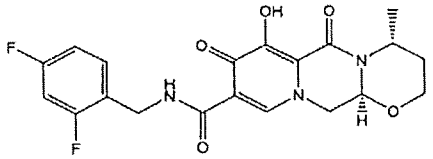
Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)

SUMMARY OF THE DISCLOSURE

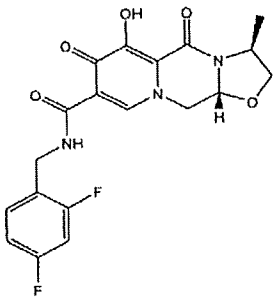
The present disclosure relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents useful in the treatment of HIV infection. Such combinations are useful in the inhibition of HIV-1. Such combinations may be useful for the inhibition of HIV replication, or the prevention and/or treatment of infection by HIV, or may be useful in the treatment of AIDS and/or ARC. The present disclosure also features pharmaceutical compositions containing HIV integrase inhibitors.

DETAILED DESCRIPTION OF THE DISCLOSURE

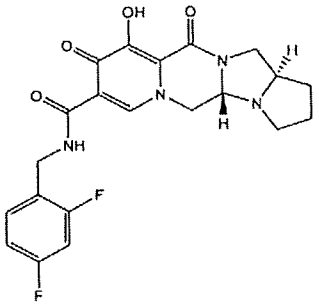
The present disclosure relates to combinations comprising a compound of the following formula (I), (II), or (III):



(I)



(II)



(III)

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.

The present disclosure may further provide 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.

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.

A chemical name of the compound of formula (II) is (3*S*, 11a*R*)-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.

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

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this disclosure, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

The term "treatment" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. Treatment may include prophylaxis which refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

As used herein, the term "subject" refers to a patient, animal or a biological sample.

Pharmaceutically acceptable salts of the compounds according to the disclosure include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the disclosure and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. An advandtageous salt is sodium salt.

Salts of the compounds of the present disclosure may be made by methods known to a person skilled in the art. For example, treatment of a compound of the present disclosure with an appropriate base or acid in an appropriate solvent can yield the corresponding salt.

The present disclosure may also provide 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.

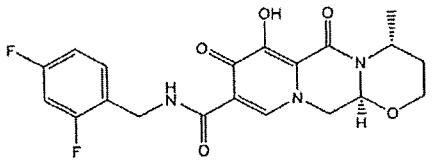
The compounds of formula (I), (II) and (III) may be particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment may extend to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

Combination therapies comprise the administration of a compound of the present disclosure 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.

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, for example (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, for example 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, for example indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, lopinavir, atazanavir, tipranavir, darunavir, brecanavir, palinavir, lasinavir, TMC-310911, DG-17, PPL-100, and SPI-256; non-nucleoside reverse transcriptase inhibitors (NNRTIs), for example nevirapine, delavirdine, efavirenz, GSK2248761 (IDX-12899), lersivirine (UK-453,061), rilpivirine (TMC-278),

etravirine, loviride, immunocal, oltipraz, capravirine, and RDEA-806; integrase inhibitors, for example raltegravir, elvitegravir, and JTK-656; CCR5 and/or CXCR4 antagonists, for example, maraviroc, vicriviroc (Sch-D), TBR-652 (TAK-779), TAK-449, PRO-140, GSK706769, and SCH-532706; fusion inhibitors, for example 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, for example, bevirimat (PA-344 and PA-457).

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



(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.

The present disclosure 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, or lopinavir. The present disclosure features a combination comprising of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and abacavir.

The present disclosure may provide 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.

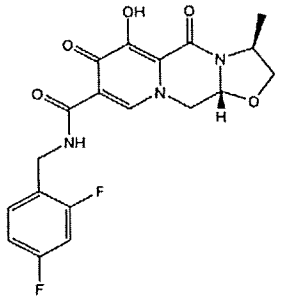
The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (I) or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir. The present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

The present disclosure 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.

The present disclosure 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 disclosure 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.

The present disclosure features a combination comprising a compound of formula (II)



(II)

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.

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

The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (II) 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.

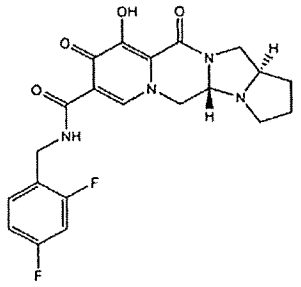
The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (II) or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir. The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

HIV infection comprising administering to a subject a compound of formula (II) or a pharmaceutically acceptable salt thereof, and abacavir.

The present disclosure features a pharmaceutical composition comprising a compound of formula (II) 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 together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a pharmaceutical composition comprising a compound of formula (II) 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 disclosure features a pharmaceutical composition comprising a compound of formula (II) or a pharmaceutically acceptable salt thereof, and abacavir together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a combination comprising a compound of formula (III)



(III)

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

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

The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (III) 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.

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

The present disclosure features a pharmaceutical composition comprising a compound of formula (III) 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 together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a pharmaceutical composition comprising a compound of formula (III) 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 disclosure features a pharmaceutical composition comprising a compound of formula (III) or a pharmaceutically acceptable salt thereof, and abacavir together with a pharmaceutically acceptable carrier therefor.

The present disclosure 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.

The present disclosure 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, for example, abacavir hemisulfate, fosamprenavir calcium, atazanavir sulfate, tenofovir disoproxil sulfate, vicriviroc maleate or bevirimat dimeglumine.

The present disclosure may provide methods of treatment as described above wherein the subject is a human.

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

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

Compounds of formula (I), (II), and (III) may be made by methods disclosed in WO 2006/116764, U.S. 61/193,634 (WO2010/068253) or 61/193,636 (WO2010/068262).

Abacavir may be made by methods disclosed in U.S. Patent Nos. 5,034,394; 5,089,500; 6,294,540; 5,641,889; 5,840,990; 5,919,941; 5,808,147; 6,392,085; 6,448,403; 5,917,041; 6,087,501; 5,917,042; 6,555,687; 6,552,193; 6,870,053; 6,294,540; 6,340,587; or 6,646,125.

Lamivudine may be made by methods disclosed in U.S. Patent Nos. 5,047,407; 7,119,202; 5,905,082; 5,696,254; 5,663,320; 5,693,787; 6,051,709; or 6,329,522.

Tenofovir may be made by U.S. Patent Nos. 5,922,695; 5,935,946; 5,977,089; 6,043,230, 6,069,249.

Efavirenz may be made by may be made by methods disclosed in U.S. Patent Nos. 5,519.021; 5,663,169; 5,811,423; 6,555,133; 6,639,071; or 6,939,964.

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

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

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

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

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

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

In an aspect of the disclosure, 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 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 disclosure effective to inhibit HIV-1 or potentially treat or prevent viral infection, for example an HIV infection, in a biological sample or in a patient. In another embodiment, combinations of the disclosure and pharmaceutical compositions thereof, comprising an amount of a combination of the present disclosure effective to inhibit HIV-1 or potentially inhibit viral replication or to treat or prevent a viral infection or disease or disorder, for example an HIV infection, and a pharmaceutically acceptable carrier, adjuvant or vehicle, may be formulated for administration to a patient, for example, for oral administration.

The present disclosure features combinations that may be used in medical therapy, for example to inhibit HIV-1 or potentially for the treatment or prophylaxis of a viral infection, for example an HIV infection and associated conditions. The compounds according to the disclosure may be 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.

According to another aspect, the present disclosure may provide a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected patient, for example, a mammal including a human, which comprises administering to said patient a pharmaceutically effective amount of a combination according to the disclosure. According to one aspect , the viral infection is a retroviral infection, in particular an HIV infection.

The present disclosure further includes the use of a combination in the manufacture of a medicament for simultaneous (concurrent) or sequential administration to a subject for the inhibition of HIV-1 or potentially for the treatment of a viral infection, in particular an HIV infection.

The present disclosure may further provide a method for the treatment of a clinical condition in a patient, for example, a mammal including a human which clinical condition includes those which have been discussed hereinbefore, which comprises treating said patient with a pharmaceutically effective amount of a compound according to the disclosure. The present disclosure may further provide a method for the treatment or prophylaxis of any of the aforementioned diseases or conditions.

Compounds of the present disclosure may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present disclosure may provide a method for the treatment or prophylaxis of a disease as hereinbefore described by administration of a compound of the present disclosure in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

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, in the range of 0.1 to 100 mg per kilogram body weight per day; in the range 1 to 30 mg per kilogram body weight per day; 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 alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 2000 mg; 5 to 500 mg; 10 to 400 mg, 20 to 300 mg of each active ingredient per unit dosage form.

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

While it is possible for the active ingredients to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present disclosure 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.

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 disclosure 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.

The present disclosure further includes a pharmaceutical composition as hereinbefore defined wherein a compound as described herein or a pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3(6), 318 (1986).

Pharmaceutical compositions of the present disclosure suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray. Pharmaceutical compositions may contain in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

Pharmaceutical compositions of the present disclosure may be presented as patient packs containing one or more courses of treatment in a single package, for example, a blister pack. It will be understood that the administration of the combination of the disclosure by means of a single patient pack, or patient packs of each composition, is an additional feature of the disclosure .

It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this disclosure may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

Examples

Example 1: Biological Activity

Assays

Method

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 (RPMI 1640, 10% vol./vol. fetal bovine serum (FBS), and 10 μg/mL gentamicin), 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 (RapidPlate-96, Zymark Corp.). 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 4 12). Cell pellets were re-suspended in fresh medium (RPMI 1640, 20% vol./vol. FBS, 20% vol./vol. IL-2, and 10 μg/mL gentamicin) 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).

Virus used

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

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.

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.

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.

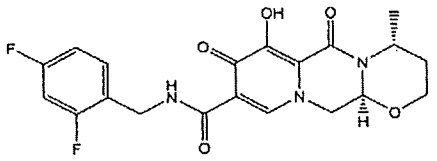
Results

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.

CLAIMS

What is claimed is:

1. A combination comprising a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,
and abacavir or a pharmaceutically acceptable salt thereof.

2. The combination according to claim 1 wherein the pharmaceutically acceptable salt of abacavir is an hemisulfate salt.

3. The combination of claim 1 or 2, further comprising lamivudine.

4. The combination according to any one of claims 1 to 3 wherein the pharmaceutically acceptable salt of a compound of formula (I) is the sodium salt.

5. A pharmaceutical composition comprising a combination according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier therefor.

6. Use of an effective amount of a combination according to any one of claims 1 to 4 for inhibiting HIV-1.

7. Use of an effective amount of a combination according to any one of claims 1 to 4 for treating an HIV infection.

8. The use according to claim 6 or 7, wherein the combination is for simultaneous administration.

9. The use according to claim 6 or 7, wherein the combination is for sequential administration.

10. The pharmaceutical composition of claim 5 for use in the inhibition of HIV-1.

11. The pharmaceutical composition of claim 5 for use in the treatment of an HIV infection.

12. A patient pack comprising a combination according to any one of claims 1 to 4 and instructions for use in the treatment of an HIV infection.

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).

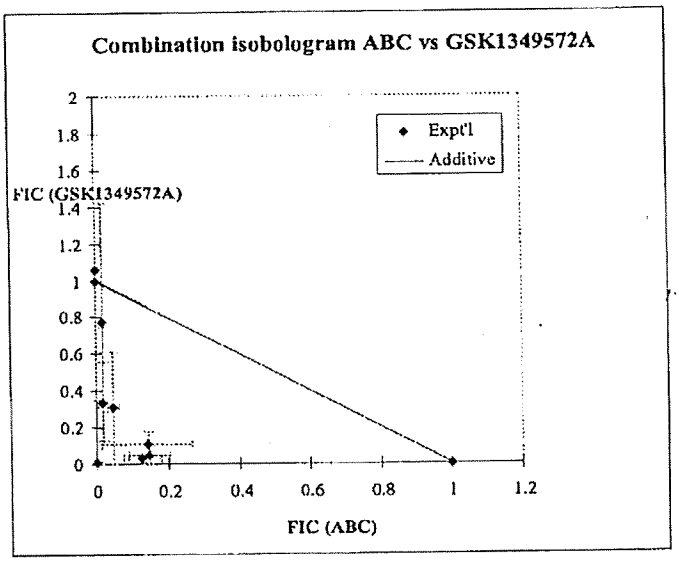


Figure 2: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with efavirenz (EFV).

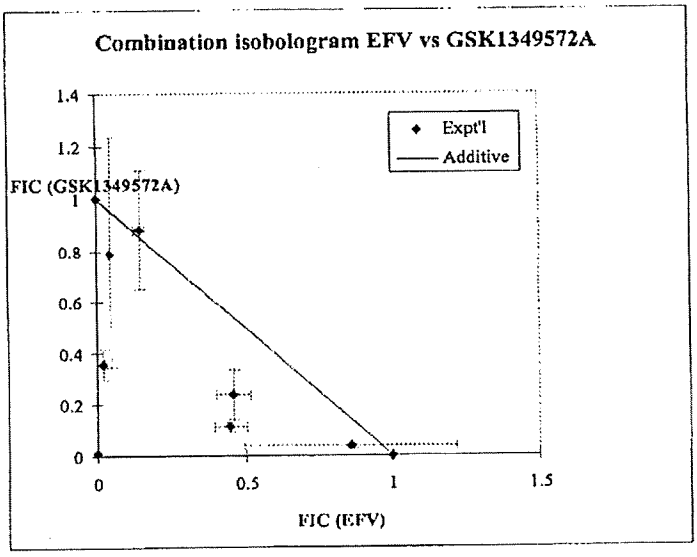
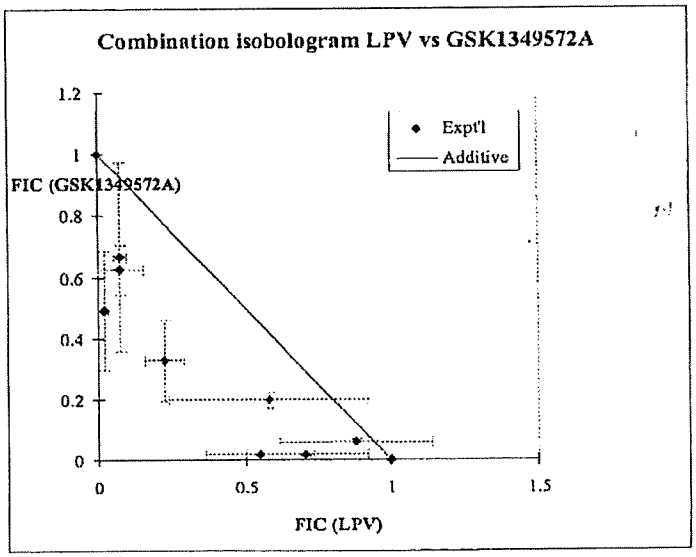


Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)



Schedule "B"

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CERTIFICATION

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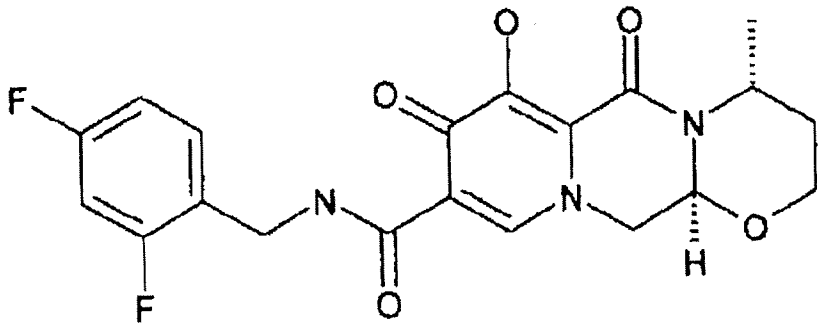
(54) Titre : COMBINAISONS A UTILISER POUR L'INHIBITION DU VIH-1
(54) Title: COMBINATIONS FOR USE IN THE INHIBITION OF HIV-1



(I)

(57) Abrégé/Abstract:
The present disclosure relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents. Such combinations may be useful in the inhibition of HIV-1 or potentially the inhibition of HIV replication, or for the prevention and/or treatment of infection by HIV, or in the treatment of AIDS and/or ARC.

COMBINATIONS FOR USE IN THE INHIBITION OF HIV-1

This is a division of Canadian patent application no. 2,787,691 filed January 24, 2011.

BACKGROUND OF THE DISCLOSURE

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the 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 may inhibit replication of HIV in infected cells. Such compounds may be useful in the prevention or treatment of HIV infection in humans.

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.

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.

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.

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.

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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 combinations. 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.

There is continued need to find therapeutic agents suitable for use in combination and feasible pharmaceutical compositions to inhibit HIV-1 and potentially treat HIV infection. Due to their high potency and pharmacokinetic profile, certain HIV integrase inhibitors are attractive as components in combination therapy.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).

Figure 2: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with efavirenz (EFV).

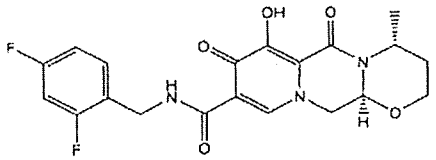
Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)

SUMMARY OF THE DISCLOSURE

The present disclosure relates to combinations of compounds comprising HIV integrase inhibitors and other therapeutic agents useful in the treatment of HIV infection. Such combinations are useful in the inhibition of HIV-1. Such combinations may be useful for the inhibition of HIV replication, or the prevention and/or treatment of infection by HIV, or may be useful in the treatment of AIDS and/or ARC. The present disclosure also features pharmaceutical compositions containing HIV integrase inhibitors.

DETAILED DESCRIPTION OF THE DISCLOSURE

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



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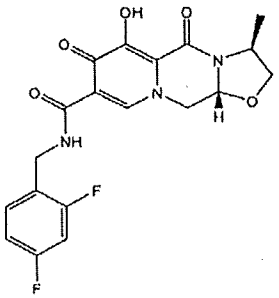
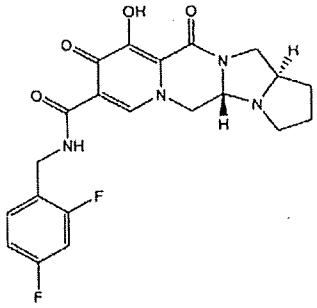


(II)



(III)

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.

The present disclosure may further provide 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.

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.

A chemical name of the compound of formula (II) is (3*S*, 11a*R*)-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.

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

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this disclosure, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

The term "treatment" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. Treatment may include prophylaxis which refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

As used herein, the term "subject" refers to a patient, animal or a biological sample.

Pharmaceutically acceptable salts of the compounds according to the disclosure include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the disclosure and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. An advandtageous salt is sodium salt.

Salts of the compounds of the present disclosure may be made by methods known to a person skilled in the art. For example, treatment of a compound of the present disclosure with an appropriate base or acid in an appropriate solvent can yield the corresponding salt.

The present disclosure may also provide 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.

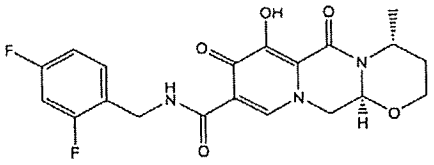
The compounds of formula (I), (II) and (III) may be particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment may extend to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

Combination therapies comprise the administration of a compound of the present disclosure 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.

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, for example (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, for example 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, for example indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, lopinavir, atazanavir, tipranavir, darunavir, brecanavir, palinavir, lasinavir, TMC-310911, DG-17, PPL-100, and SPI-256; non-nucleoside reverse transcriptase inhibitors (NNRTIs), for example nevirapine, delavirdine, efavirenz, GSK2248761 (IDX-12899), lersivirine (UK-453,061), rilpivirine (TMC-278),

etravirine, loviride, immunocal, oltipraz, capravirine, and RDEA-806; integrase inhibitors, for example raltegravir, elvitegravir, and JTK-656; CCR5 and/or CXCR4 antagonists, for example, maraviroc, vicriviroc (Sch-D), TBR-652 (TAK-779), TAK-449, PRO-140, GSK706769, and SCH-532706; fusion inhibitors, for example 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, for example, bevirimat (PA-344 and PA-457).

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



(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.

The present disclosure 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, or lopinavir. The present disclosure features a combination comprising of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and abacavir.

The present disclosure may provide 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.

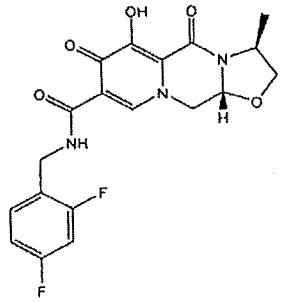
The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (I) or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir. The present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

The present disclosure 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.

The present disclosure 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 disclosure 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.

The present disclosure features a combination comprising a compound of formula (II)



(II)

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.

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

The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (II) 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.

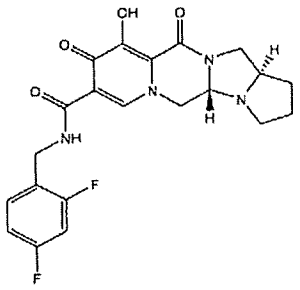
The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (II) or a pharmaceutically acceptable salt thereof, with one or more therapeutic agents selected from the group consisting of abacavir, efavirenz, and lopinavir. The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

HIV infection comprising administering to a subject a compound of formula (II) or a pharmaceutically acceptable salt thereof, and abacavir.

The present disclosure features a pharmaceutical composition comprising a compound of formula (II) 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 together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a pharmaceutical composition comprising a compound of formula (II) 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 disclosure features a pharmaceutical composition comprising a compound of formula (II) or a pharmaceutically acceptable salt thereof, and abacavir together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a combination comprising a compound of formula (III)



(III)

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

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

The present disclosure may provide a method of treatment of HIV infection comprising administering to a subject, a compound of formula (III) 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.

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

The present disclosure features a pharmaceutical composition comprising a compound of formula (III) 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 together with a pharmaceutically acceptable carrier therefor.

The present disclosure features a pharmaceutical composition comprising a compound of formula (III) 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 disclosure features a pharmaceutical composition comprising a compound of formula (III) or a pharmaceutically acceptable salt thereof, and abacavir together with a pharmaceutically acceptable carrier therefor.

The present disclosure 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.

The present disclosure 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, for example, abacavir hemisulfate, fosamprenavir calcium, atazanavir sulfate, tenofovir disoproxil sulfate, vicriviroc maleate or bevirimat dimeglumine.

The present disclosure may provide methods of treatment as described above wherein the subject is a human.

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

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

Compounds of formula (I), (II), and (III) may be made by methods disclosed in WO 2006/116764, U.S. 61/193,634 (WO2010/068253) or 61/193,636 (WO2010/068262).

Abacavir may be made by methods disclosed in U.S. Patent Nos. 5,034,394; 5,089,500; 6,294,540; 5,641,889; 5,840,990; 5,919,941; 5,808,147; 6,392,085; 6,448,403; 5,917,041; 6,087,501; 5,917,042; 6,555,687; 6,552,193; 6,870,053; 6,294,540; 6,340,587; or 6,646,125.

Lamivudine may be made by methods disclosed in U.S. Patent Nos. 5,047,407; 7,119,202; 5,905,082; 5,696,254; 5,663,320; 5,693,787; 6,051,709; or 6,329,522.

Tenofovir may be made by U.S. Patent Nos. 5,922,695; 5,935,946; 5,977,089; 6,043,230, 6,069,249.

Efavirenz may be made by may be made by methods disclosed in U.S. Patent Nos. 5,519.021; 5,663,169; 5,811,423; 6,555,133; 6,639,071; or 6,939,964.

GSK2248761 may be made by methods disclosed in U.S. Patent No. 7,534.809.

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

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

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

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

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

In an aspect of the disclosure, 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 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 disclosure effective to inhibit HIV-1 or potentially treat or prevent viral infection, for example an HIV infection, in a biological sample or in a patient. In another embodiment, combinations of the disclosure and pharmaceutical compositions thereof, comprising an amount of a combination of the present disclosure effective to inhibit HIV-1 or potentially inhibit viral replication or to treat or prevent a viral infection or disease or disorder, for example an HIV infection, and a pharmaceutically acceptable carrier, adjuvant or vehicle, may be formulated for administration to a patient, for example, for oral administration.

The present disclosure features combinations that may be used in medical therapy, for example to inhibit HIV-1 or potentially for the treatment or prophylaxis of a viral infection, for example an HIV infection and associated conditions. The compounds according to the disclosure may be 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.

According to another aspect, the present disclosure may provide a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected patient, for example, a mammal including a human, which comprises administering to said patient a pharmaceutically effective amount of a combination according to the disclosure. According to one aspect , the viral infection is a retroviral infection, in particular an HIV infection.

The present disclosure further includes the use of a combination in the manufacture of a medicament for simultaneous (concurrent) or sequential administration to a subject for the inhibition of HIV-1 or potentially for the treatment of a viral infection, in particular an HIV infection.

The present disclosure may further provide a method for the treatment of a clinical condition in a patient, for example, a mammal including a human which clinical condition includes those which have been discussed hereinbefore, which comprises treating said patient with a pharmaceutically effective amount of a compound according to the disclosure. The present disclosure may further provide a method for the treatment or prophylaxis of any of the aforementioned diseases or conditions.

Compounds of the present disclosure may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present disclosure may provide a method for the treatment or prophylaxis of a disease as hereinbefore described by administration of a compound of the present disclosure in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

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, in the range of 0.1 to 100 mg per kilogram body weight per day; in the range 1 to 30 mg per kilogram body weight per day; 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 alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 2000 mg; 5 to 500 mg; 10 to 400 mg, 20 to 300 mg of each active ingredient per unit dosage form.

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

While it is possible for the active ingredients to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present disclosure 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.

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 disclosure 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.

The present disclosure further includes a pharmaceutical composition as hereinbefore defined wherein a compound as described herein or a pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3(6), 318 (1986).

Pharmaceutical compositions of the present disclosure suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray. Pharmaceutical compositions may contain in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

Pharmaceutical compositions of the present disclosure may be presented as patient packs containing one or more courses of treatment in a single package, for example, a blister pack. It will be understood that the administration of the combination of the disclosure by means of a single patient pack, or patient packs of each composition, is an additional feature of the disclosure .

It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this disclosure may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

Examples

Example 1: Biological Activity

Assays

Method

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 (RPMI 1640, 10% vol./vol. fetal bovine serum (FBS), and 10 μg/mL gentamicin), 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 (RapidPlate-96, Zymark Corp.). 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 4 12). Cell pellets were re-suspended in fresh medium (RPMI 1640, 20% vol./vol. FBS, 20% vol./vol. IL-2, and 10 μg/mL gentamicin) 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).

Virus used

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

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.

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.

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.

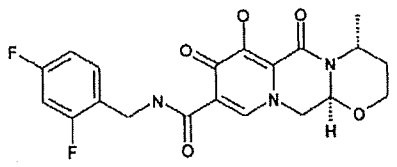
Results

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.

CLAIMS

What is claimed is:

1. A combination comprising a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,
and lamivudine, or a pharmaceutically acceptable salt thereof.

2. The combination according to claim 1 wherein the pharmaceutically acceptable salt of a compound of formula (I) is a sodium salt.

3. A pharmaceutical composition comprising a combination as defined in any one of claims 1 to 2 and a pharmaceutically acceptable carrier thereof.

4. Use of an effective amount of a combination as defined in any one of claims 1 to 2 for inhibiting HIV-1.

5. Use of an effective amount of a combination as defined in any one of claims 1 to 2 for treating an HIV infection.

6. The use according to claim 4 or 5, wherein the combination is for simultaneous administration.

7. The use according to claim 4 or 5, wherein the combination is for sequential administration.

8. The pharmaceutical composition of claim 3 for use in the inhibition of HIV-1.

9. The pharmaceutical composition of claim 3 for use in the treatment of an HIV infection.

10. A patient pack comprising a combination as defined in any one of claims 1 to 2 and instructions for use in the treatment of an HIV infection.

Figure 1: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with abacavir (ABC).

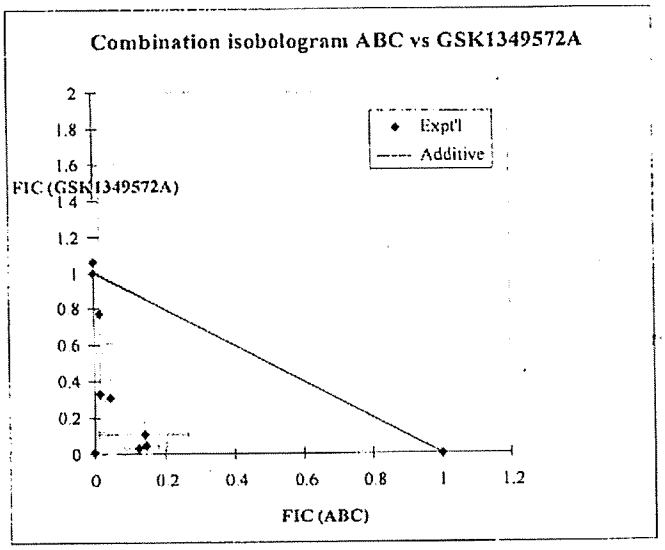


Figure 2: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with efavirenz (EFV).

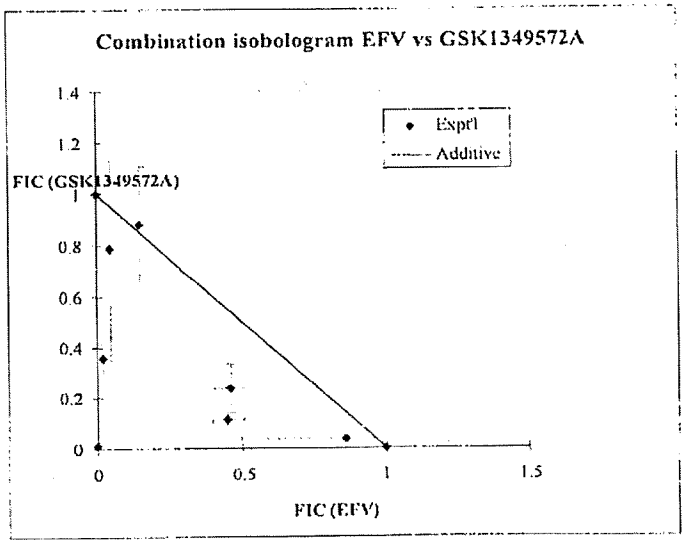
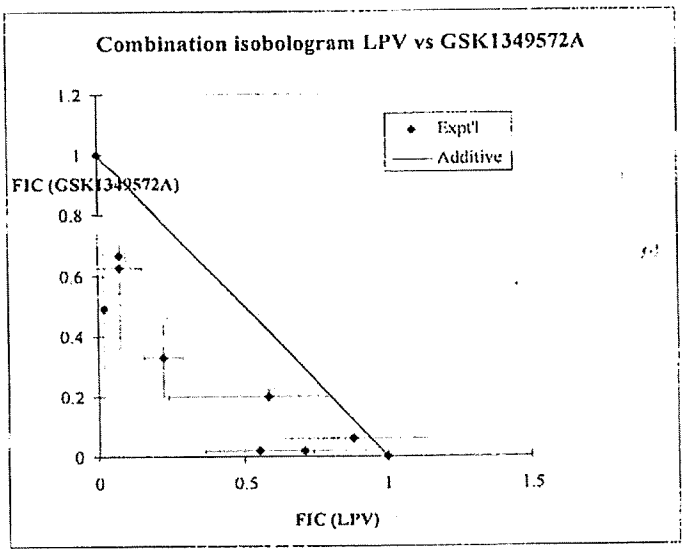


Figure 3: Inhibition of HIV-1_{IIIB} by a compound of formula (I), GSK1349572A, in combination with lopinavir (LPV)



I HEREBY CERTIFY that the above document is a true copy of the original issued out of / filed in the Court on the APR 05 2024 day of _____ A.D. 20____

Dated this _____ day of APR 05 2024 20____

VANESSA GEORGE
REGISTRY [illegible]
AGENT DU GREFFE