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DECEMBER 26, 2025

THE CONTROLLER OF PATENTS
INDIAN PATENT OFFICE
NEW DELHI

Re: Pre-grant Opposition against Indian Patent Application No. **202417029733** filed on **12/04/2024** – By **VIIV HEALTHCARE UK (NO.5) LIMITED**
Title: **INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION**
Opponent: **SANKALP REHABILITATION TRUST**

Dear Sir/Madam,

We are filing this representation by way of Pre-Grant Opposition along with annexures u/s 25 (1) of the Patents Act, 1970 and Rule 55 of the Patent Rules, 2003 in Form 7A.

The Learned Controller is requested to take said opposition along with annexures on record and proceed further in the matter and keep the Opponent advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents and/or evidence to support any of the averments in the representation as may be necessitated during future proceedings.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the present Opposition is finally decided.

Thanking you,

Yours faithfully,

MARIAM SADAF (IN /PA – 5231)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

Encl.: As stated

C.C: PATENTS@REMFRY.COM; REMFRY-SAGAR@REMFRY.COM

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application number 202417029733 dated 12/04/2024 in the name of VIIV HEALTHCARE UK (NO. 5) LIMITED.

REPRESENTATION BY:

SANKALP REHABILITATION TRUST ..... OPPONENT

VS.

VIIV HEALTHCARE UK (NO. 5) LIMITED ….. APPLICANT

REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)

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11.	Annexure 9: Power of Attorney	Will follow

Dated this day 26th day of December 2025

MARIAM SADAF (IN /PA – 5231)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, SANKALP REHABILITATION TRUST, Sankalp Rehabilitation Trust, an organization based in India, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, India, hereby give representation by way of opposition to the grant of patent in respect of application No. 202417029733 filed on 12/04/2024 made by VIIV HEALTHCARE UK (NO. 5) LIMITED on the grounds:

i. Section 25(1)(b): lack of Novelty
ii. Section 25(1)(e): Lack of inventive step
iii. Section 25(1)(f): Not patentable under sections 3(d), 3(e), 3(i), 2(1)(j),
iv. Section 25(1)(g): The complete specification does not sufficiently describe the invention or the method by which it is to be performed.
v. Section 25(1)(h): Non-compliance of section 8.

(Detailed grounds are set out in the Opposition as attached)

My address in India is:

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Dated this day 26th day of December 2025

MARIAM SADAF (IN /PA – 5231)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application number 202417029733 dated 12/04/2024 in the name of VIIV HEALTHCARE UK (NO. 5) LIMITED.

REPRESENTATION BY:

SANKALP REHABILITATION TRUST ..... OPPONENT

VS.

VIIV HEALTHCARE UK (NO. 5) LIMITED ….. APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

We, Sankalp Rehabilitation Trust, an organization based in India, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, India hereby submit our representation by way of oppostion to the patent application in respect of Indian Patent Application Number 202417029733 (hereinafter referred to as "the Impugned Application") dated 12/04/2024 in the name of VIIV HEALTHCARE UK (NO. 5) LIMITED entitled "INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION".

STATEMENT OF THE OPPONENT

I. About the Impugned Application

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application number 202417029733 (hereinafter "the impugned application") on 12/04/2024.

2. The Impugned patent application 202417029733 is the Indian application. It is national phase entry of international application PCT/IB2022/059780, filed on 12/10/2022, and published as WO2023062559 on 12/08/2021. The impugned application claims priority to US63/255056 dated 13/10/2021, and US63/257212 dated 19/10/2021. The impugned application was published in the Official Journal of the patent office on 15/11/2024. Request for examination was filed on 29/04/2024 but the FER has not yet been issued by Indian Patent Office in this application.

3. The Opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims which are currently on record are annexed herewith as Annexure-1.

4. The impugned application relates to compositions of the anti-HIV compounds denoted as Formula Ia and Ib in the impugned application comprising PEG and ethanol as essential components.

5. There are several classes of HIV inhibitors known in the art, including reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, entry inhibitors, and more recently capsid inhibitors. It is well recognized that many HIV inhibitors, owing to their complex and highly substituted chemical structures, frequently suffer from pharmacokinetic and formulation-related challenges, such as poor aqueous solubility, limited bioavailability, and difficulties in achieving stable dosage forms. These challenges have been widely discussed in the context of antiretroviral drug development and are not unique to any one mechanistic class of HIV inhibitors. Capsid inhibitors, despite their therapeutic promise and recent clinical success, have likewise been reported to present significant formulation challenges, particularly when developed as injectable or long-acting dosage forms. [*See* De Clercq, E. "Antiviral drug discovery: ten more compounds, and ten more stories (Part B)"; Cevik, M., & Orkin, C. (2019). Insights into HIV-1 capsid inhibitors in preclinical and early clinical development as antiretroviral

agents. *Expert Opinion on Investigational Drugs*, *28*(12), 1021–1024. https://doi.org/10.1080/13543784.2019.1692811.]

6. To address such well-known limitations, formulation science is routinely applied to improve the deliverability, stability, and bioavailability of poorly soluble antiviral compounds. Established formulation approaches include the use of co-solvent systems such as polyethylene glycol (PEG) and ethanol, which are widely employed to enhance the solubility of hydrophobic drug substances and maintain them in solution. PEGs of varying molecular weights are commonly selected to balance solubilisation capacity, viscosity, and injectability, while ethanol is frequently used as a low-molecular-weight co-solvent to further improve dissolution of poorly water-soluble drugs.

7. In addition, surfactants and stabilising agents such as poloxamers and lecithin are routinely incorporated into injectable formulations. Poloxamers are well known for their ability to stabilise solutions and suspensions, reduce particle aggregation, and improve physical stability in parenteral products. Lecithin, a naturally occurring phospholipid, has long been used in injectable and sustained-release formulations to enhance compatibility, dispersion stability, and biocompatibility. These excipients are particularly common in formulations intended for intramuscular or subcutaneous administration.

8. However, from the perspective of inventive step, these formulation approaches do not constitute a technical innovation, as they fall squarely within the common general knowledge of pharmaceutical formulation science. The use of PEG and ethanol as co-solvents for poorly soluble drug substances is a long-established and routine technique. Likewise, lecithin and poloxamers have for decades been used as surfactants and stabilisers in injectable formulations, particularly for hydrophobic drugs and sustained-release preparations. The preparation of aqueous suspensions with controlled particle size to achieve prolonged drug release is also a widely known and routinely applied strategy, especially in the development of long-acting injectable medicines for chronic conditions such as HIV infection.

9. Further, standard formulation measures such as particle size reduction, pH adjustment using acetate buffers, and control of tonicity through agents such as mannitol or sodium chloride represent routine steps that are extensively documented in pharmacopeias and pharmaceutical formulation textbooks. These techniques form part of the ordinary skill

set of a formulation scientist and are typically arrived at through straightforward optimisation and routine experimentation, rather than through inventive insight.

10. It is further submitted that the use of PEG/ethanol co-solvent systems and poloxamer- or lecithin-containing suspensions for poorly soluble antivirals is not a recent or niche development but a long-standing and widely adopted formulation paradigm. Standard pharmaceutical references and regulatory guidance recognize PEGs (particularly PEG 200–400) and ethanol as prototypical co-solvents for hydrophobic drug substances, while poloxamers (including grades 188, 237, 338 and 407) and lecithin are repeatedly cited as typical surfactants/wetting agents in parenteral, depot and long-acting formulations. In this context, a formulation scientist addressing the poor solubility and long-acting delivery of a capsid inhibitor would naturally first turn to these well-established excipient classes.

11. Furthermore, the concept of achieving long-acting therapy by either: (i) suspensions with controlled micro- or nano-particle size to provide a "depot" at the injection site; or (ii) viscous PEG-rich solutions with slow absorption from the injection site, is comprehensively described in the literature and in earlier HIV drug patents. These documents consistently treat such design choices as matters of routine optimization—balancing solubility, viscosity, injectability and depot behavior—rather than as inventive breakthroughs, reinforcing that the present formulation strategies are squarely within common general knowledge.

12. The invention described in the patent titled "Inhibitors of Human Immunodeficiency Virus Replication" (WO 2023/062559) relates to novel pharmaceutical compositions used for the treatment and prevention of HIV infection. Specifically, the invention covers compounds of Formula Ia and Formula Ib, or their pharmaceutically acceptable salts, which act as HIV capsid inhibitors. Because the active compounds of Formula Ia and Ib have poor aqueous solubility, formulation science is applied to improve their deliverability, stability, and bioavailability. The impugned application describes several formulation approaches, including homogeneous solvent-based solutions and heterogeneous aqueous suspensions. Solvent systems using polyethylene glycol (PEG) and ethanol are employed to dissolve hydrophobic drugs, while surfactants such as lecithin and poloxamers are used to stabilize the formulations. In suspension formulations, particle size is carefully controlled (micro- or nano-sized particles) to allow

slow release after intramuscular or subcutaneous injection, enabling long-acting therapy. These formulation strategies are aimed at achieving sustained drug exposure, improved patient compliance, and reduced dosing frequency. However, the formulation approaches themselves are not inventive, as they are already part of common general knowledge in pharmaceutical sciences. Thus the use of PEG and ethanol as co-solvents for poorly soluble drugs is a well-established and routine technique. Similarly, lecithin and poloxamers have long been used as surfactants and stabilizers in injectable formulations, particularly for hydrophobic or long-acting drugs.

Grounds of Opposition

13. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds as below:

i. Section 25(1)(b): lack of Novelty
ii. Section 25(1)(e): Lack of inventive step
iii. Section 25(1)(f): Not patentable under sections 3(d), 3(e), 3(i), 2(1)(j),
iv. Section 25(1)(g): The complete specification does not sufficiently describe the invention or the method by which it is to be performed.
v. Section 25(1)(h): Non-compliance of section 8.

14. **PRIOR ARTS:**

The opponent wishes to rely on the following prior art documents evidence in support of the grounds of opposition.

i. **D1** – WO2020254985, hereinafter referred to as WO985, published in 2020. (*annexed herewith as Annexure 2*).
ii. **D2** – WO2021116872, hereinafter referred to as WO'872, published on 17 June 2021. (*annexed herewith as Annexure 3*)
iii. **D3** – WO2018035359, hereinafter referred to as WO359, published in 2018. (*annexed herewith as Annexure 4*)
iv. **D4** – WO20200185459, hereinafter referred to as WO459, published in 2020. (*annexed herewith as Annexure 5*)
v. **D5** – Hoogevest et., al., The Use of Phospholipids to Make Pharmaceutical Form Line Extensions, Eur. J. Lipid Sci. Technol. 2021, 123, 2000297, 1-38,

hereinafter referred to as Hoogevest, published on 28 January 2021 (*annexed herewith as Annexure 6*)

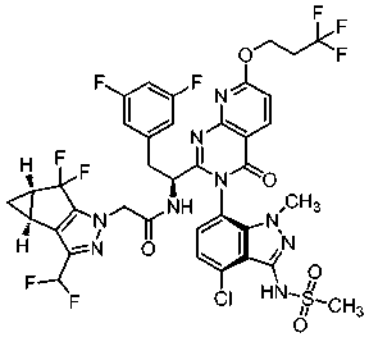
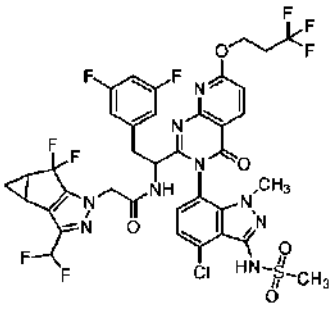
vi. **D6** – Peter van Hoogevest and Armin Wendel, The use of natural and synthetic phospholipids as pharmaceutical excipients, Eur. J. Lipid Sci. Technol. 2014, 116, 1088–1107. (*annexed herewith as Annexure 7*)

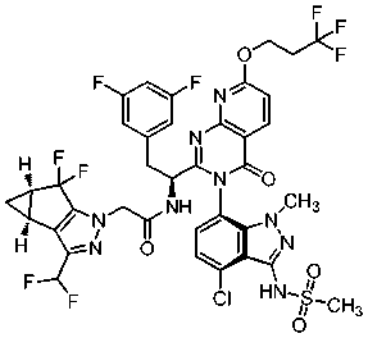
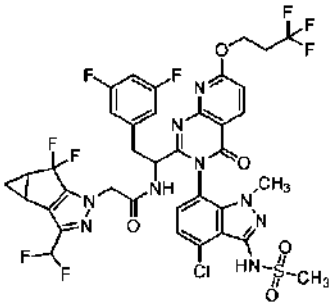
vii. **TPO** – Third party observation in respect of Application No. PCT/IB2022/059780 which is PCT application from which the present impugned Indian application is derived. The Opponent reserves the right to rely on the same during the entirety of the opposition proceedings (*annexed herewith as Annexure 8)*

GROUND 1: LACK OF NOVELTY

15. Opponent submits that the independent claims 2 and 18 of the impugned application lack novelty in light of disclosure of prior art document WO985.

16. The claim mapping of claims 2 and 18 against the disclosure of WO985 is as follows:

Claim of the Impugned Application	**Disclosure of WO985**
2. A pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof,  Formula Ib wherein the composition comprises polyethylene glycol and ethanol.	WO 985 discloses "the compound" depicted below  and pharmaceutically acceptable salts thereof (referred to as "the compound or salt of the invention"). It further discloses a pharmaceutical composition comprising the compound shown above or its salt form. [lines 1-6 on page 3]

	In the examples WO985 discloses that the compound was formulated in 90% PEG 400, 10% ethanol for IV administration and in 90% PEG400, 5% ethanol for PO administration. [lines 3-5 on page 41]
18. A pharmaceutical composition comprising a compound of Formula Ib,  Formula Ib wherein the composition comprises polyethylene glycol and ethanol	WO 985 discloses "the compound" depicted below  and pharmaceutically acceptable salts thereof (referred to as "the compound or salt of the invention"). It further discloses a pharmaceutical composition comprising the compound shown above or its salt form. [lines 1-6 on page 3] In the examples WO985 discloses that the compound was formulated in 90% PEG 400, 10% ethanol for IV administration and in 90% PEG400, 5% ethanol for PO administration. [lines 3-5 on page 41]

17. It is also pertinent that the impugned claims do not impose any novel or restrictive limitation on the relative amounts or grades of PEG and ethanol that could distinguish them from WO985. On the contrary, WO985 already exemplifies compositions in which the same capsid inhibitor is formulated in PEG 400 with 5–10% ethanol for both parenteral and oral administration, explicitly teaching PEG/ethanol systems for this very molecule. The present claims merely re-state this known formulation concept in generic terms, which cannot restore novelty.

18. Further, neither does the impugned specification disclose any unique compositional feature – such as a mandatory third essential excipient, a specific PEG molecular weight window, or a narrowly defined PEG: ethanol ratio. In the absence of a clearly delimited and technically meaningful distinction, the broad requirement that the composition comprises polyethylene glycol and ethanol is entirely anticipated by the explicit disclosure of 90% PEG 400 with 5–10% ethanol in WO985 and therefore fails the novelty requirement under Section 25(1)(b).

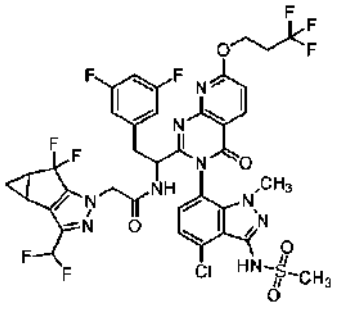
19. In view of the aforementioned disclosure of WO985, independent claims 2 and 18 of the impugned application lack novelty and all the claims dependent on said independent claims also lack novelty at least by virtue of their dependency on claim 2 and 18.

20. Therefore, the impugned application should be rejected on this ground alone.

GROUND 2: LACK OF INVENTIVE STEP

21. Opponent submits that the claims of the impugned application lack inventive step over the teaching of the prior art documents discussed below and taking into consideration the common general knowledge in the field of pharmaceuticals.

22. Prior art document D1 WO 985 discloses “the compound” depicted below



and pharmaceutically acceptable salts thereof (referred to as “the compound or salt of the invention”). It further discloses a pharmaceutical composition comprising the compound shown above or its salt form. [lines 1-6 on page 3]

23. Representative pharmaceutically acceptable base addition salts of the compound disclosed in WO985 include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-l, 3-propanediol (TRIS, tromethamine), arginine, benethamine (/V-benzylphenethylamine), benzathine (/V,/V-dibenzylethylenediamine), Zvs-(2-

hydroxyethyl)amine, bismuth, calcium, chloroprocaine, **choline**,…… [lines 24-27 on page 5]

24. WO985 discloses a method of treating HIV infection in a human comprising administering the compound or salt of the invention. This document also discloses the compound or salt of the invention for use in therapy. In another aspect, WO985 discloses the compound or salt of the invention for use in treating HIV infection in a human and the use of a compound or salt of the invention in the manufacture of a medicament for the treatment of HIV infection in a human. [lines 7-14 on page 3]

25. The pharmaceutical compositions disclosed in WO985 further comprise a pharmaceutically acceptable carrier, excipient, and/or diluent. In one embodiment of WO985, the pharmaceutical compositions further comprise a pharmaceutically acceptable excipient. [lines 16-18 on page 5]

26. In the method disclosed in WO985, preferred routes of administration are oral and by injection to deliver subcutaneously or intramuscularly. Therefore, preferred pharmaceutical compositions of WO985 include compositions suitable for oral administration (for example tablets) and compositions suitable for injection, for example subcutaneous or intramuscular injection. [lines 19-22 on page 5]

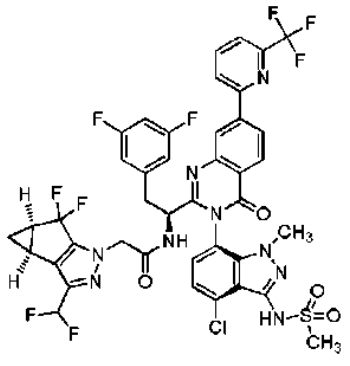
27. In the examples WO985 discloses that the compound was formulated in 90% PEG 400, 10% ethanol for IV administration and in 90% PEG400, 5% ethanol for PO administration. [lines 3-5 on page 41]

28. In another example under the heading of “Procedure for measuring pharmacokinetic parameters in a subcutaneous in vivo experiment” in WO985 the compound was formulated in 1% Kolliphor P188/l% PEG3350/3.5% Mannitol/94.5% Water and then administered to Wistar Han Rats as a subcutaneous injection at a dose of 20 mg/kg. [lines 24-25 on page 43] {Note: Kolliphor is a tradename for Poloxamer, both names are synonymous and commonly known and used in the field of pharmaceuticals}

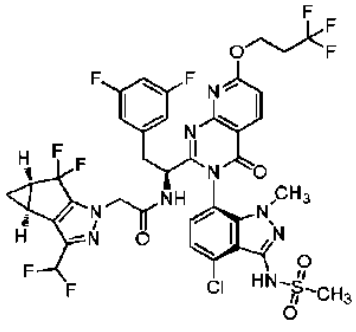
29. From the perspective of Section 2(1)(ja), WO985 therefore already provides the skilled person with: (i) the same capsid inhibitor as claimed; (ii) clear teaching that PEG-rich solutions with ethanol are suitable for this molecule across multiple routes of

administration; and (iii) an alternative SC formulation using PEG 3350, poloxamer and mannitol. Faced with the routine task of optimizing an injectable or oral formulation for Formula Ib, the skilled person would view these disclosures as a ready-made starting point and would seek only to fine-tune excipient grades, concentrations and vehicle composition within the familiar PEG/ethanol/poloxamer/mannitol toolkit. Such fine-tuning—substituting one PEG grade for another, adjusting PEG: ethanol ratios to balance solubility and tolerability, or moving between solution and suspension formats—is the very essence of ordinary formulation practice. The impugned claims do not introduce any qualitatively new formulation concept, but merely select combinations that are directly suggested, or at least plainly foreshadowed, by WO985, and therefore cannot be regarded as involving an inventive step.

30. Another prior art document WO872 relates to long-acting suspension formulations for the treatment of HIV. In particular, WO872 relates to a pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer useful as a long-acting HIV treatment. [Abstract] WO also explicitly discloses Lenacapavir, compound 1 and compound 2, which have following structures, as compounds which can be combined in the cabotegravir compositions disclosed therein.



Compound 1,



Compound 2,

31. WO872 discloses that the pharmaceutical compositions described therein may be administered parenterally (including subcutaneous, intramuscular, intravenous, or intradermal).

32. WO872 discloses that the pharmaceutical compositions described therein comprise cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

33. Poloxamer grades exemplified in WO872 are P237, P388, P407 and the exemplified grade of PEG is PEG3350. In the exemplified composition PEG3350, Poloxamer338, and mannitol are present as excipients [lines 20-21 and table 2a on page 6]. As per the disclosure of WO872 the actives present in such compositions can be cabotegravir alone or in combinations with other actives such capsid inhibitors Lenacapavir, Compound 1 or Compound 2 which have the structures as shown in para 15 above. [lines 30-31 on page 9, lines 24-27 on page 10, lines 1-8 on page 11]

34. WO872 teaches that "*Pharmaceutical compositions of the present invention may retain their particle size over time. This is advantageous as increase in particle size can lead to poor resuspension. Poor resuspension can, for example, make it difficult for healthcare professionals to withdraw a pharmaceutical composition from, for example, a vial or flask. Particle size stability is believed to be important for resuspension of the composition over time and reduces the risk of changing pharmacokinetics*." [lines 14-19 on page 7]

35. For maintaining particle size over time WO872 teaches that the particle size of the active should be between 0.1µm to 10 µm, preferably between 0.1 µm to 0.4 µm, more preferably between 0.15 µm to 0.25 µm, and most preferably about 0.2 µm since such particle size of the active in the compositions taught therein have improved resuspension over compositions with larger particle sizes (as used here 'resuspension' means dispersion of sedimented product to a free-flowing suspension). [lines 14-19 on page 7]

36. WO872 also teaches that compositions disclosed therein are amenable to incorporation of high quantities of the active from 300 to 600mg/ml. [lines 1-2 on page 2].

37. When WO872 is considered together with WO985, the lack of inventive step becomes even more apparent. WO872 not only confirms that cabotegravir long-acting suspensions with PEG 3350, poloxamer and mannitol are technically feasible and clinically useful, but also expressly teaches that structurally distinct capsid inhibitors (lenacapavir, compounds 1 and 2) can be incorporated into the same suspension platform without

destabilising the formulation. This directly signals to the skilled person that the excipient system is a generic vehicle applicable to multiple capsid inhibitors, rather than a bespoke solution unique to cabotegravir.

38. In light of this teaching, a formulation scientist would logically apply the same PEG/poloxamer/mannitol suspension platform—or close variants thereof—to the capsid inhibitor of Formula Ib when seeking a long-acting parenteral dosage form, with a reasonable expectation of obtaining stable, high-loading suspensions having good re-suspendability and depot performance. No inventive insight is required to implement such a generic platform approach, and the claimed compositions are therefore obvious in view of the combined disclosures of WO985 and WO872

39. WO359 relates to a compound commonly known as Lenacapavir, its salts, and compositions thereof. WO359 discloses that the compound Lenacapavir and its pharmaceutically acceptable salt can be formulated as compositions which comprise poloxamer, PEG, mannitol/sodium chloride.

40. WO359 discloses that the formulations suitable for parenteral administration (e.g., intramuscular (IM) and subcutaneous (SC) administration) will include one or more excipients which are compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. [para 00179]

41. WO359 discloses examples of solubilizing excipients in a parenteral formulation (e.g., an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) and poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed therein WO359 discloses a parenteral administration composition (e.g., an SC or IM formulation) that comprises Lenacapvir, or a pharmaceutical salt thereof, and a poloxamer, in particular poloxamer 338 in quantity of less than about 5%, such as less than about 3%, about 2%, about 1 %, or about 0.5%. [para 00180 and 00181].

42. Para [00182] discloses that other excipients can include polyethylene glycol and para [00184] discloses that the average molecular weight of PEG within the pharmaceutical composition is approximately 100 to approximately 800. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is

approximately 200 to approximately 600. Specific examples of PEG, as per disclosure of WO359 include but are not limited to PEG 100, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, and so forth.

43. It is disclosed in para [00187] and in para [00188] of WO359 the concentration of poloxamer in saline or mannitol is from about 0.1 to about 20%, preferably from about 0.1 to about 10%, and the preferred poloxamer is poloxamer 188.

44. As per para [00194] and para [00196] of WO359 the parenteral formulation consists essentially of the active ingredient i.e. the capsid inhibitor or a pharmaceutical salt thereof, water, ethanol, and polyethylene glycol 200, preferably such formulation is a solution formulation comprising a mixture of ethanol, water, and PEG 200, most preferably such solution formulation comprises about 5%-20% ethanol, about 5% to 20% water, and about 60% to 90% PEG 200.

45. WO459 relates to pharmaceutical compositions of capsid inhibitors Lenacapavir and GS-CA1. WO459 discloses pharmaceutical composition is in the form of a solution comprising the active ingredient, PEG 300 and water.

46. The pharmaceutical composition disclosed in WO459 is in form of a solution which comprises about 5 w/w% to about 15 w/w% water, about 50 w/w% to about 85 w/w% PEG 300, and about 15 w/w% to about 35 w/w% of the active ingredient, and which may further comprise sodium hydroxide. [Claim 89, 91 of WO459]

47. As per claim 90 of WO459 the pharmaceutical composition is solution comprising about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, and about 5 w/w% to about 35 w/w% of a sodium salt of lenacapavir.

48. As per claim 92 of WO459 the pharmaceutical composition is solution comprising about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, about 5 w/w% to about 35 w/w% of lenacapavir, and about 0.05 w/w% to about 2 w/w% of sodium hydroxide.

49. As per claim 93 of WO459 the pharmaceutical composition is solution comprising about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about

0.5 w/w% to about 40 w/w% of a sodium salt of lenacapvir, and about 0.1 w/w% to about 10 w/w% of poloxamer 188.

50. As per claim 93 of WO459 the pharmaceutical composition is solution comprising about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about 0.5 w/w% to about 40 w/w% of lenacapvir, about 0.01 w/w% to about 3.0 w/w% of sodium hydroxide, and about 0.1 w/w% to about 10 w/w% of poloxamer 188.

51. WO459 also discloses that various solubilizers can be used with lenacapavir to fill soft gel capsules or to form solution or suspension. These solubilizers and solvents disclosed are sesame oil, mixtures of medium chain mono- and di-glycerides, mixtures of monoglycerides, diglycerides, & trigylcerides, propylene glycol, ethanol, poloxamers, phospholipids, long chain triglycerides. [lines 28-31 on page 31; lines 1-4 on page 32; lines 8-9, 14-16, 19 on page 32; lines 16-17 on page 33.]

52. In lines 33-34 on page 33, it is disclosed in WO459 that the solution composition comprises PEG, ethanol, and water. In another embodiment disclosed in lines 34-35 on same page it is disclosed in WO459 that the solution composition comprises PEG300 and water. In lines 3-5 on page 34 it is disclosed that the amount of PEG 300 ranges from 45%w/w% to 90w/w%.

53. The prior-art lenacapavir compositions of WO359 and WO459 further confirm that PEG-rich solution systems and poloxamer-containing suspensions are standard, interchangeable vehicles for long-acting capsid inhibitors. These documents teach solution formulations comprising high levels of PEG 200 or PEG 300 with water and ethanol, as well as suspension formulations in which poloxamer 188 is used at low percentages alongside mannitol or saline, again reinforcing that such excipient choices reflect routine formulation design and not technical ingenuity.

54. Hoogevest publication discloses that for preparing alternative compositions of already known formulations of any active (commonly known as pharmaceutical form line extensions), phospholipids are an apt ingredient since phospholipids are biocompatible, biodegradable, non-toxic, and available at large scale and of pharmaceutical grade, they are well known to regulatory authorities, and they can be used as an emulsifier, wetting

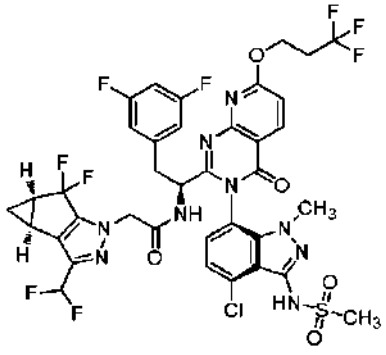
agent, solubilizer, for controlled release or targeted delivery, increasing therapeutic index of the formulated drug.

55. Hoogevest discloses several examples of drugs were reformulated using phospholipids in which it can be seen that the most common source of phospholipids used in the formulations is egg lecithin followed by soybean phospholipids.

56. Hoogevest and Wendel discloses that phospholipids are one of the most commonly used pharmaceutical excipient and that the most common sources of phospholipids used are egg lecithin and soybean lecithin.

57. Hoogevest and Wendel discloses that lecithin from these sources (egg, soybean) has very high percentage of phosphatidylcholine (upto 98%) as well as triglycerides, free & saturated fatty acids. It is also disclosed that lecithin derived soybean was safely used in parenteral and oral formulations of various drugs.

58. Prior art WO985 discloses that a compound of the structure which is the same as the Compound 2 taught in WO872 is effective as an anti-HIV agent.



Compound 2,

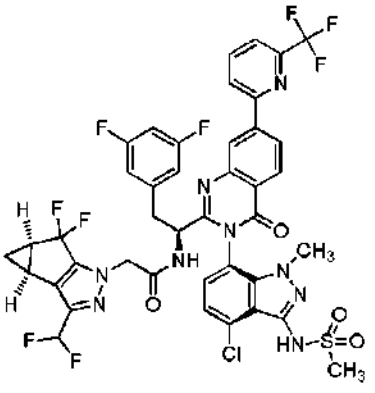
59. WO985 discloses that compositions of this compound and salts thereof can be prepared for use HIV treatment and these compositions can be formulated for oral use or for subcutaneous or intramuscular route.

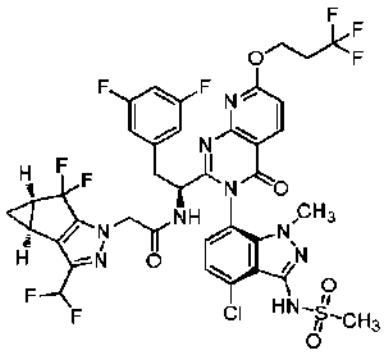
60. For subcutaneous route WO985 teaches that the composition comprises aforementioned compound or its salt and 1%PEG3350, 1%poloxamer 388, 3.5% mannitol, and 94% water. WO985 also teaches that if the composition is for oral administration then it comprises 90% PEG400 with either 10% or 5% ethanol.

61. Another prior art document WO872 also discloses the same capsid inhibitor compound as disclosed in WO985. Along with said compound the document also discloses two other capsid inhibitors which it considers to be alternatives of said compound. These two other alternative capsid inhibitor compounds disclosed in WO872 are lenacapavir and the compound of following formula.

62. WO872 primarily relates to anti-HIV long acting compositions comprising cabotegravir and other capsid inhibitors are disclosed in WO872 as compounds which can be combined together with cabotegravir without any deleterious effects on physical and chemical characteristics of the long acting compositions disclosed in that document.

63. Reading WO872 teaches a person skilled in the art that if capsid inhibitors lenacapavir and the compounds of structure shown below, denoted as Compound 1 and Compound 2 in WO872,


Compound 1,


Compound 2,

can be incorporated into the compositions designed for cabotegravir and discussed in WO872 without the need for making any changes in the disclosed compositions, it implies that the same compositions can also be used to formulate the capsid inhibitor compounds, shown above, even without incorporating cabotegravir and similar effects can reasonably be expected with such formulated compositions as that disclosed WO872.

64. This reasonable expectation also finds basis in the fact that the excipients disclosed in WO872 are same as those disclosed in WO985. Like WO985, WO872 also discloses that the compositions may be administered parenterally (including subcutaneous, intramuscular, intravenous, or intradermal) and comprise PEG3350, Poloxamer338, and mannitol in the composition to be administered subcutaneously. WO872 discloses that

instead of poloxamer 338 other grades like P237, P388, P407 can also be used in the composition.

65. Therefore, since same excipients are taught by both WO985 and WO872 for the subcutaneous composition, a person skilled in the art formulating subcutaneous compositions of the capsid inhibitors disclosed in WO872 and WO985 is motivated to use the same excipients in similar concentrations.

66. The compositions disclosed in WO872 are suspension compositions and it is taught in WO872 that if the particle size of the active ingredient incorporated in the composition is between 0.1µm to 10 µm, preferably between 0.1 µm to 0.4 µm, more preferably between 0.15 µm to 0.25 µm, and most preferably about 0.2 µm since such particle size of the active in the compositions imparts improved resuspension over compositions with larger particle sizes.

67. WO872 also discloses that although conventionally incorporation of high quantity of active in a composition i.e. beyond 285mg/ml was considered problematic, the compositions disclosed therein are such that high quantities of the active from 300-600mg/ml can be incorporated into the composition without any instability issues.

68. Since obtaining a stable composition with high drug loading and good redispersibility is every formulator's goal, a person skilled in the art is motivated to use capsid inhibitor compound in the particle size range as taught in WO872 as well incorporate high amount of active i.e. incorporate 300mg/ml of active in the composition with the reasonable expectation that the resulting compositions will be stable and have good resuspension (i.e. redispersibility).

69. Since lenacapavir was taught as an alternative to the capsid inhibitors denoted as Compound 1 and Compound 2 in WO872, and lenacapavir being the first capsid inhibitor which had already been successful in the clinical trials, a person skilled in the art is motivated to refer to the compositions of lenacapavir also.

70. WO359 discloses compositions of lenacapavir which are for parenteral administration (subcutaneous, intramuscular, intravenous, intraperitoneal). The compositions disclosed in WO359 are both in the form of solution as well as in the form of suspension.

71. Like WO985 and WO872, WO359 also discloses that the compositions of lenacapavir for subcutaneous administration comprise of PEG, poloxamer, and mannitol/sodium chloride. It is taught in WO985 that poloxamer 338 in quantity of less than about 5%, such as less than about 3%, about 2%, about 1 %, or about 0.5% can be used in the composition while for PEG various grades of PEG ranging from PEG 100, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, and so forth can be used.

72. In a preferred embodiment WO359 discloses that the concentration of poloxamer in saline or mannitol is from about 0.1 to about 20%, preferably from about 0.1 to about 10%, and the preferred poloxamer is poloxamer 188.

73. In another preferred embodiment it is disclosed in WO359 that when the composition is in solution form such formulation comprises a mixture of ethanol, water, and PEG 200, most preferably such solution formulation comprises about 5%-20% ethanol, about 5% to 20% water, and about 60% to 90% PEG 200.

74. Yet another document pertaining to compositions of lenacapavir WO459 discloses that a solution composition comprises about 45 w/w% to about 85 w/w% PEG300 and comprises about 5 w/w% to about 15 w/w% water. WO459 discloses that the compositions can further comprise of about 0.1 w/w% to about 10 w/w% of poloxamer 188 and/or about 0.05 w/w% to about 2 w/w% of sodium hydroxide.

75. WO459 also discloses that various solubilizers and solvents can be used in the composition to form solution or suspension. These solubilizers and solvents disclosed are sesame oil, mixtures of medium chain mono- and di-glycerides, mixtures of monoglycerides, diglycerides, & trigylcerides, propylene glycol, ethanol, poloxamers, phospholipids, long chain triglycerides.

76. As far as choice of solubilizers is concerned a person skilled in the art is taught by Hoogevest that phospholipids are a great choice not only because they have excellent solubilizing and wetting properties but also because they are biocompatible, non-toxic, available in pharmaceutical grade, generally considered as safe by regulatory authorities, and have been extensively and successfully used for the purposes of reformulating actives. Hoogevest also teaches that most commonly used source of phospholipids is egg lecithin and which in turn contains high amounts of phosphatidylcholines.

77. A person skilled in the art is taught by Hoogevest and Wendel that lecithin is a good source of phospholipids and that it can be derived from eggs or soybean or other such sources but egg lecithin and soybean lecithin have been used in pharmaceutical compositions. A person skilled in the art is also motivated to choose lecithin as a source of phospholipid for use as a solubilizer in the compositions of capsid inhibitors denoted as Compound 1 and Compound 2 in WO872 because Hoogevest and Wendel discloses that lecithin especially egg lecithin and soybean lecithin contains fatty acids, tri-and di-glycerides and very high amounts of phosphatidylcholine, and these solubilizers are taught by WO459 also.

78. A person skilled in the art finds that the excipients used in WO359 and WO459 are same as those taught in WO985 and WO872 except that the grade of PEG changes when the composition is formulated as a suspension or as solution. Thus, a person skilled in the art is motivated to use the same excipients as disclosed in said documents for formulating compositions of capsid inhibitors, denoted as Compound 1 and Compound 2 in WO872, in either solution or suspension form. These commonly used excipients as taught by said documents are PEG200-600; poloxamers P188 P237, P388, P407; ethanol; mannitol/sodium chloride, sodium hydroxide, water, and combinations thereof. WO872 and WO985 teaches PEG3350 to be used in subcutaneous compositions but WO459 teaches that even for subcutaneous compositions lower grades of PEG like PEG 200 or PEG 300 can be used. The percentages in which these excipients can be used either alone or in combination are also taught by the prior art documents discussed hereinabove.

79. Further, document WO872 teaches a person skilled in the art that when formulating suspension formulations using active in a certain particle size range i.e. between 0.1µm to 10 µm is ideal to obtain good resuspension and stability.

80. WO459 teaches a person skilled in the art that while formulating the compositions as solutions various solubilizers and solvents can be used alone or in combination. A person skilled in the art is motivated to use the solubilizing ingredients taught by WO459 with reasonable expectation of obtaining a solution formulation. Furthermore, the two publications by Hoogevest teach that many of the solubilizing substances taught in WO459 are present in lecithin and that lecithin by virtue of having phospholipids acts as a biocompatible, non-toxic, pharmaceutically acceptable solubilizer and wetting agent.

This motivates a person skilled in the art to incorporate lecithin as a solubilizer in compositions of Compound 1 and Compound 2 of WO872 while preparing them in solution form. A person skilled in the art is also motivated to use lecithin in compositions of Compound 1 and Compound 2 of WO872 when compositions are formulated as suspensions since Hoogevest and Wendel disclose that the phospholipids in the lecithin also work as wetting agents and it is common general knowledge in the field of pharmaceuticals that wetting agents are added to suspension compositions to make them more stable and help redispersibility.

81. When the teachings of WO985, WO872, WO359, WO459 and Hoogevest are viewed in combination, the skilled person is presented with a coherent and predictable formulation landscape for capsid inhibitors: PEG solutions with ethanol, and PEG/poloxamer-based suspensions optionally including phospholipids such as lecithin. The impugned application simply re-packages these known strategies for the same or analogous capsid inhibitors without demonstrating any unexpected property or technical advance, and thus fails to meet the inventive-step standard under Section 2(1)(ja) read with Section 25(1)(e). Therefore, the claimed subject matter of the impugned application is obvious in view of the combination of teachings of documents D1 to D6 as discussed above and the impugned application ought to be rejected on this ground alone.

82. With regard to technical advancement, the impugned application purports that the advantage of the invention is high bioavailability and long action. However, the prior art documents WO872, WO459 disclose anti-HIV compositions which are long acting and have high bioavailability, and compositions disclosed in WO985 and WO872 also have the same compounds as the ones comprising the compositions of impugned invention. Hence, the compositions of the impugned application are merely alternatives of the anti-HIV compositions already known in the art at the time of the invention and lack any technical advancement over what was already known in the art. For this reason the impugned application should be rejected.

83. As discussed hereinabove, the subject matter claimed in the impugned application is obvious in light of combination of teachings of the prior art documents D1 to D6 and is also not a technical advancement over existing knowledge. Therefore, the impugned application should be rejected in toto.

84. Therefore, the impugned application fails to establish the technical advancement of the claimed subject matter over what was known in the art at the time of the invention and the claimed subject matter is also obvious in view of the combined reading of the cited prior arts as discussed above.

GROUND 3: Claims not patentable under Section 25(1)(f)

The claimed subject matter in not patentable under Section 3(d) of the Act

85. It is submitted that the impugned patent application should not be allowed under Section 3(d) which states that "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation - For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

86. As submitted under the grounds of lack of novelty and lack of inventive step the subject matter claimed in impugned application is neither novel nor inventive and hence, squarely falls under the ambit of Section 3(d) of the Act.

87. It is further submitted that Applicant failed to provide any data in the specification to demonstrate enhanced therapeutic efficacy with respect to compositions as disclosed in WO872 document which discloses long-acting anti-HIV compositions of comprising cabotegravir and Compound 1 or Compound 2. The compositions claimed in impugned application are merely new form of compositions disclosed in the document WO872 since the compositions are same as disclosed in WO872 with the difference that Cabotegravir has been removed from the compositions claimed in impugned application.

88. Hence compositions disclosed in WO872 document are the “known substance” for the purpose of section 3(d) of the Act for the impugned application and the compositions claimed in the impugned application are new form of compositions disclosed in WO872.

89. According to section 3(d) of the act it was incumbent upon the Applicant to establish enhanced therapeutic efficacy of the claimed compositions as compared to the compositions disclosed in document WO872.

90. The impugned specification provides no comparative data establishing enhanced therapeutic efficacy of the claimed compositions over the compositions known in document WO872.

91. Without prejudice to the above, it is submitted that Applicant failed to provide any data in the specification to demonstrate enhanced therapeutic efficacy with respect to compositions as disclosed in WO985 document discloses anti-HIV compositions of compound of Compound 2 which is the same as compound of formula Ib of the impugned application. The compositions claimed in impugned application comprising compound of formula Ib are merely new form of the compositions disclosed in the document WO985 since the compositions are same as disclosed in WO985 with the difference that in some embodiments of the impugned application lecithin and/or propylene glycol have been added to the compositions.

92. Hence compositions disclosed in WO985 document are the “known substance” for the purpose of section 3(d) of the Act for the impugned application and the compositions claimed in the impugned application are merely new form of compositions disclosed in WO985 document. For the avoidance of doubt, the “known substance” under Section 3(d) in this case is not limited to the free capsid inhibitor, but includes the specific PEG- and PEG/poloxamer-based compositions of WO985 and WO872, which already disclose: (i) the same active compound (Formula Ib / compound 2); (ii) the same or closely similar excipients (PEG 3350, poloxamers, mannitol, ethanol, water); and (iii) the same routes and objectives of administration (long-acting, parenteral or oral HIV treatment). The claimed compositions are, at most, new forms or line extensions of these known formulations, obtained by minor excipient variation within the same formulation class

93. In these circumstances, Section 3(d) requires the applicant to establish enhanced therapeutic efficacy relative to those prior-art compositions, not merely differences in solubility, bioavailability, residence time or other pharmacokinetic parameters. The complete specification is devoid of any comparative antiviral data—such as viral load reduction, duration of suppression, or resistance outcomes—against the compositions known in document WO985 and therefore fails to satisfy the statutory threshold for patentability of new forms of known substance.

94. The invention as claimed relates to anti-HIV pharmaceutical compositions; however, the complete specification does not establish any antiviral activity of the claimed compositions. No experimental data demonstrating inhibition of HIV replication, antiviral efficacy, or biological activity against HIV is provided. The only biological data disclosed in the specification relates to plasma residence time and pharmacokinetic **profiles** of certain formulations. While pharmacokinetic data may indicate systemic exposure, it does not, by itself, establish anti-HIV activity or therapeutic efficacy. In the absence of any antiviral activity data, the skilled person is unable to determine whether the claimed compositions actually achieve the stated therapeutic effect.

95. Therefore, the claimed subject matter of the impugned application squarely falls under the ambit of section 3(d) and the impugned patent application should be rejected on this ground alone.

Claims of impugned application are not patentable as per Section 3(e) of the Act

96. Section 3(e) which states that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance is not patentable.

97. The Applicant has failed to demonstrate any unexpected or synergistic effect of the claimed composition in the impugned specification as compared to other formulations already known in the art at the time of the invention such as compositions of WO985. The Applicant has failed to establish that the claimed compositions have any unexpected or surprising effect as compared to similar compositions that were known in the art at the time of the invention.

98. It is further submitted that the excipient systems recited in the claims—combinations of PEG (various grades), ethanol, poloxamer, lecithin, mannitol or sodium chloride, buffering agents, and water—are all well-known formulation components that each perform their conventional, additive roles in the claimed compositions. PEG and ethanol act as co-solvents, poloxamer and lecithin as surfactants and stabilisers, mannitol or sodium chloride as tonicity agents, and buffers for pH control, exactly as taught in WO985, WO872, WO359, WO459 and Hoogevest. The impugned application does not disclose any unexpected synergy or cooperative interaction among these excipients that results in a new or improved property of the composition as a whole.

99. On the contrary, the advantages asserted—such as high drug loading, physical stability, and long-acting behaviour—are precisely those that the skilled person would predict from using PEG-based solutions or finely dispersed suspensions with appropriate surfactants and tonicity agents, in line with the prior art. The claimed compositions therefore constitute a classic case of "mere admixture resulting only in the aggregation of the properties of the components thereof" under Section 3(e), and are not patentable. Therefore, the impugned application fails to establish any synergistic effect of the compositions claimed in the impugned application which are merely an admixture which falls under the prohibition of Section 3(e) read with Section 25(1)(f) of the Act. Thus, impugned application is liable to be rejected on this ground alone.

Claims of impugned application are not patentable as per Section 3(i) of the Act and as per Section 2(1)(j) of the Act.

100. As per Section 3(i) of the Act method of treatment of humans and animals is not patentable and as per Section 2(1)(j) of the Act only 'product' or 'process' is patentable subject matter in India.

101. It is submitted that the claims 58-59 though worded as product claims essentially claim method of treatment generally and method of treatment of HIV in humans.

102. Further, claim 58-60 though worded as product claims, these claims in substance recite and claim the 'use' of the claimed composition. Moreover, claim 60 is a Swiss-type claim which is not allowable in India.

103. It is submitted that is settled legal principal that the claims are to be viewed from the perspective of the doctrine of "pith and marrow," also known as the "substance of the invention" doctrine. This legal principle in patent law calls for focusing on the essential elements of an invention recited in a claim rather than its exact wording or specific features.

104. Accordingly, the substance of the subject matter claimed in claims 58-60 is not patentable subject matter under Section 3(i) and Section 2(1)(j) of the Act.

GROUND 4: INSUFFICIENCY OF DISCLOSURE

105. The Opponent submits that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed and the claims are not supported by the specification.

106. The Opponent states that it is a well settled in patent law that the specification should clearly and fairly describe the invention, unambiguously define the scope of the claims, enable the entire breadth of claimed subject matter, and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue experimentation and without application of inventive faculty. It is submitted that the impugned application suffers from insufficiency of disclosure and is liable to be rejected on this ground alone.

107. The Indian Patent Office Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals state that

"*11.5 Sufficient disclosure of the invention in the patent specification is the consideration for which a patent is granted. While assessing the sufficiency of disclosure, it must be ensured that the best method for performing the invention known to the applicant is described so that the whole subject-matter that is claimed in the claims, and not only a part of it, must be capable of being carried out by a skilled person in the relevant art*

without the burden of an undue amount of experimentation or application of inventive ingenuity

11.6 It may be noted that the IPAB has distinguished the person skilled in the art involved in assessing "Inventive step" and "Enablement". In one case (please see the discussion under Inventive Step) the IPAB observed: The Act makes a distinction between the person skilled in the art (the obviousness person) and the person who has average skill (enablement man)"26. In the opinion of the IPAB, in the context of enablement, the person to whom the complete specifications are addressed is a person "who has average skill and average knowledge." The description in the specification should contain at least one example or more than one example, covering the full breadth of the invention as claimed, which enable(s) the person skilled in the art to carry out the invention. If the invention is related to product per se, description shall be supported with examples for all the compounds claimed or at least all the genus of the compounds claimed. Method for preparation and experimental data relating to properties of representatives of each embodiments claimed shall be incorporated in the description, which enable a person having ordinary skilled in the art can make use of the invention without undue burden." [Emphasis added]

108. It is submitted that the claims as presently worded are too broad, and indefinite.

109. Claim 33-34, 46-47 recite composition of compound of Formula Ia and Ib contains less than 1% by weight of polyethylene glycol. Claims 40-42, 53-55, mean particle diameter of compound of Formula Ia and Ib is $\leq 0.2\mu m$

110. It is submitted that the term "less than" is indefinite and creates an ambiguity with respect to the actual scope of the claim.

111. The claims 45, 58 recite that the composition is a heterogenous suspension. However, as commonly understood in the field of pharmaceuticals suspensions are always inherently heterogenous. Moreover, the Applicant has not provided any definition of the term "heterogenous suspension" in the specification. As a result, the subject matter claimed is not clear since it is not clear what the Applicant intends to convey by the term "heterogenous suspension".

112. The claims 14, 30 recite that the composition is a heterogenous suspension. However, as commonly understood in the field of pharmaceuticals solutions are always inherently homogenous. Moreover, the Applicant has not provided any definition of the term “homogenous suspension” in the specification. As a result, the subject matter claimed is not clear since it is not clear what the Applicant intends to convey by the term “homogenous solution”.

113. The ambiguity surrounding terms such as “heterogenous suspension” and “homogenous suspension/solution” is compounded by the absence of clear methodological disclosure on how key parameters—especially mean particle diameter ≤0.2 µm—are to be measured and controlled. The specification does not identify the analytical technique (e.g. dynamic light scattering, laser diffraction, microscopy), sample preparation conditions, dispersants or measurement protocols needed to obtain reproducible particle-size data for these highly loaded suspensions. Without such guidance, the person of average skill cannot reliably determine whether a given formulation falls within or outside the claimed particle-size limitations.

114. Furthermore, the claims contemplate extremely broad ranges of excipient contents (e.g. “less than 1%” PEG in certain embodiments) without providing worked examples or experimental data that show how such low-PEG formulations are actually prepared, stabilised and administered. This disconnect between broad functional claim language and sparse, narrowly focused examples imposes an undue experimental burden on the skilled person, who would be forced to undertake extensive trial-and-error formulation development to identify workable embodiments across the full claim scope, contrary to the enablement standard articulated in the Pharmaceutical Examination Guideline

115. Claims 59–61 relate to therapeutic use, treatment of HIV infection, and manufacture of medicaments. The specification provides only general statements of intended use and limited animal pharmacokinetic data, without data, dosage guidance, or formulation-specific therapeutic justification. These claims therefore lack sufficient support in the Complete Specification.

116. Considering above submissions, impugned application does not sufficiently describe the invention. Therefore, the impugned application should be refused on this ground alone.

GROUND 5 -Section 25(1)(h)

117. Opponent submits that the Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications to the Indian application to the Patent Office in writing within the prescribed time.

118. The opponent understands that the prescribed time for filing information under section 8 is still available to the Applicant but it is expected under the general practice of patents in India that the hearing on the present opposition might be taken up after the prescribed time for complying with present requirement is over and at that point of time the opponent will be barred from taking up new ground.

119. Therefore, the opponent reserves to right to submit detailed contentions under present ground at a later point of time and craves leave to file further submissions and evidence with respect to this ground.

CONCLUSION

120. In view of the above, the claimed subject matter is not inventive, not patentable and the impugned application is insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

HEARING REQUESTED

121. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinafter referred to as "the Rules").

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Controller take the present Opposition on record; that the Indian application 202417029733 dated 12/04/2024, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;

iii. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;

iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

v. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;

vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

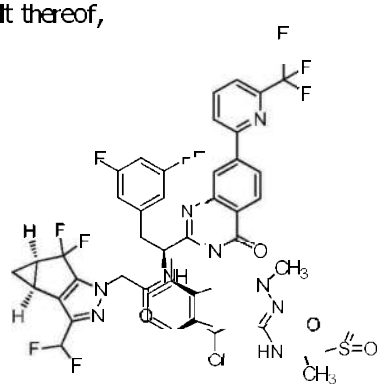
Dated this 26th day of December, 2025

AGENT FOR THE OPPONENT
MARIAM SADAF (IN /PA – 5231)
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

What is claimed is:

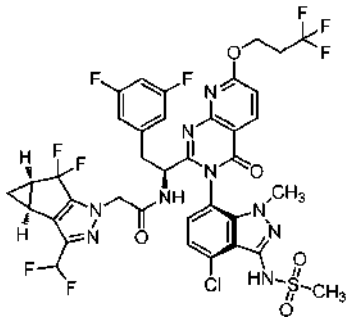
1. A pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprises polyethylene glycol and ethanol.

2. A pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises polyethylene glycol and ethanol.

3. The pharmaceutical composition according to Claim 1 or Claim 2 wherein the composition further comprises one or more of water, lecithin, propylene glycol, benzyl alcohol, or sesame oil.

4. The pharmaceutical composition according to Claim 3 wherein the composition comprises lecithin.

5. The pharmaceutical composition according to Claim 4 wherein the lecithin is egg-based or soy-based and is about 80 weight% phosphatidylcholine.

6. The pharmaceutical composition according to Claim 4 wherein the lecithin is egg-based or soy-based and is about 100 weight% phosphatidylcholine.

7. The pharmaceutical composition according to any of Claims 4 to 6 further comprising propylene glycol, benzyl alcohol, or sesame oil.

8. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 200 (PEG 200).

9. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 300 (PEG 300).

10. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 400 (PEG 400).

11. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of ethanol is about 5-25 weight%.

12. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of ethanol is about 20 weight%.

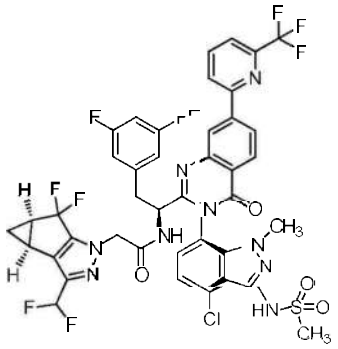
13. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of polyethylene glycol is about 40-50% by weight.

14. The pharmaceutical composition according to any of Claims 1-13 wherein the composition is a homogeneous solution.

15. The pharmaceutical composition according to any of Claims 1 and 3-14 comprising about 20% by weight of the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

16. The pharmaceutical composition according to any of Claims 2-14 comprised of about 20% by weight of the compound of Formula Ib, or a pharmaceutically acceptable salt thereof, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

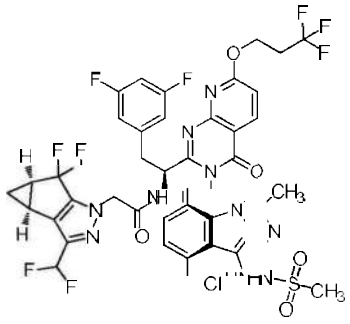
17. A pharmaceutical composition comprising a compound of Formula Ia,



Formula Ia

wherein the composition comprises polyethylene glycol and ethanol.

18. A pharmaceutical composition comprising a compound of Formula Ib,



Formula Ib

wherein the composition comprises polyethylene glycol and ethanol.

19. The pharmaceutical composition according to Claim 17 or Claim 18 wherein the composition further comprises one or more of water, lecithin, propylene glycol, benzyl alcohol, or sesame oil.

20. The pharmaceutical composition according to Claim 19 wherein the composition comprises lecithin.

21. The pharmaceutical composition according to Claim 20 wherein the lecithin is egg-based or soy-based and is about 80 weight% phosphatidylcholine.

22. The pharmaceutical composition according to Claim 20 wherein the lecithin is egg-based or soy-based and is about 100 weight% phosphatidylcholine.

23. The pharmaceutical composition according to any of Claims 20-22 further comprising propylene glycol, benzyl alcohol, or sesame oil.

24. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 200 (PEG 200).

25. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 300 (PEG 300).

26. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 400 (PEG 400).

27. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of ethanol is about 5-25 weight%.

28. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of ethanol is about 20 weight%.

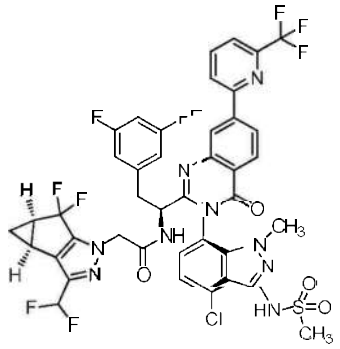
29. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of polyethylene glycol is about 40-50% by weight.

30. The pharmaceutical composition according to any of Claims 17-29 wherein the composition is a homogeneous solution.

31. The pharmaceutical composition according to any of Claims 17 and 19-30 comprised of about 20% by weight of the compound of Formula Ia, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

32. The pharmaceutical composition according to any of Claims 18-30 comprised of about 20% by weight of the compound of Formula Ib, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

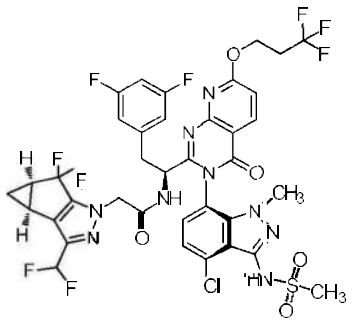
33. A pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

34. A pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

35. The pharmaceutical composition according to Claim 33 or Claim 34 further comprising one or more of sodium acetate, acetic acid, mannitol, sodium chloride, Poloxamer 338, or Poloxamer 188.

36. The pharmaceutical composition according to Claim 35 wherein the composition comprises Poloxamer 338 or Poloxamer 188.

37. The pharmaceutical composition according Claim 36 wherein the composition further comprises sodium acetate and acetic acid.

38. The pharmaceutical composition according to Claim 37 wherein the composition further comprises mannitol or sodium chloride.

39. The pharmaceutical composition according any of Claims 33 and 35-38 wherein the mean particle diameter of the compound of Formula Ia is 0.2 μm to 0.5 μm.

40. The pharmaceutical composition according any of Claims 33 and 35-38 wherein the mean particle diameter of the compound of Formula Ia is ≤ 0.2 μm.

41. The pharmaceutical composition according any of Claims 34-38 wherein the mean particle diameter of the compound of Formula Ib is 0.2 μm to 0.5 μm.

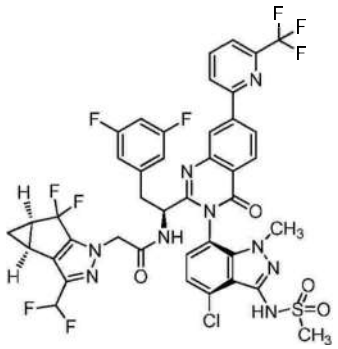
42. The pharmaceutical composition according any of Claims 34-38 wherein the mean particle diameter of the compound of Formula Ib is ≤ 0.2 μm.

43. The pharmaceutical composition according any of Claims 33 or Claims 35-40 comprising about 300 mg/mL of the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

44. The pharmaceutical composition according any of Claims 34, Claims 35-38 or Claims 41-42 comprising about 300 mg/mL of the compound of Formula Ib, or a pharmaceutically acceptable salt thereof, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

45. The pharmaceutical composition according to any of Claims 33-44 which is a heterogeneous suspension.

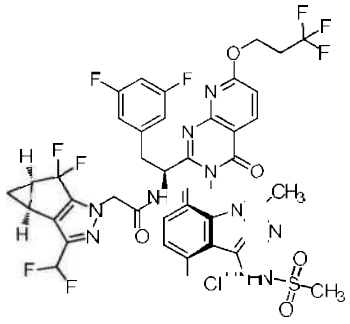
46. A pharmaceutical composition comprising a compound of Formula Ia,



Formula Ia

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

47. A pharmaceutical composition comprising a compound of Formula Ib,



Formula Ib

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

48. The pharmaceutical composition according to Claim 46 or Claim 47 further comprising one or more of sodium acetate, acetic acid, mannitol, sodium chloride, Poloxamer 338, or Poloxamer 188.

49. The pharmaceutical composition according to Claim 48 wherein the composition comprises Poloxamer 338 or Poloxamer 188.

50. The pharmaceutical composition according Claim 49 wherein the composition further comprises sodium acetate and acetic acid.

51. The pharmaceutical composition according to Claim 50 wherein the composition further comprises mannitol or sodium chloride.

52. The pharmaceutical composition according any of Claims 46 and 48-51 wherein the mean particle diameter of the compound of Formula Ia is 0.2 μm to 0.5 μm.

53. The pharmaceutical composition according any of Claims 46 and 48-51 wherein the mean particle diameter of the compound of Formula Ia is ≤ 0.2 μm.

54. The pharmaceutical composition according any of Claims 47-51 wherein the mean particle diameter of the compound of Formula Ib is 0.2 μm to 0.5 μm.

55. The pharmaceutical composition according any of Claims 47-51 wherein the mean particle diameter of the compound of Formula Ib is ≤ 0.2 μm.

56. The pharmaceutical composition according any of Claims 46 or Claims 48-53 comprising about 300 mg/mL of the compound of Formula Ia, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

57. The pharmaceutical composition according any of Claims 47, Claims 48-51 or Claims 54-55 comprising about 300 mg/mL of the compound of Formula Ib, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

58. The pharmaceutical composition according to any of Claims 46-57 which is a heterogeneous suspension.

59. A pharmaceutical composition according to any of Claims 1-58 for use in therapy.

60. A pharmaceutical composition according to any of Claims 1-58 for use in treating HIV infection in a human.

61. A pharmaceutical composition according to any of Claims 1-58 for use in the manufacture of a medicament for the treatment of HIV infection in a human.

Dated this 12th day of April, 2024

[MAHUA RAY]
--DIGITALLY SIGNED—
IN/PA-867
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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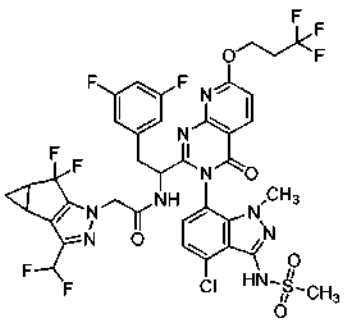
(54) **Title:** PYRIDO[2,3-D]PYRIMIDINE DERIVATIVES AS INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION



(57) **Abstract:** The compound and pharmaceutically acceptable salts thereof, and compositions and methods for treating human immunodeficiency virus (HIV) infection are set forth.

WO 2020/254985 A1

INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

FIELD OF THE INVENTION

The invention relates to compounds, compositions, and methods for the treatment of human immunodeficiency virus (HIV) infection. More particularly, the invention provides novel inhibitors of HIV, pharmaceutical compositions containing such compounds, and methods for using these compounds in the treatment of HIV infection. The invention also relates to methods for making the compounds hereinafter described.

BACKGROUND OF THE INVENTION

Acquired immunodeficiency syndrome (AIDS) is the result of infection by HIV. HIV continues to be a major global public health issue. In 2015, an estimated 36.7 million people were living with HIV (including 1.8 million children) – a global HIV prevalence of 0.8%. The vast majority of this number live in low- and middle- income countries. In the same year, 1.1 million people died of AIDS-related illnesses.

Current therapy for HIV-infected individuals consists of a combination of approved anti-retroviral agents. Close to four dozen drugs are currently approved for HIV infection, either as single agents, fixed dose combinations or single tablet regimens; the latter two containing 2-4 approved agents. These agents belong to a number of different classes, targeting either a viral enzyme or the function of a viral protein during the virus replication cycle. Thus, agents are classified as either nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), or entry inhibitors (one, maraviroc, targets the host CCR5 protein, while the other, enfuvirtide, is a peptide that targets the gp41 region of the viral gp160 protein). In addition, a pharmacokinetic enhancer (cobicistat or ritonavir) can be used in combinations with antiretroviral agents (ARVs) that require boosting.

Despite the armamentarium of agents and drug combinations, there remains a medical need for new anti-retroviral agents. High viral heterogeneity, drug-associated toxicity, tolerability problems, and poor adherence can all lead to treatment failure and may result in the selection of viruses with mutations that confer resistance to one or more antiretroviral agents or even multiple drugs from an entire class (Beyrer, C., Pozniak A. HIV drug resistance – an emerging threat to epidemic control. N. Engl. J. Med. 2017, 377, 1605-1607; Gupta, R. K., Gregson J., et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect. Dis. 2017, 18, 346-355; Zazzi, M., Hu, H., Prosperi,

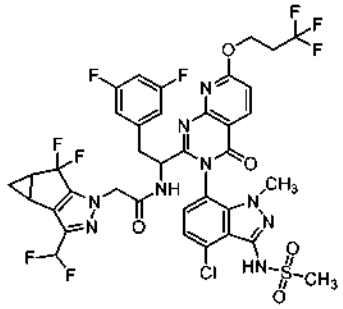
M. The global burden of HIV-1 drug resistance in the past 20 years. PeerJ. 2018, DOI 10.7717/peerj.4848). As a result, new drugs are needed that are easier to take, have high genetic barriers to the development of resistance, and have improved safety over current agents. In this panoply of choices, novel mechanisms of action (MOAs) that can be used as part of the preferred antiretroviral therapy (ART) can still have a major role to play since they should be effective against viruses resistant to current agents. The improvements that would make drugs easier to take for long periods of time or even for a lifetime could include all or some of the following: reduced side effects, reduced drug-drug interactions, increased duration between dosing, or alternate routes of administration which match to individual patient preferences. The goals of improved safety would definitely include high therapeutic indices towards any toxicities that would cause discontinuation of dosing, and could also include reduced side-effects or reduced drug-drug interactions. The potential to use fewer overall drugs in a combination regimen would also likely lead to improved compliance and safety. Increased potency against the antiviral target, especially if maintained in the presence of human plasma and serum albumin, would also lead to a reduced dose and could directly and positively affect the duration of dosing and the therapeutic index over side effects and toxicities. To summarize, maximum benefits to HIV infected patients would be achieved if anti-HIV drugs with new mechanisms of action were discovered which also have the other benefits described above which facilitate long term compliance and safety.

Certain potentially therapeutic compounds have now been described in the art and set forth in Blair, Wade S. et.al. Antimicrobial Agents and Chemotherapy (2009), 53(12), 5080-5087, Blair, Wade S. et al. PLoS Pathogens (2010), 6(12), e1001220, Thenin-Houssier, Suzie; Valente, Susana T. Current HIV Research, 2016, 14, 270-282, and PCT Patent applications with the following numbers: WO 2012065062, WO 2013006738, WO 2013006792, WO 2014110296, WO 2014110297, WO 2014110298, WO 2014134566, WO 2015130964, WO2015130966, WO 2016033243, WO2018035359, and WO2018203235.

What is now needed in the art are additional compounds which are novel and useful in the treatment of HIV. Additionally, these compounds should provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanisms of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, bioavailability and/or reduced frequency of dosing. Also needed are new formulations and methods of treatment which utilize these compounds.

SUMMARY OF THE INVENTION

Briefly, in one aspect, the present invention discloses the compounds depicted below



and pharmaceutically acceptable salts thereof (hereinafter "compounds and salts of the invention").

In another aspect, the present invention discloses a pharmaceutical composition comprising a compound or salt of the invention.

In another aspect, the present invention discloses a method of treating HIV infection in a human comprising administering a compound or salt of the invention.

In another aspect, the present invention discloses a compound or salt of the invention for use in therapy.

In another aspect, the present invention discloses a compound or salt of the invention for use in treating HIV infection in a human.

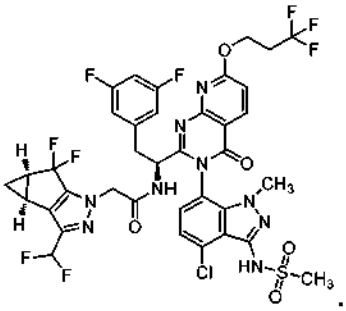
In another aspect, the present invention discloses the use of a compound or salt of the invention in the manufacture of a medicament for the treatment of HIV infection in a human.

BRIEF DESCRIPTION OF THE FIGURES

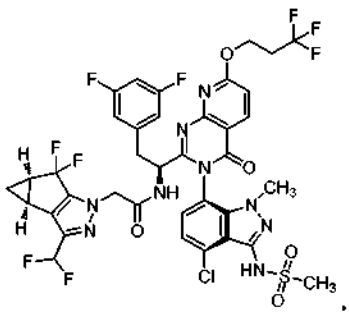
Figure 1 is a summary of the mean plasma concentration-time profiles in rats in the study described below.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the compounds and salts of the invention have the stereochemistry depicted below



In another aspect, the compounds and salts of the invention have the stereochemistry depicted below



The salts of the invention are pharmaceutically acceptable. Such salts may be acid addition salts or base addition salts. For a review of suitable pharmaceutically acceptable salts see, for example, Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977.

Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphorate, glycolate, hexylresorcinate, hippurate, hydrabamine (*N,N'*-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicyclate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolildine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium,

lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

In an embodiment, acid addition salts are selected from the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulfate, nitrate, phosphate, hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate. In an embodiment, base addition salts include metal salts (such as sodium, potassium, aluminium, calcium, magnesium and zinc) and ammonium salts (such as isopropylamine, diethylamine, diethanolamine salts). Other salts (such as trifluoroacetates and oxalates) may be used in the manufacture of the compounds and salts of the invention, and are included within the scope of the invention.

All possible stoichiometric and non-stoichiometric forms of the salts of the compound of the invention are included within the scope of the invention. Acid and base addition salts may be prepared by the skilled chemist, by treatment of a compound of the invention with the appropriate acid or base in a suitable solvent, followed by crystallization and filtration.

The pharmaceutical compositions of the invention further comprise a pharmaceutically acceptable carrier, excipient, and/or diluent. In one embodiment, the pharmaceutical compositions of this invention further comprise a pharmaceutically acceptable excipient.

In the method of this invention, preferred routes of administration are oral and by injection to deliver subcutaneously or intramuscularly. Therefore, preferred pharmaceutical compositions include compositions suitable for oral administration (for example tablets) and compositions suitable for injection, for example subcutaneous or intramuscular injection.

In another aspect the present invention discloses methods of preventing HIV infection in a human or reducing the risk of infection, comprising administering a compound or salt of the invention. Pre-exposure prophylaxis (or PrEP) is when people at risk for HIV infection take daily medicine to lower their chances of getting HIV infection. PrEP has been shown to be effective in reducing the risk of infection. As used herein, "HIV" or "Human Immunodeficiency Virus" refers to HIV-1 and/or to HIV-2.

The compounds and salts of the invention are believed to have as their biological target the HIV capsid and thus their mechanism of action is to modify in one or more ways the function of the HIV capsid. For example, the compounds and salts of the invention may act as capsid inhibitors.

The compounds and salts of the invention may be employed alone or in combination with other therapeutic agents. Combination therapies according to the present invention thus comprise the administration of at least one compound or salt of the invention, and the administration of at least one other agent which may be useful in the treatment of HIV infection. The compounds and salts of the invention and any other pharmaceutically active

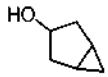
agent(s) may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. For example, a compound or salt of the invention, and the other agent may be formulated and administered together in a single pharmaceutical composition or may be formulated and administered separately.

The amounts of the compound and salts of the present invention and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of the compound of the present invention and salts, solvates, or other pharmaceutically acceptable derivatives thereof with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including multiple compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa, and the different agents could be administered on different schedules if appropriate. Such sequential administration may be close in time or remote in time. The amounts of the compound of the invention, or salts thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

As such, the compounds and salts of the present invention may be used in combination with one or more agents useful in the prevention or treatment of HIV. Such agents include, for example, nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors. Suitable other agents include, for example, abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, indinavir, islatravir, lamivudine, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, saquinavir, slatravir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, the antibody N6LS, GSK3739937/VH3739937, and S-648414. Additional suitable other agents include Dolutegravir, lamivudine, Fostemsavir, Cabotegravir, maraviroc, rilpiverine, Reyataz, Tenofovir, Afenamide, EfDA, Doravirine, and Preziata. Further suitable other agents include Dolutegravir, lamivudine, Fostemsavir, and Cabotegravir.Preferred agents include, for example, bictegravir, cabotegravir, dolutegravir, fostemsavir, islatravir, and lamivudine. Particularly preferred agents include, for example, bictegravir, cabotegravir, dolutegravir, fostemsavir, and lamivudine.

EXAMPLES

Preparation of bicyclo[3.1.0]hexan-3-ol

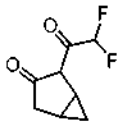


To a stirred solution of cyclopent-3-enol (130 g, 1545 mmol) in DCM (1200 mL) under N_2 atmosphere at 0-5 °C was added dropwise a solution of diethyl zinc in hexane (1.0 M, 3091 mL, 3091 mmol) over a period of 3 h. To the solution at 0 °C was added dropwise a solution of diiodomethane (249 mL, 3091 mmol) in DCM (300 mL) over a period of 1h. The reaction mixture was allowed to warm to 27 °C upon which formation of a white precipitation was observed. The mixture stirred for 16 h. Progress of the reaction was monitored by TLC (SiO_2, 20% EtOAc/pet, Rf = 0.3, UV-inactive, PMA-active). The reaction mixture was quenched via the careful addition of aq. saturated NH_4Cl solution (1.5 L). The mixture was filtered through pad of Celite. The aqueous layer was extracted with DCM (2 x 1L). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure to afford crude bicyclo[3.1.0]hexan-3-ol as red liquid, 180 g. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.41 - 4.35 (m, 1H), 2.18 - 2.05 (m, 2H), 1.73 (d, *J* = 13.9 Hz, 2H), 1.35 - 1.25 (m, 2H), 1.21 - 1.14 (m, 1H), 0.57 - 0.43 (m, 2H). GCMS: m/z = 98.1).

Preparation of bicyclo[3.1.0]hexan-3-one

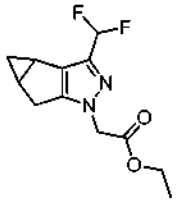
To a stirred solution of bicyclo[3.1.0]hexan-3-ol (210 g, 2054 mmol) in DCM (5000 mL) under N_2 atmosphere at 0 °C was added portion-wise Dess-Martin periodinane (954 g, 225 mmol). The mixture was allowed to warm to 27 °C and was then stirred for 16 h. Progress of the reaction was monitored by TLC (SiO_2, 20% Acetone/Hex, Rf = 0.3, UV in-active, PMA-active). The reaction mixture was filtered through pad of Celite and the filtrate was washed with aq. NaOH (1N, 8x 1 L). The combined aqueous phases were extracted with DCM (5 X 1 L). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure (bath temperature: 20 °C) to afford crude bicyclo[3.1.0]hexan-3-one as brown liquid. The liquid was further purified by downward distillation at 70 °C to afford bicyclo[3.1.0]hexan-3-one as a pale-yellow viscous liquid, 125 g (62%). ^1H NMR (400 MHz, $CDCl_3$) δ = 2.61 - 2.54 (m, 2H), 2.17 - 2.12 (m, 2H), 1.54 - 1.46 (m, 2H), 0.92 - 0.86 (m, 1H), -0.01 - -0.08 (m, 1H); GCMS: M/Z = 96.1.

Preparation of 2-(2,2-difluoroacetyl)bicyclo[3.1.0]hexan-3-one



To a stirred solution of bicyclo[3.1.0]hexan-3-one (125 g, 1274 mmol) in THF (1500 mL) under N_2 atmosphere at -78 °C was added LDA (2.0 M in THF, 0.701 L, 1402 mmol). The solution was stirred for 1 h at -78 °C. To the solution was added slowly over 30 minutes a solution of ethyldifluoroacetate (174 g, 1402 mmol) in THF (300 mL) maintaining a temperature of -78 °C. The reaction mixture was allowed to warm to 27 °C and was then stirred for 1 h. Progress of the reaction was monitored by TLC (SiO_2, 20% Acetone/Hexane, Rf = 0.3, UV -active). The reaction mixture was quenched via the addition of aq. HCl (1N, 2000 mL). The mixture was stirred for 30 min. and then was extracted with EtOAc (3 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 2-(2,2-difluoroacetyl)bicyclo[3.1.0]hexan-3-one as a pale-yellow viscous liquid, 180 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.18 (t, *J* = 54.8 Hz, 1H), 2.70 - 2.62 (m, 1H), 2.35 (d, *J* = 19.4 Hz, 1H), 2.14 (br s, 1H), 1.26 - 1.21 (m, 1H), 1.04-1.03 (m, 1H), 0.22-0.21 (m, 1H), LCMS: M/Z = 173.17).

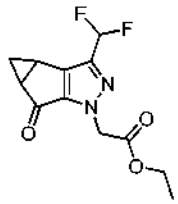
Preparation of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate.



To a stirred solution of 2-(2,2-difluoroacetyl)bicyclo[3.1.0]hexan-3-one (180 g, 910 mmol) in ethanol (2 L) under N_2 atmosphere at 27 °C was added ethyl 2-hydrazinylacetate hydrochloride (422 g, 2729 mmol) followed by sulfuric acid (20 mL, 375 mmol). The mixture was stirred for 30 min. and then was was heated to 100 °C and stirred for 16 h. Progress of the reaction was monitored by TLC (SiO_2, 20% Acetone/Hexane, Rf = 0.3, UV-active). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (2000 mL) and was washed with water (2 x 1 L), brine (1.0 L), dried over anhydrous Na_2SO_4, filtered, and then was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (pet.:acetone 100:0→98:2) to afford ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate as an off-white solid, 110 g (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.86 (t, *J* =

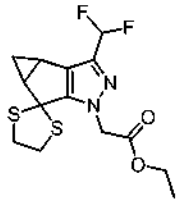
54.8 Hz, 1H), 4.93 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.88 - 2.79 (m, 1H), 2.76 - 2.68 (m, 1H), 2.14 - 2.04 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.10 - 1.03 (m, 1H), 0.14 (q, *J* = 4.3 Hz, 1H).

Preparation of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate.



To a stirred solution of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (110 g, 422 mmol) and Celite (395 g) in cyclohexane (3.5 L) at 0 °C was added portionwise pyridinium dichromate (794 g, 2110 mmol). To the mixture under nitrogen atmosphere was added dropwise tert-butyl hydroperoxide (355 mL, 2130 mmol) over a period of 10 min. The reaction mixture was warmed to 27 °C and was then stirred at that temperature for 48 h. Progress of the reaction was monitored by TLC (SiO_2, 30% Acetone/pet, Rf = 0.4, UV -active). The reaction mixture was filtered, and the filter cake was extracted with EtOAc (1000 mL). The filtrate was washed with saturated aq. $Na_2S_2O_3$ (2x500 mL); saturated aq. $FeSO_4$ (300 mL); and then brine (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude title compound (150 g).

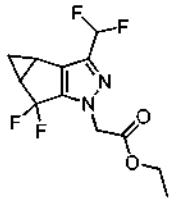
Preparation of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate.



To a stirred solution of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (75 g, 269 mmol) in DCM (1500 mL) at 27 °C under nitrogen atmosphere was added ethane-1,2-dithiol (43.0 mL, 511 mmol) followed by the addition of boron trifluoride acetic acid (72.6 mL, 511 mmol). The solution was stirred for 16 h. Progress of the reaction was monitored by TLC (SiO_2, 20% Acetone/Pet, Rf = 0.35, UV -Active). After completion, the reaction mixture was cooled to 0 °C and quenched via the addition of aq. saturated $NaHCO_3$ (500 mL). The mixture was extracted with DCM (2 X 1000 mL). The combined organics were washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain a brown liquid. This

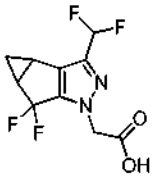
material was subjected to silica gel column chromatography (Pet.:EtOAc 95:5→90:10) to afford ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate as an off-white solid, 80 g (74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.61 (t, *J* = 55.2 Hz, 1H), 5.00 - 4.85 (m, 2H), 4.29 - 4.19 (m, 2H), 3.55 - 3.46 (m, 4H), 2.63 - 2.53 (m, 1H), 2.49 - 2.38 (m, 1H), 1.30 - 1.24 (m, 4H), 0.65 - 0.60 (m, 1H). LCMS M+H = 346.9.

Preparation of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate



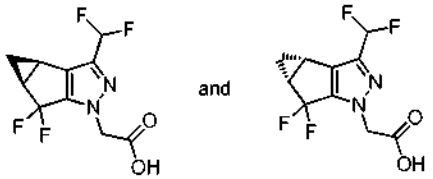
To a stirred solution of 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (26.3 g, 92 mmol) in DCM (20 mL) at -70 °C under N_2 atmosphere was added HF-pyridine (2.460 g, 24.83 mmol). The solution was for 30 min. To the solution was added a solution of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-1,3]dithiolane]-1(3bH)-yl)acetate (10 g, 25 mmol) in DCM (20 mL). The reaction mixture was allowed to warm to -40 °C and then was stirred at that temperature for 1 h. Progress of the reaction was monitored by TLC (SiO2, 30% EtOAc/Pet, Rf = 0.3, UV in-active). The reaction mixture was quenched via the addition of aq. sat. $NaHCO_3$ (200 mL). The mixture was warmed to room temperature and was then extracted with EtOAc (2 x 100 mL). The combined organics were washed with brine (50 mL); dried over anhydrous Na_2SO_4; filtered; and were concentrated under reduced pressure to afford a brown solid. This material was subjected to silica gel column chromatography (Pet.:EtOAc 100:0→75-25) to afford ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate as a pale yellow solid, 8.5 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.62 (t, J = 55.2 Hz, 1H), 4.82 (s, 2H), 4.30 - 4.18 (m, 2H), 2.51 - 2.37 (m, 2H), 1.42 - 1.35 (m, 1H), 1.31 - 1.23 (m, 3H), 1.14 - 1.08 (m, 1H). LCMS M+H = 293.07.

Preparation of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid



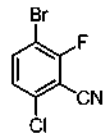
To a stirred solution of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (15 g, 50 mmol) in THF (17 mL) and MeOH (66 mL) at 0 °C under N_2 atmosphere was added a solution of LiOH (1.788 g, 74.7 mmol) in water (66 mL). The reaction mixture was allowed to warm to 27 °C and was then stirred for 3 h at that temperature. Progress of the reaction was monitored by TLC (SiO_2, 5% MeOH/DCM, Rf = 0.2, UV Active). After completion, the reaction mixture was concentrated under reduced pressure; diluted with water (50 mL); and washed with EtOAc (2 x 250 mL) to remove impurities. The aqueous layer was adjusted to pH 2-3 using aq. HCl (1M), then was extracted with EtOAc (3 x 1000 mL). The combined organics were dried over anhydrous Na_2SO_4; filtered; and concentrated under reduced pressure to afford 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid as an off white solid, 14 g (98%). LCMS M+H = 265.15.

Separation affording 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid and 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid



2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (5.5 g) was dissolved in isopropanol (20 mL). The solution was subjected portion-wise to SFC chiral separation as follows: Instrument = Thar 80; column = Chiralpak IC 30x250mm, 5 micron; solvent A = super critical CO_2; solvent B = isopropanol with 0.5% isopropylamine (v/v); eluent composition = 70%A:30%B; flow-rate = 65 g/min; back-pressure = 100 bar; temperature = 30 °C; injection volume = 2.5 mL; detection = 220 nm. 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid was collected as peak eluting from 7.5 min. to 14 min; 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid was collected as a peak eluting from 2.7 min. to 5.8 min. For each enantiomer, the resulting solution was concentrated under reduced pressure and the resulting solids were dissolved in EtOAc, then twice washed with aq. citric acid (1M) followed by water followed by brine. The organic solution was dried over Na_2SO_4; filtered; then concentrated in vacuo to afford the separated enantiomer in 80-90% recovery.

Preparation of 3-bromo-6-chloro-2-fluorobenzonitrile

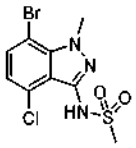


To a stirred solution of 3-bromo-6-chloro-2-fluorobenzaldehyde (210.0 g, 0.89 mol, 1.0 equiv.) in water (2.1 L) at room temperature was added hydroxylamine-O-sulfonic acid (175.15 g, 1.55 mol, 1.75 equiv.). The reaction mixture was heated to 50 °C and stirred for 18 h). The mixture was cooled to room temperature and stirred for 1–1.5 h. The solids were isolated via filtration and were then washed with water. The wet solid was dried under vacuum at 50 °C for 12–15 h to afford 3-bromo-6-chloro-2-fluorobenzaldehyde, 190.0 g (91%).

Preparation of 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine

To a solution of 3-bromo-6-chloro-2-fluorobenzonitrile (360.0 g, 1.55 mol, 1.0 equiv.) in ethanol (1.08 L) was added methylhydrazine sulphate (1.11 kg, 7.73 mol, 5.0 equiv.) followed by the addition of triethylamine (1.3 L, 9.3 mol, 6.0 equiv.) at 25-35 °C. The reaction mixture was heated to 110 °C and maintained for 15 h (the reaction was monitored by TLC). After completion of the reaction the mixture was cooled to room temperature. Water (3.0 L) was added and the mixture was stirred for 1 h at room temperature. The solids were isolated via filtration and were washed with water. The wet solid was dried under vacuum at 50 °C for 12–15 hours. The crude solid was purified by column chromatography (10% EA/hexanes to 40% EA/Hexanes) to afford the product as a pale yellow solid. Yield: 185.0 g (46.0 %).

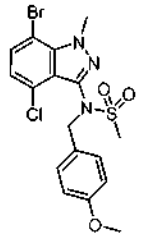
Preparation of N-(7-bromo-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide



To a solution of 7-bromo-4-chloro-1-methyl-1H-indazol-3-amine (1.40 g, 5.37 mmol) in DCM (30 mL) was added Hunig's Base (3.75 mL, 21.5 mmol) and then the reaction was cooled in an ice bath and methanesulfonyl chloride (1.26 mL, 16.1 mmol) was added. The reaction mixture was stirred at this temperature for 1h (precipitate formed). Mixture was then diluted with dichloromethane (100 mL) and washed with water, 1 M HCl and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was taken up in EtOH (30 ml) and 10 ml of 20% aq. NaOH. The resulted mixture heated with a heat gun until it became a homogenious

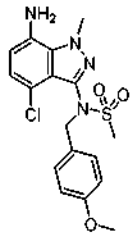
solution and stirred at rt for 30 min. The mixture was diluted with water (80 mL) and acidified with 1 N HCl (60 mL). The precipitate was filtered, washed with water, and dried in vacuo to afford the title product (1.5 g) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J=7.9 Hz, 1H), 7.24 (br s, 1H), 6.95 (d, J=7.9 Hz, 1H), 4.38 (s, 3H), 3.42 (s, 3H). LC/MS $(M+H)^+$ = 337.80.

Preparation of N-(7-bromo-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methanesulfonamide



To a mixture of N-(7-bromo-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (1.3 g, 3.84 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.625 mL, 4.61 mmol) in DMF (30 mL) was added cesium carbonate (1.626 g, 4.99 mmol) and the mixture was heated at 80 °C for 2 h. The mixture was poured into water (100 mL) and extracted with EtOAc (50 ml, 2x). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by Bioateg (0~35% EtOAc-hexanes) to afford the title product (1.5 g) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J=7.9 Hz, 1H), 7.31 (d, J=8.5 Hz, 2H), 6.99 (d, J=7.9 Hz, 1H), 6.84 (d, J=8.5 Hz, 2H), 4.99 (br s, 1H), 4.76 (br s, 1H), 4.40 (s, 3H), 3.80 (s, 3H), 3.01 (s, 3H).

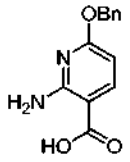
Preparation of N-(7-amino-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methanesulfonamide



Following the reference: Andersen, Jacob *et al, Synlett* **2005** (14), 2209-2213. To a mixture of N-(7-bromo-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methane sulfonamide (600.0 mg, 1.308 mmol), copper(I) iodide (49.8 mg, 0.262 mmol), sodium ascorbate (518 mg, 2.62 mmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (46.5 mg, 0.327 mmol) in NMP (10 mL) was added a solution of sodium azide (255 mg, 3.92 mmol) in Water (2.0 mL). The mixture was then sealed and heated in a microwave system at 120 °C

for 2.5 h. The mixture was then filtered through a pad of Celite and the pad was washed with EtOAc. The filtrate was poured into water (100 mL) and extracted with EtOAc (50 ml, 2x). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by Bioatge (5-100% EtOAc/hexanes) to afford the title product (400 mg) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.29 (m, 2H), 6.89 (d, J=7.8 Hz, 1H), 6.85 - 6.79 (m, 2H), 6.48 (d, J=7.8 Hz, 1H), 5.11 (br.s, 1H), 4.81 (br.s, 1H), 4.30 (s, 3H), 3.80 (br s, 2H), 3.79 (s, 3H), 2.99 (s, 3H). LC/MS $(M+H)^+$ = 395.00.

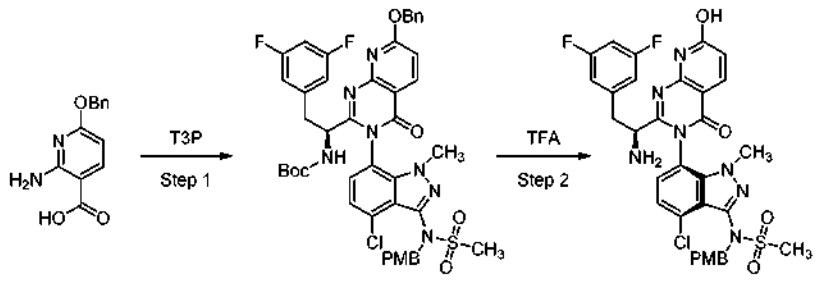
Preparation of 2-amino-6-(benzyloxy)nicotinic acid



A solution of 2-amino-6-chloronicotinic acid (5 g, 29 mmol) and potassium tert-butoxide (9.75 g, 87 mmol) in benzyl alcohol (97 mL) was heated to 120 °C for 3 h. After cooling to ambient temperature, the very dark reaction mixture was added to water and washed with ether (x3). The aqueous layer was then acidified with 0.5 M citric acid. The tan precipitate filtered to provide the product (4.4 g, 62%) which was used in the next reaction without further purification. ^1H NMR (500 MHz, DMSO-d6) δ 12.40 (br s, 1H), 7.94 (d, J=8.55 Hz, 1H), 7.06-7.52 (m, 5H), 6.04 (d, J=8.24 Hz, 1H), 5.33 (s, 2H). LC/MS: m/z = 245.15 $[M+1]^+$.

Preparation of N-[(6P)-7-{2-[(1S)-1-amino-2-(3,5-difluorophenyl)ethyl]-7-hydroxy-4-oxo-3H,4H-pyrido[2,3-d]pyrimidin-3-yl}-4-chloro-1-methyl-1H-indazol-3-yl]-N-[(4-methoxyphenyl)methyl]methanesulfonamide

Scheme:



Step 1:

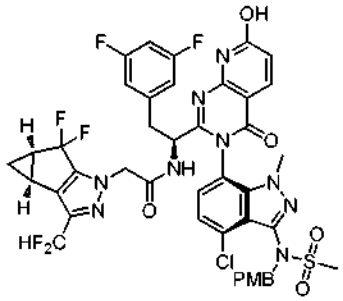
To a suspension of (S)-2-((tert-butoxycarbonyl)amino)-3-(3,5-difluorophenyl)propanoic acid (5.49 g, 18.23 mmol) and 2-amino-6-(benzyloxy)nicotinic acid (4.45 g, 18.23 mmol) in acetonitrile (92 mL) (yellow solution) at -25 °C was added pyridine (9.83 mL, 122 mmol) followed by 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide ("T3P", 45.2 ml, 76 mmol). The reaction mixture (became a clear solution after T_3P addition) was stirred at -25 °C to 10 °C over 4.5 h, then N-(7-amino-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methanesulfonamide (6 g, 15.19 mmol) was added and the mixture was stirred for 18 h while warming to rt. The reaction mixture was diluted with ethyl acetate, washed with 1N NaOH, then water, then 0.5 M citric acid, then water, then dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified on silica (330 g RediSep Gold column) using 0-60 % ethyl acetate in hexanes over 15 CV, then holding at 60% EtOAc for 10 CV. The desired fractions were pooled and concentrated to afford a pale yellow solid (8.1 g, 9.14 mmol, 60.1 % yield), a mixture of tert-butyl N-[(1S)-1-[(3P,3P)-7-(benzyloxy)-3-(4-chloro-3-{N-[(4-methoxyphenyl)methyl]methanesulfonamido}-1-methyl-1H-indazol-7-yl)-4-oxo-3H,4H-pyrido[2,3-d]pyrimidin-2-yl]-2-(3,5-difluorophenyl)ethyl]carbamate (major) and tert-butyl N-[(1S)-1-[(3M,3M)-7-(benzyloxy)-3-(4-chloro-3-{N-[(4-methoxyphenyl)methyl]methanesulfonamido}-1-methyl-1H-indazol-7-yl)-4-oxo-3H,4H-pyrido[2,3-d]pyrimidin-2-yl]-2-(3,5-difluorophenyl)ethyl]carbamate (minor). LC/MS: m/z = 886.25 $[M+1]^+$.

Step 2:

TFA (21.1 mL, 274 mmol) was added to a solution of tert-butyl (S)-(1-(7-(benzyloxy)-3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (Product from Step 1, 8.1 g, 9.14 mmol) in dichloromethane (45.7 mL). The mixture was stirred at rt for 2 h. The resultant pale-yellow solution was concentrated. The residue was taken up in ethyl acetate, then washed three times with 1 N NaOH, then dried over Na2SO4 and then concentrated in vacuo to afford an oily residue. The residue was purified on silica gel (330 g RediSep Gold column) by a gradient method of Solvent A:Solvent B 65:35→0:100 (2 CV), then 0:100 (9 CV); Solvent A = hexanes; Solvent B = 9:9:2 hexanes:ethyl acetate:MeOH. The first eluting isomer (major) was collected and concentrated in vacuo to afford N-[(6P)-7-{2-[(1S)-1-amino-2-(3,5-difluorophenyl)ethyl]-7-hydroxy-4-oxo-3H,4H-pyrido[2,3-d]pyrimidin-3-yl}-4-chloro-1-methyl-1H-indazol-3-yl]-N-[(4-methoxyphenyl)methyl]methanesulfonamide (4.1 g, 5.89 mmol, 64.5 % yield). ^1H NMR (500 MHz, DMSO-d6) δ 7.86 - 7.98 (m, 1 H) 7.15 - 7.37 (m, 4 H) 6.97 - 7.06 (m, 1 H) 6.70 - 6.89 (m, 4 H) 6.40 - 6.48 (m, 1 H) 4.70 - 4.88 (m, 2 H) 3.41 - 3.81 (m,

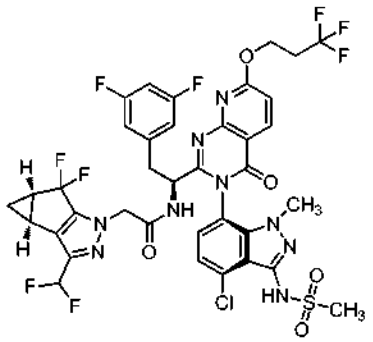
7 H) 3.20 - 3.28 (m, 1 H) 3.08 - 3.12 (m, 3 H) 2.71 - 2.79 (m, 1 H) 1.69 - 2.00 (m, 2 H). LC/MS: m/z = 696.20 $[M+1]^+$.

Preparation of N-((S)-1-((3P)-3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-7-hydroxy-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide



To a stirred solution of N-[(6P)-7-{2-[(1S)-1-amino-2-(3,5-difluorophenyl)ethyl]-7-hydroxy-4-oxo-3H,4H-pyrido[2,3-d]pyrimidin-3-yl}-4-chloro-1-methyl-1H-indazol-3-yl]-N-[(4-methoxyphenyl)methyl]methanesulfonamide (0.926 g, 1.330 mmol) in DMF (13 ml) was added 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (0.351 g, 1.330 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) ("HATU", 0.531 g, 1.397 mmol), and DIPEA (0.581 ml, 3.33 mmol). The reaction mixture was stirred for 2 h after which the reaction mixture was diluted with water and extracted with ethyl acetate. The combined EtOAc extractions were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via silica gel flash chromatography using 10-100% ethyl acetate in hexanes to provide N-((S)-1-((3P)-3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-7-hydroxy-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (1.1 g, 88%) as an off-white foamy solid. LC/MS: m/z = 942.25 $[M+1]^+$.

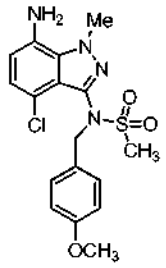
Preparation of Example 1: N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide



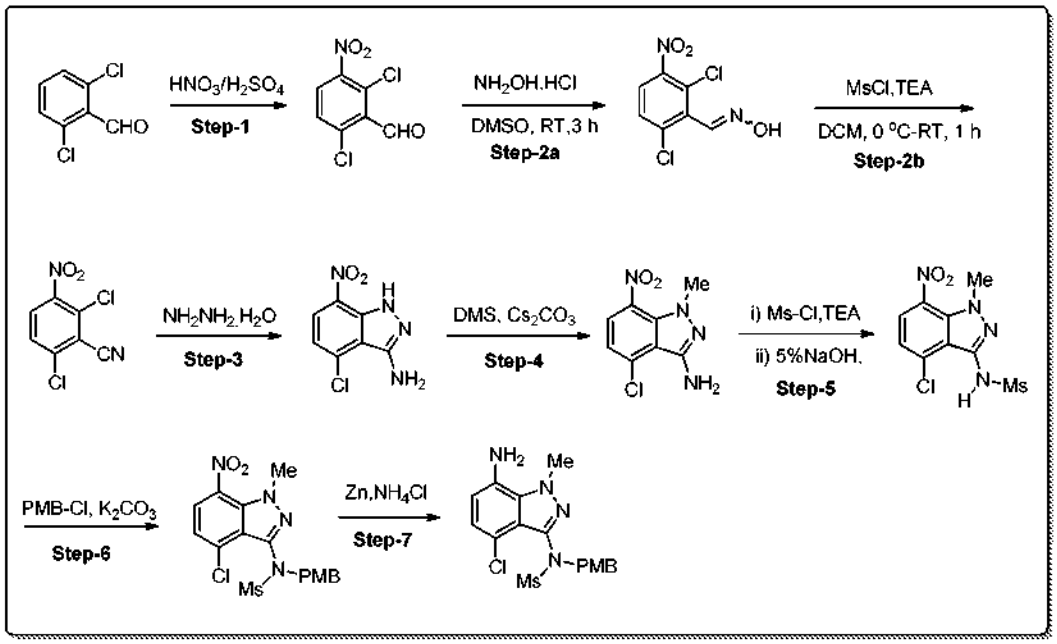
A solution of diisopropyl (E)-diazene-1,2-dicarboxylate ("DIAD", 0.125 ml, 0.637 mmol) in THF (0.2 mL) was added dropwise to a mixture of N-(1-((3P)-3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-7-hydroxy-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (0.2 g, 0.212 mmol)), 3,3,3-trifluoropropan-1-ol (0.073 g, 0.637 mmol) and triphenylphosphine (0.178 g, 0.679 mmol) in Tetrahydrofuran (2.1 mL) at rt. The reaction mixture was stirred for 18 h at rt and then was concentrated *in vacuo*. The residue was purified on silica gel (24 g RediSep Gold column) using a gradient of 0-60 % ethyl acetate in hexanes over 15 CV, and then holding at 60 % ethyl acetate in hexanes for 5 CV. Fractions containing the pure product were pooled and then concentrated to give a yellow solid. This solid was taken up in DCM (1 mL):TFA (0.5 mL); the solution was cooled to 0 °C; and to the solution was added triflic acid (0.057 mL, 0.637 mmol). The mixture was stirred for 1 h and then concentrated *in vacuo*. The residue was taken up in ethyl acetate; washed with 1 N NaOH; washed with 0.5M citric acid; dried over Na_2SO_4; filtered; and then was concentrated *in vacuo*. The residue was subjected to silica gel chromatography (24 g RediSep Gold column) using 0-60 % ethyl acetate in hexanes over 20 CV, then at 60 % ethyl acetate for 10 CV. Fractions containing the pure product were pooled and then concentrated *in vacuo* to give N-(1-((6P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (0.078 g, 0.081 mmol, 38.0 % yield) as a brown solid. ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.46 - 8.53 (m, 1 H) 7.28 - 7.34 (m, 1 H) 7.19 - 7.24 (m, 1 H) 7.03 - 7.09 (m, 1 H) 6.53 - 6.81 (m, 4 H) 4.80 (dd, J=5.96, 2.98 Hz, 3 H) 4.49 - 4.62 (m, 2 H) 3.58 - 3.62 (m, 3 H) 3.40 - 3.49 (m, 1 H) 3.22 - 3.24 (m, 3 H) 3.06 - 3.14 (m, 1 H) 2.80 - 2.89 (m, 2 H) 2.37 - 2.44 (m, 2 H) 1.32 - 1.37 (m, 1 H) 0.96 - 1.01 (m, 1 H). LCMS Analysis Method: Column = Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 µm particles; Injection Volume = 5.00 µL; Flowrate = 0.80 mL/min; Solvent A = 95:5 Water:MeCN w/ 0.1% v/v formic acid; Solvent B = 5:95 Water:MeCN w/ 0.1% v/v formic acid;

Elution profile = Start %B: 0, End %B: 100, Gradient Time: 3.5 min. then hold at 100% B for 1 min.; Detection wavelength 1 = 220 nm, wavelength 2 = 254 nm. LCMS retention time = 3.097 min; m/z = 918.05 $[M+1]^+$.

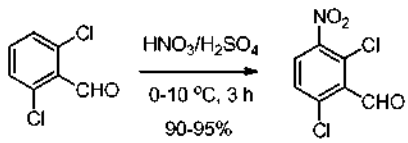
Alternate preparation of N-(7-amino-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methanesulfonamide



Synthesis Scheme:



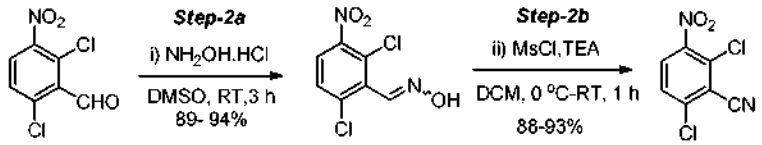
Step 1: Preparation of 2,6-dichloro-3-nitrobenzaldehyde



To a solution of sulfuric acid (H_2SO_4) (5.63 L, 4.5 V) in a round-bottom flask at 0-5 °C was added 2,6-dichlorobenzaldehyde (1.25 kg, 7.10 mol, 1.0 equiv.) in portions at below 15 °C. The reaction mass was stirred at 0-5 °C for 30 min. A solution of freshly prepared nitration

mixture [Prepared from Conc. H_2SO_4 (0.425 L, 0.34 V) and 70% HNO_3 (0.85 kg, 13.49 mol, 1.30 equiv.) at 0 °C] was added to the above reaction mixture at below 10 °C [**Note**: Reaction is slightly exothermic (3-6 °C); so that addition is preferred at lower temperature]. The reaction mixture was stirred at 5-10 °C for 2-3 h. After completion of the reaction (monitored by TLC), it was quenched with ice cold water (18.75 L, 15 V) at below 25 °C. Then the reaction mass was allowed warm to room temperature and stirred for 2 h. The solids were isolated by filtration and then were washed with water (2.5 L, 2.0 V). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The crude wet solid was initially dried under air atmosphere; then in a hot air oven at 50-55 °C for 10-12 h (until moisture content is not more than 5.0 %) to get the dried title product, 2,6-dichloro-3-nitrobenzaldehyde (1.44 kg, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ10. 44 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H).

Step 2: Preparation of 2,6-dichloro-3-nitrobenzonitrile

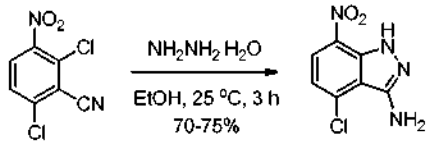


(Step-2a) To a solution of DMSO (5.9 L, 5.0 V)) in a round-bottom flask was added 2,6-dichloro-3-nitrobenzaldehyde (1.17 kg, 5.31 mol, 1.0 equiv.) at room temperature. After being stirred for 30 min at room temperature, hydroxylamine hydrochloride (0.63 kg, 9.04 mol, 1.70 equiv.) was added and the reaction mass was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mass was quenched by the addition of ice-cold water (18.0 L, 15.0 V) added at a rate sufficient to maintain the temperature below 30 °C (Observation: Solids formed upon water addition). The reaction mass was stirred at room temperature for 60-90 min. The solids were isolated by filtration; washed with water (2.5 L, 2.0 V); followed by washing with a mixture of acetone and hexanes (6.0 L, 1:1 ratio). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The wet solid was initially air dried and then finally dried in a hot air oven at 50-55 °C for 10-12 h (until moisture content was not more than 1.0 %) to get the dried target product, 2,6-dichloro-3-nitrobenzaldehyde oxime (1.22 kg, 92% yield) as an off-white solid. The crude product (which contains 10-20% of 2,6-dichloro-3-nitrobenzonitrile) was used directly in the next step without further purification.

(Step-2b) To a stirred solution of the crude oxime (preparation described above, 1.13 kg, 4.80 mol, 1.0 equiv.) in DCM (9.04 L, 8.0 V) at 0-5 °C was added triethylamine ("TEA", 1.02 kg, 10.09 mol, 2.1 equiv.). After being stirred for 5 min, methanesulfonyl chloride (0.60 kg, 5.29 mol, 1.1 equiv.) was added (Observation: An exotherm is noted during the addition)

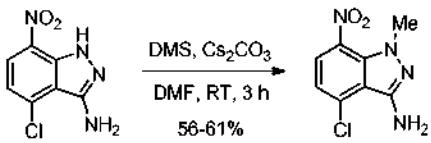
slowly at 15 °C. Then the reaction mass was stirred at room temperature for 30-45 min. After completion of the reaction (progress of reaction was monitored by TLC; mobile phase: 20% ethyl acetate in hexanes), the reaction mass was diluted with water (6.78 L, 6.0 V); the organic layer was separated; and the aqueous layer was extracted with DCM (3.4 L, 3.0 V). The combined organic layers were washed with brine (5.65 L, 5.0 V); dried over Na_2SO_4; and concentrated under vacuum. The resulting crude solids were triturated with hexanes (4.50 L, 4.0 V) at room temperature. The wet material was dried in a hot air oven at 50-55 °C for 5- 6 h to get the dried product, 2,6-dichloro-3-nitrobenzonitrile (0.95 kg, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H).

Step 3: Preparation of 4-chloro-7-nitro-1*H*-indazol-3-amine



To a stirred solution of 2,6-dichloro-3-nitrobenzonitrile (750.0 g, 3.45 mol, 1.0 equiv.) in ethanol (7.5 L, 10.0 V) at 15-20 °C. was slowly added hydrazine hydrate (519.0 g, 10.36 mol, 3.0 equiv.) while maintaining the reaction mass below 25 °C (Observation: Addition is slightly exothermic and solid formation will begin upon addition). The reaction mixture temperature was slowly raised to room temperature and then the mixture was stirred for 3 h (Observation: the quantity of solids will increase during this time). After completion of the reaction (monitored by TLC), the mixture was diluted with water (7.5 L, 10.0 V) and further stirred for 1 h at room temperature. The solids were isolated via filtration and then were washed with water (2.25 L, 3.0 V). The wet solid was washed with a 1:1 ratio mixture of acetone (1.875 L, 2.5 V) and hexanes (1.875 L, 2.5 V). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The wet solid was finally dried in a hot air oven for 7-8 h at 50 °C (until moisture content reaches below 1.5%) to get the dried product, 4-chloro-7-nitro-1*H*-indazol-3-amine (549.0 g, 75% yield) as a brick red-colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (bs, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.40 Hz, 1H), 4.73 (bs, 2H).

Step 4: Preparation of 4-chloro-1-methyl-7-nitro-1*H*-indazol-3-amine



To a stirred solution of 4-chloro-7-nitro-1*H*-indazol-3-amine (500 g, 0.42 mol, 1.0 equiv.) in DMF (5.0 L, 10.0 V) at 5-10 °C was slowly added cesium carbonate (Cs_2CO_3) (1.91

kg, 5.88 mol, 2.5 equiv.) while maintaining the reaction mass below 10 °C. After being stirred for 5-10 min, dimethyl sulphate (326.3 g, 2.59 mol, 1.1 equiv.) was added while maintaining the reaction mass below 10 °C (Note: Slow addition is preferred for obtaining more favorable regio-selectivity). Then, the reaction temperature was slowly raised to room temperature and stirring was continued an additional 2 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mass was quenched by the addition of ice-cold water (15.0 L, 30.0 V) and the resulting mixture was then stirred for 6-8 h at room temperature. The solids were isolated via filtration and were then washed with water (1.5 L, 3.0 V). The wet solid was washed with IPA (1.5 L, 3.0 V) followed by hexanes (1.0 L, 2.0 V). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The wet solid was dried in a hot air oven for 7-8 h at 50 °C (until moisture content is below 1.0%). The isolated material, 4-chloro-1-methyl-7-nitro-1*H*-indazol-3-amine (319.0 g, 60% yield), was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.32 Hz, 1H), 6.97 (d, J = 8.24 Hz, 1H), 4.63 (bs, 2H), 3.96 (s, 3H).

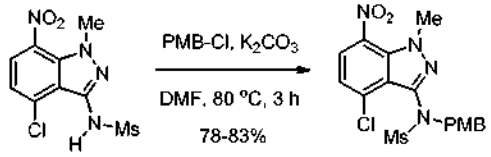
Step 5: Preparation of *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)methanesulfonamide

(Step 5a) To a solution of 4-chloro-1-methyl-7-nitro-1*H*-indazol-3-amine (625.0 g, 2.76 mol, 1.0 equiv.) in DCM (6.25 L, 10.0 V) at 0-5 °C. was added triethylamine (TEA) (837.0 g, 8.27 mol, 3.0 equiv.); followed by the addition of 4-dimethylaminopyridine (DMAP) (20.60 g, 0.165 mol, 0.06 equiv.). The reaction mass was stirred for 5-10 min., then methanesulfonyl chloride (MsCl) (790.0 g, 6.89 mol, 2.5 equiv.) added slowly while maintaining the reaction mass below 10 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 1.5-2.0 h. After completion of the reaction (monitored by TLC), the mixture was diluted with water (6.25 L, 10.0 V) and then stirred at room temperature for 15 min. The organic layer was separated, and the aqueous layer was extracted with DCM (6.25 L, 10.0 V). The combined organic layers were washed with brine (1.25 L, 2.0 V), dried over Na_2SO_4 and concentrated to get the crude solids. The solids were triturated with hexanes (1.25 L, 2.0 V) at room temperature to obtain the intermediate, N-(4-chloro-1-methyl-7-nitro-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide, which was used directly in the next step.

(ii) To a stirred solution of N-(4-chloro-1-methyl-7-nitro-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (prepared above) in ethanol (10.5 L, 20.0 V) at room temperature was added slowly an aq. 5% NaOH solution (4.38 L, 7.0 V) [Note: Slow addition is preferred via dropping funnel]. The reaction mass was stirred at the same temperature for 3

h. After completion of the reaction (monitored by TLC) [Sample preparation for TLC analysis: ~1.0 ml of sample acidified with aq. 2.0 N HCl to reach the pH: 2-3, extract it with ethyl acetate and analyze the organic layer by TLC], the reaction mass was cooled to 0-5 °C and the pH was adjusted to 2-3 by the addition of aq. 2.0 N HCl (3.13 L, 5.0 V) while maintain the reaction temperature below 10 °C [Note: Precipitation occurred upon addition of HCl and increased with stirring]. The reaction mixture was warmed to room temperature and then stirred for 1.5-2.0 h. Solids obtained were isolated via filtration and were then washed with water (1.25 L, 2.0 V); followed by washing with hexanes (1.25 L, 2.0 V). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The wet material was dried in a hot air oven at 50 °C for 6-7 h (Until the moisture content is below 1.0%) to get the dried product, *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)methanesulfonamide (640.0 g, 76%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.32 Hz, 1H), 7.32 (bs, 1H), 7.17 (d, J = 8.28 Hz, 1H), 4.15 (s, 3H), 3.45 (s, 3H).

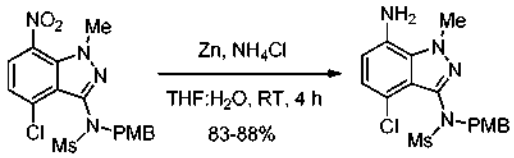
Step 6: Preparation of *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)-*N*-(4-methoxybenzyl)methanesulfonamide



To a mixture of *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)methanesulfonamide (635.0 g, 2.08 mol, 1.0 equiv.) and 1-(chloromethyl)-4-methoxybenzene (359.0 g, 2.30 mol, 1.1 equiv.) in DMF (6.35 L, 10.0 V) at room temperature was added potassium carbonate (374.7 g, 2.70 mol, 1.3 equiv.). The reaction mixture was heated to 80-90 °C and maintained at that temperature for 3 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice cold water (19.05 L, 30.0 V) [Note: Slow quenching with vigorous stirring is preferred to avoid clumping as the product precipitates]. The resulting solids were isolated via filtration and washed with water (1.90 L, 3.0 V); then the solids were washed with hexanes (1.27 L, 2.0 V). Bulk residual water was removed from the solids by maintaining vacuum filtration for 60-90 min. The isolated solid was dissolved in Ethyl acetate (12.7 L, 20.0 V) and charcoal was added (63.5 g). The mixture was heated to 60-70 °C and then stirred for 30-45 min. at that temperature. The mixture was filtered while still hot (40-50 °C) through a pad of Celite and the Celite pad was then extracted with ethyl acetate (3.17 L, 5.0 V). The combined filtrates were concentrated to dryness under reduced pressure at below 50 °C. Ethyl acetate (0.635 L, 1.0 V) was added to the solids at room temperature. The resultant solid suspension was stirred for 30 min. The solids were isolated via filtration and then were washed with hexanes (1.27 L, 2.0 V). Residual water was removed from the solids by

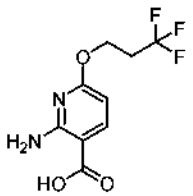
maintaining vacuum filtration for 45-60 min. to afford the product *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)-*N*-(4-methoxybenzyl) methane sulfonamide (705.0 g, 80% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.24 Hz, 1H), 7.27 (d, J = 8.68 Hz, 2H), 7.19 (d, J = 8.24 Hz, 1H), 6.80 (d, J = 8.44 Hz, 2H), 4.95-4.76 (m, 2H), 4.17 (s, 3H), 3.76 (s, 3H), 3.01 (s, 3H).

Step 7: Preparation of *N*-(7-Amino-4-chloro-1-methyl-1*H*-indazol-3-yl)-*N*-(4-methoxybenzyl)methanesulfonamide

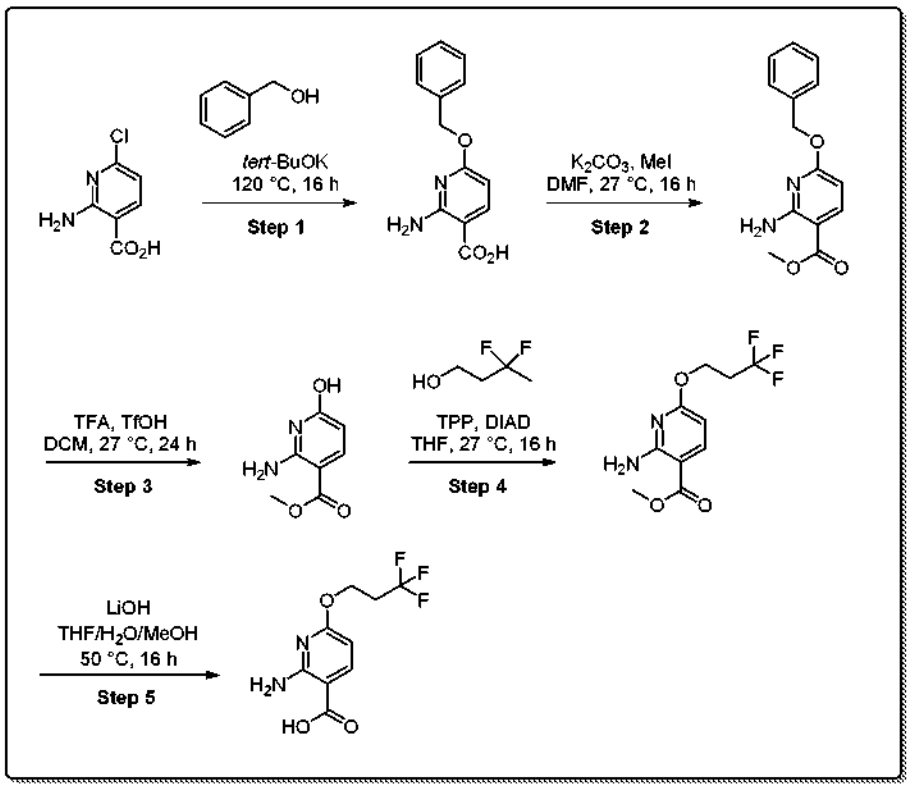


To a stirred suspension of zinc powder (540.0 g, 8.23 mol, 10.0 equiv.) in a mixture of THF (3.50 L, 10.0 V) and water (7.0 L, 20.0 V) at room temperature was added ammonium chloride (NH_4Cl) (449.0 g, 8.23 mol, 10.0 equiv.). To the mixture was added *N*-(4-chloro-1-methyl-7-nitro-1*H*-indazol-3-yl)-*N*-(4-methoxybenzyl)methanesulfonamide (350 g, 0.823 mol, 1.0 equiv.) in THF (7.0 L, 20.0 V). The reaction mixture was stirred at room temperature for 3-4 h. After completion of the reaction (monitored by in-process TLC/HPLC), the mixture was diluted with ethyl acetate (3.5 L, 10.0 V) and water (1.12 L, 2.5 V). The mixture was stirred for 15 min. The reaction mass was filtered through a pad of Celite bed washing with ethyl acetate (1.75 L, 5.0 V). The bi-phasic filtrate was collected, and the phases were separated. The aqueous layer was extracted with ethyl acetate (3.50 L, 10.0 V). The combined organic layers were washed with brine (3.50 L, 10 V), dried over Na_2SO_4, and then concentrated in *vacuo* to afford a crude solid. To the crude product was added MTBE (3.25 L, 10 V) and the suspension was stirred for 30 min at room temperature. The solids were isolated by filtration. Bulk residual water was removed from the solids by maintaining vacuum filtration for 30-45 min. The wet product was dried in a hot air oven (50 °C) for 2 h to afford the title product, *N*-(7-amino-4-chloro-1-methyl-1*H*-indazol-3-yl)-*N*-(4-methoxybenzyl)methanesulfonamide (276.0 g, 85% yield) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 6.86-6.79 (m, 2H), 6.42 (d, J = 7.80 Hz, 1H), 4.99-4.70 (m, 2H), 4.25 (s, 3H), 3.77 (s, 5H), 2.98 (s, 3H).

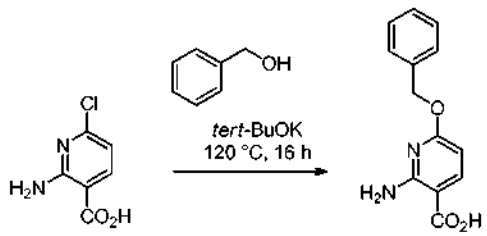
Preparation of 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid



Synthesis Scheme:

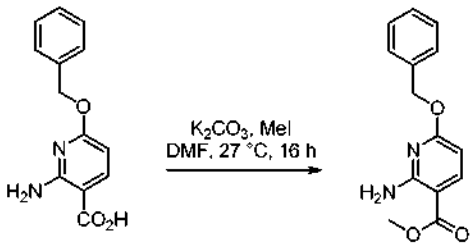


Step 1: Preparation of 2-amino-6-(benzyloxy) nicotinic acid



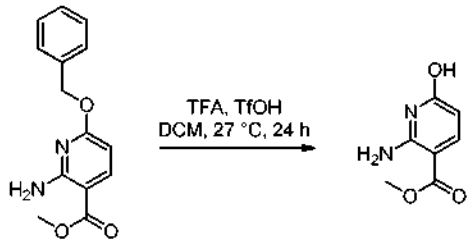
To a stirred solution of 2-amino-6-chloronicotinic acid (200 g, 1159 mmol) in benzyl alcohol (1400 mL, 13464 mmol) at 26 °C under N_2 atmosphere was added potassium tert-butoxide (390 g, 3477 mmol). The reaction mixture was heated to 120 °C and stirred for 16 hr at that temperature. The progress of reaction was monitored by TLC (SiO_2, 10% MeOH in DCM, Rf = 0.5). On completion, the reaction mixture was diluted with water (3 L) and extracted with diethyl ether (2 x 1000 mL). The organic layer was separated and the aqueous layer was acidified to pH 4 using aq. citric acid solution (0.5 M). The precipitated solid was collected by filtration and then dried under reduced pressure to afford 2-amino-6-(benzyloxy) nicotinic acid as an off-white solid (220 g, yield = 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.56 - 12.32 (m, 1H), 7.97 - 7.91 (m, 1H), 7.52 - 7.41 (m, 2H), 7.38 - 7.11 (m, 5H), 6.03 (d, J = 8.5 Hz, 1H), 5.39 - 5.31 (m, 2H). LCMS Purity = 93%; m/z = 245.29 (M+H).

Step 2: Preparation of methyl 2-amino-6-(benzyloxy)nicotinate



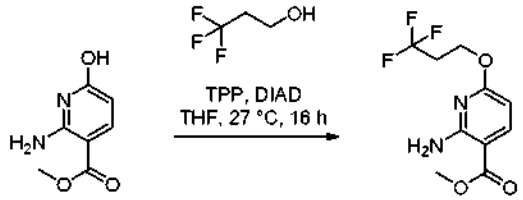
To a stirred solution of 2-amino-6-(benzyloxy)nicotinic acid (220 g, 901 mmol) in DMF (2.5 L) at 26 °C under N_2 atmosphere were slowly added potassium carbonate (373 g, 2702 mmol) and iodomethane (0.282 L, 4504 mmol). The reaction mixture was stirred at 27 °C for 16 hr. The progress of reaction was monitored by TLC (SiO_2, 40% EtOAc/Pet., Rf = 0.6). On completion, the reaction mixture was diluted with water (5 L). The precipitated solid was isolated by filtration and then dried under vacuum to afford methyl 2-amino-6-(benzyloxy)nicotinate as an off-white solid (220 g, yield= 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.4 Hz, 1H), 7.42–7.40 (m, 2H), 7.39–7.35 (m, 2H), 7.34–7.31 (m, 1H), 6.01 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 3.84 (s, 3H). LCMS Purity = 97%, m/z = 259.30 (M+H).

Step 3: Preparation of methyl 2-amino-6-hydroxynicotinate



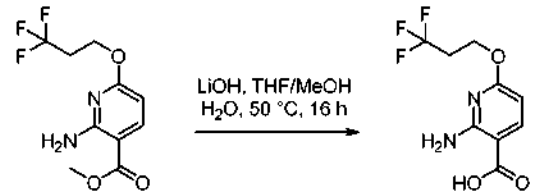
To a stirred solution of methyl 2-amino-6-(benzyloxy)nicotinate (50 g, 190 mmol) in DCM (500 mL) at 26 °C under N_2 atmosphere were slowly added TFA (800 mL) and triflic acid (25 mL, 282 mmol). The reaction mixture was stirred at 26 °C for 16 hr. The progress of reaction was monitored by TLC (SiO_2, EtOAc, Rf = 0.2). On completion, the volatiles were removed under vacuum to afford the crude product. This material was triturated with diethyl ether (3 x 1000 mL) and the precipitated solid was then isolated by filtration. To the solid was added water (2 L) and the mixture was then 5 h. The solid was collected by filtration and was washed with water. The solid was dried under vacuum to afford methyl 2-amino-6-hydroxynicotinate as an off-white solid (25 g, yield = 78%). 1H NMR (300 MHz, DMSO-d_6) δ = 10.92–10.76 (m, 1H), 7.65 (d, J = 9.5 Hz, 1H), 7.43–6.87 (m, 2H), 5.51 (d, J = 9.5 Hz, 1H), 3.69 (s, 3H). LCMS Purity = 99.32%; m/z = 169.32 (M+H). The absence of TFA and triflic acid in the product was confirmed by ^{19}F-NMR. The product was used directly in the next step without additional purification.

Step 4: Preparation of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate



To a stirred solution of methyl 2-amino-6-hydroxynicotinate (50 g, 297 mmol) in THF (1000 mL) at 27 °C under nitrogen atmosphere was added triphenylphosphine (156 g, 595 mmol). The reaction mass was cooled to 0 °C and to the reaction mass was added drop-wise diisopropyl azodicarboxylate ("DIAD" 116 mL, 595 mmol). The solution was stirred for 30 min. To the solution at 0 °C was added a solution of 3,3,3-trifluoropropan-1-ol (52.4 mL, 595 mmol) in THF (200 mL). The reaction mass was then allowed to slowly warm to 27 °C and was then stirred at that temperature for 16 hrs. The progress of the reaction was monitored by TLC (SiO_2, 10% EtOAc/Pet. Rf = 0.5). On completion, the reaction mixture was diluted with water (500 mL) and extracted with EtOAc (2 × 500 mL). The combined organics were washed with water (500 mL) and then brine solution (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to afford the crude product as a yellow semi-solid (100 g). This material was purified via silica gel chromatography eluting with 5-10% EtOAc in pet. The fractions containing the desired product were pooled and concentrated under reduced pressure to afford methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate as a as yellow liquid (50 g, 60% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.8 Hz, 1H), 7.21–6.85 (brs, 1H), 6.04 (d, J = 8.4 Hz, 1H), 4.50 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 2.63–2.55 (m, 2H). LCMS analysis method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in CAN; Gradient = Time (min.) / %B: 0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4/3; Column Temp. = 35 °C; Flow Rate = 0.6 mL/min. LCMS result: retention time = 2.03 mins.; observed ion = 265.15 (M+H); LCMS Purity = 93%.

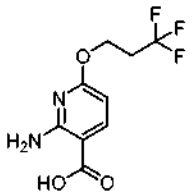
Step 5: Preparation of 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid



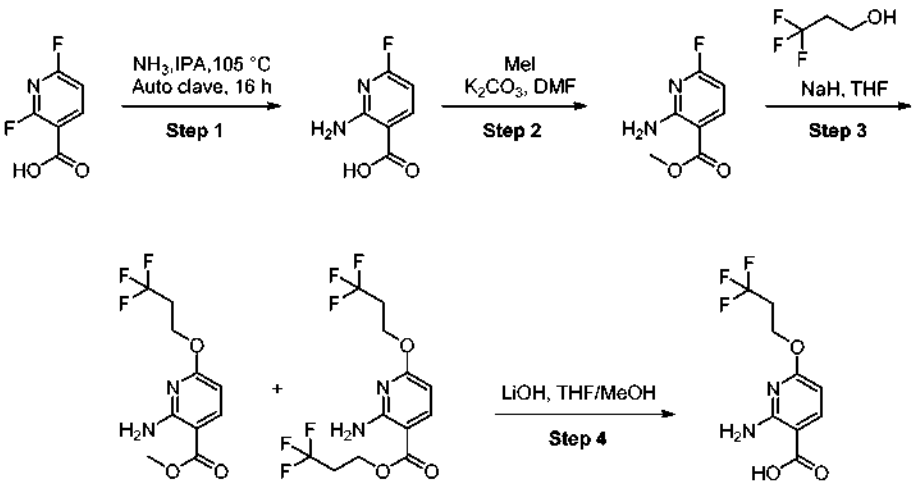
To a stirred solution of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate (50 g, 189 mmol) in tetrahydrofuran (THF) (500 mL), methanol (150 mL) and water (80 mL) at 0 °C under nitrogen atmosphere was added lithium hydroxide monohydrate (22.66 g, 946 mmol). The reaction mixture was stirred at 50°C for 16 hr. The progress of the reaction was

monitored by TLC (SiO_2, 50% EtOAc/Pet. Rf = 0.3). On completion, the reaction mixture was concentrated under reduced pressure to afford an aqueous residue. The residue was then acidified to pH 4 via the addition of 1N HCl. The resulting precipitate was collected via filtration and was washed with water (500 mL), then n-hexane (400 mL), and then dried to afford 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid as an off-white solid (45 g, 90% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.47 (brs, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.35 (brs, 2H), 5.98 (d, J = 8.8 Hz, 1H), 4.44 (t, J = 6.1 Hz, 2H), 2.84–2.73 (m, 2H). The product was used directly in the next step without further purification.

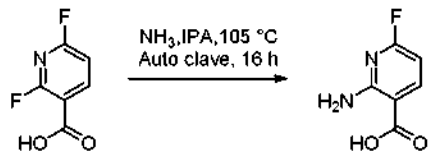
Alternate preparation of 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid



Synthesis Scheme:



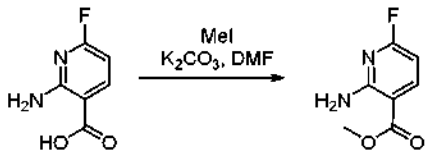
Step 1: Preparation of 2-amino-6-fluoronicotinic acid



A mixture of NH_3 in water ("25% NH_3 in H_2O", 1 L, 4V) and isopropanol (6.5 L, 26V) at 0 °C was sparged ammonia gas for 1 hr. To the mixture in an autoclave (25 L) was added 2,6-difluoronicotinic acid (250 g, 1571 mmol). Then the reaction mixture was stirred at 105 °C for 20 hr. The progress of the reaction was monitored by TLC (SiO_2, 80% EtOAc/Pet. Rf = 0.3).

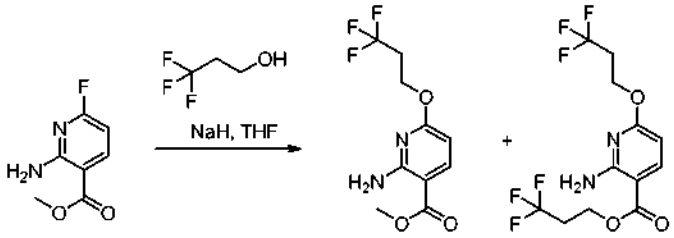
On completion, the reaction mixture was allowed to cool to 20 °C and then was concentrated under reduced pressure at below 20 °C to a volume of 4-6V (1.5 L). The residue was dissolved in water (5 L) and acidified to pH 2-3 via the addition of 2N HCl (700 mL) and then stirred for 2 hrs. The resulting precipitate was collected via filtration and was washed with water (4000 mL), then n-hexane (5000 mL), and then dried in a vacuum oven at 50 °C to afford 2-amino-6-fluoronicotinic acid as an off-white solid (250 g, 92% yield). This product was blended with the product of other batches prepared by the same method to afford 2000 g of combined product. Residual solvent was removed from the solids by suspending the solids in toluene (10 L) and then removing the toluene by distillation. The resulting solids were dried in a vacuum oven at 60 °C for 7 days to afford 2-amino-6-fluoronicotinic acid as an off-white solid (1.6 kg, 77% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.94 (brs, 1H), 8.17 (t, J = 8.8 Hz, 1H), 7.56 (brs, 2H), 6.25 (dd, J = 8.2, 2.8 Hz, 1H). LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min) /%B: 0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4/3; Column Temperature = 35 °C; Flow Rate= 0.6 mL/min. LCMS Result: retention time = 1.24 mins.; observed ion = 157.04 (M+H); LCMS Purity = 96%.

Step 2: Preparation of methyl 2-amino-6-fluoronicotinate



To a stirred solution of 2-amino-6-fluoronicotinic acid (150 g, 961 mmol) and potassium carbonate (398 g, 2882 mmol) in DMF (1500 mL) was added iodomethane (300 mL, 4804 mmol). The reaction mixture was stirred at 27 °C for 16 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC (SiO_2, 30% EtOAc/Pet. Rf = 0.7). On completion, the reaction mixture was quenched by the addition of ice-cold water (5000 mL). The resulting precipitate was collected via filtration and was washed with water (2000 mL), then n-hexane (1000 mL), and then dried to afford methyl 2-amino-6-fluoronicotinate as a brown solid (120 g, 70% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.20 (t, J = 8.8 Hz, 1H), 7.54 (brs, 2H), 6.29 (dd, J = 8.4, 2.8 Hz, 1H), 3.82 (m, 3H). LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min) /%B: 0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4/3; Column Temp. = 35 °C; Flow Rate = 0.6 mL/min. LCMS Result: retention time = 1.55 mins.; observed ion = 171.07 (M+H); LCMS Purity = 96%. The product was used directly in the next step without further purification.

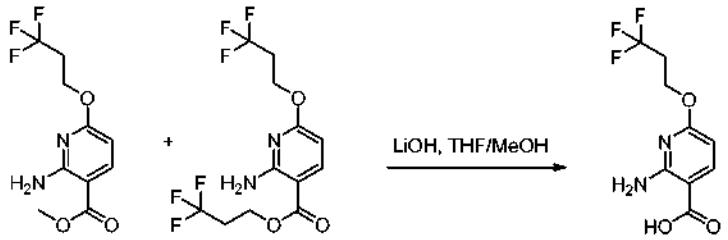
Step 3: Preparation of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate and 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate



To a stirred solution of methyl 2-amino-6-fluoronicotinate (25 g, 147 mmol) and 3,3,3-trifluoropropan-1-ol (15.54 mL, 176 mmol) in THF (500 mL) at 0 °C under nitrogen atmosphere was added portion-wise sodium hydride (60% disp. in oil, 8.82 g, 220 mmol). The reaction mixture was stirred at 0 °C for 30 min and then allowed to slowly warm to 27 °C and stirred at that temperature for 16 hrs. The progress of the reaction was monitored by TLC (SiO_2, 10% EtOAc/Pet. Rf = 0.5). On completion, the reaction mixture was cooled 0 °C and quenched with saturated aqueous NH_4Cl solution (300 mL). The mixture was extracted with EtOAc (2 × 500 mL). The combined organics were washed with brine solution (200 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to afford methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate as a yellow liquid (40 g). Formation of the transestrification byproduct 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate was also observed in the reaction. LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min)/%B: 0/97, 0.4/97, 2.5/2, 3.4/2, 3.5/97, 4.0/97; Column Temp. = 35 °C; Flow Rate = 0.6 mL/min. LCMS Result: retention time = 2.04 & 2.22 mins.; observed ion = 265.18 & 347.29 (M+H); LCMS Purity = 57% of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate and 15% of 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate. This crude product mixture was blended with two other batches of crude products prepared by the same method (40 g and 50 g). The combined material (130 g) was purified by silica gel chromatography eluting with 10-20% EtOAc in pet. The fractions containing the desired product were pooled and concentrated under reduced pressure to afford a 6:1 mixture of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate and 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate as a pale-yellow liquid (100 g, 90% yield). 1H-NMR (400 MHz, $CDCl_3$) δ: 8.02–7.97 (m, 1H), 7.04–6.48 (m, 1H), 6.08–6.03 (m, 1H), 4.52–4.47 (m, 2H), 3.83 (s, 3H), 2.64–2.54 (m, 2H). LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min)/%B: 0/97, 0.4/97, 2.5/2, 3.4/2, 3.5/97, 4.0/97; Column Temp. = 35 °C; Flow Rate = 0.6 mL/min. LCMS Result: retention time = 2.02 & 2.21 mins.; observed ion = 264.97 & 346.97 (M+H); LCMS Purity =

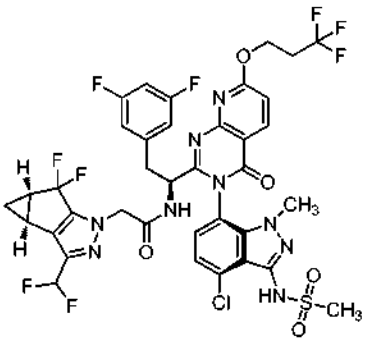
66% of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate and 11% of 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate.

Step 4: Preparation of 2-Amino-6-(3,3,3-trifluoropropoxy)nicotinic acid

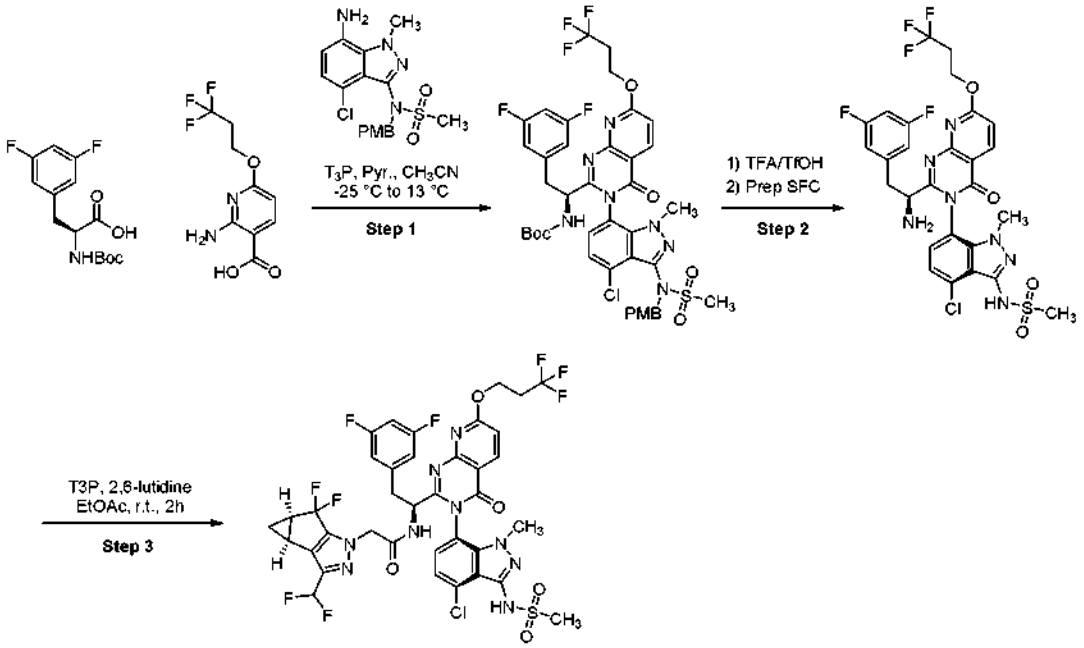


To a stirred solution of methyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate and 3,3,3-trifluoropropyl 2-amino-6-(3,3,3-trifluoropropoxy)nicotinate (6:1, 100 g, 310 mmol) in tetrahydrofuran (THF) (800 mL), Methanol (300 mL) and water (200 mL) at 27 °C under nitrogen atmosphere was added lithium hydroxide monohydrate (37.2 g, 1552 mmol). The reaction mixture was stirred at 50 °C for 8 hr. The progress of the reaction was monitored by TLC (SiO_2, 50% EtOAc/Pet. Rf = 0.3). On completion, the reaction mixture was concentrated under reduced pressure and the resulting aqueous residue was then acidified to pH 4 via the addition of 1N HCl. The resulting precipitate was collected via filtration and was washed with water (2000 mL), then n-hexane (1000 mL), and then dried to afford 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid as an off-white solid (80 g, 97% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.47 (brs, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.33 (brs, 2H), 5.99 (d, J = 8.4 Hz, 1H), 4.45 (t, J = 6.2 Hz, 2H), 2.83–2.74 (m, 2H). LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min.)/%B: 0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4/3; Column Temp.= 35 °C; Flow Rate = 0.6 mL/min. LCMS Result: retention time = 1.73 mins.; observed ion = 251.17 (M+H); LCMS Purity = 94%. The product was used directly in the next step without further purification.

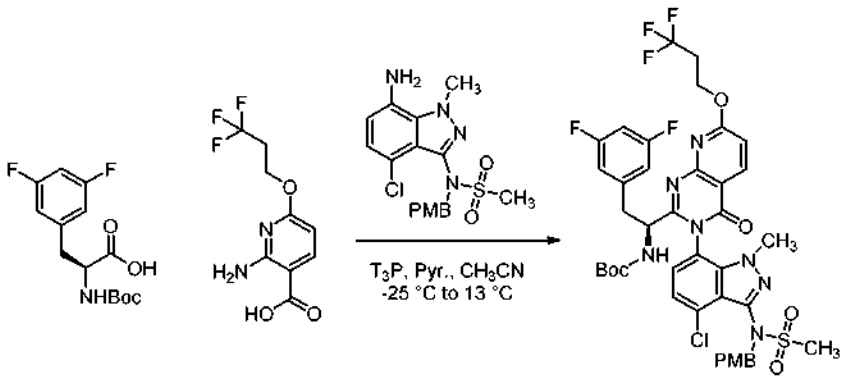
Alternate Preparation of Example 1: N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide



Synthesis Scheme:

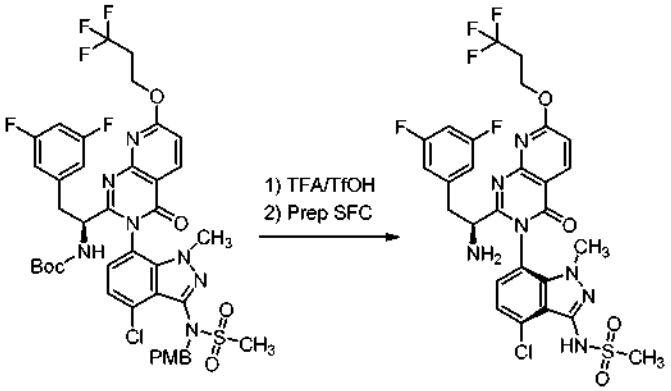


Step 1: Preparation of *tert*-Butyl (S)-(1-(3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate



To a stirred solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3,5-difluorophenyl)propanoic acid (62.3 g, 207 mmol) and 2-amino-6-(3,3,3-trifluoropropoxy)nicotinic acid (55 g, 207 mmol) in acetonitrile (600 mL) under nitrogen atmosphere at -25 °C was added pyridine (41.8 mL, 517 mmol). To the resulting mixture was added drop-wise over 15 min. 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide ("T3P", 50% wt in EtOAc, 609 mL, 1033 mmol). The solution was stirred at -25 °C for 1 hr, then was allowed to slowly warm to 13 °C and was stirred for 5 hrs. To the solution at 13 °C was added N-(7-amino-4-chloro-1-methyl-1H-indazol-3-yl)-N-(4-methoxybenzyl)methanesulfonamide (82 g, 207 mmol). The reaction mass was then allowed to slowly warm to 27 °C and was then stirred at that temperature for 16 hrs. The progress of the reaction was monitored by TLC (SiO_2, 40% EtOAc/Pet. Rf = 0.4). On completion, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL) and then washed with aq. citric acid (0.5M, 2 × 500 mL) followed by aq. NaOH (1N, 3 × 500 mL). The organic layer was dried over Na_2SO_4, filtered and then concentrated under reduced pressure to afford the crude product (180 g) which was purified by silica gel chromatography eluting with 40-50% EtOAc in pet. The fractions containing the desired product were pooled and concentrated under reduced pressure to afford tert-butyl (S)-(1-(3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate as an off-white solid (85 g, 39% yield). The product is a mixture of homochiral atropisomers (diastereomers). LCMS Method: Column = Acquity BEH C18 (50 mm × 2.1 mm, 1.7 um); Mobile Phase A = 0.05% Formic Acid in Water; Mobile Phase B = 0.05% Formic Acid in acetonitrile; Gradient = Time (min)/%B: 0/3, 0.4/3, 2.5/98, 3.4/98, 3.5/3, 4/3; Column Temp. = 35 °C; Flow Rate = 0.6 mL/min. LCMS Result: retention time = 2.46 mins.; observed ion = 892.53 (M+H); LCMS Purity = 85%.

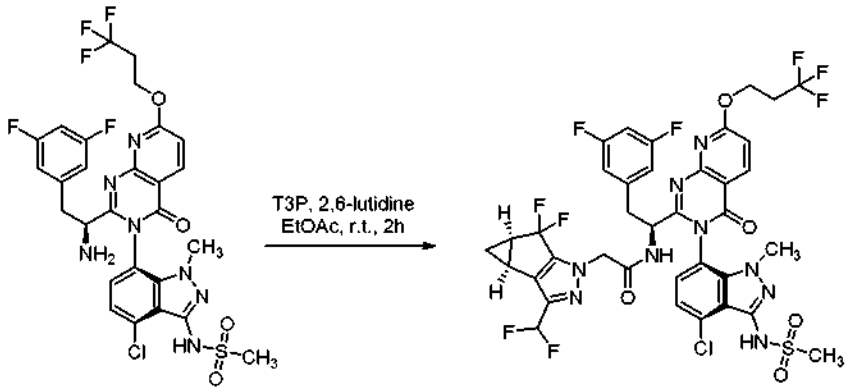
Step 2: Preparation of (S)-N-((6P)-7-((3P)-2-(1-amino-2-(3,5-difluorophenyl)ethyl)-4-oxo-7-(3,3,3-trifluoropropoxy)pyrido[2,3-d]pyrimidin-3(4H)-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide



To a stirred solution of tert-butyl (S)-(1-(3-(4-chloro-3-(N-(4-methoxybenzyl)methylsulfonamido)-1-methyl-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (85 g, 95 mmol) in DCM (300 mL) at 0 °C was added trifluoroacetic acid (TFA, 294 mL, 3810 mmol) followed by triflic acid (25.4 mL, 286 mmol). The solution was allowed to warm to 27 °C and stirred for 1 hr under nitrogen atmosphere. The progress of the reaction was monitored by TLC (SiO_2, 80% EtOAc/Pet. Rf = 0.3). On completion, the volatiles were removed under a gentle stream of nitrogen gas. The residue was dissolved in EtOAc (1000 mL) and washed with 2N NaOH (2 × 500 mL) and then brine (500 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure to afford the crude product which was purified by silica gel chromatography eluting with 50-99% EtOAc in Pet. The fractions containing the desired product were pooled and concentrated under reduced pressure to afford (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-4-oxo-7-(3,3,3-trifluoropropoxy)pyrido[2,3-d]pyrimidin-3(4H)-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide as a pale yellow solid (63 g). The material is a mixture of homochiral atropisomers (diastereomers) in a 64:26 ratio as determined by LCMS. This product was blended with three additional batches of products prepared by following the same procedure. The combined product (195 g) was dissolved in methanol:acetonitrile (80:20, 1300 mL) and this solution was purified by prep-SFC using the following method: Column = (R,R) Whelk-01 (250 × 30 × 5µ); eluent = CO_2:MeOH (65:35); Flow-rate = 90 g/min; Back-pressure = 120 bar; Detection = 214 nm (UV); Stack time = 14 min; Load per injection = 430 mg. The pure major peak was collected and concentrated under reduced pressure to afford to afford the single stereoisomer (S)-N-((6P)-7-((3P)-2-(1-amino-2-(3,5-difluorophenyl)ethyl)-4-oxo-7-(3,3,3-trifluoropropoxy)pyrido[2,3-d]pyrimidin-3(4H)-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide as an off-white solid (113 g, 63% yield). ^{1}HNMR (400 MHz, DMSO-d_6) δ: 8.42 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H) 7.03–6.97 (m, 1H), 6.75–6.70 (m, 2H), 4.73–4.69 (m, 2H), 3.68 (s, 3H), 3.58–3.52 (m, 1H), 3.28–3.24 (m, 1H), 3.22 (s, 3H), 2.97–2.83 (m, 3H).

LCMS Method: Column =XBridge C18 (75 mm × 4.6 mm, 3.5 µm); Mobile Phase A = 5 mM ammonium bicarbonate in water; Mobile Phase B= acetonitrile; Gradient = Time (min)/%B: 0/5, 0.5/5, 1.0/15, 4.0/98, 7.0/98, 7.5/5, 8.0/5; Column Temp =35 °C; Flow Rate = 1.3 mL/min. LCMS Result: retention time = 4.03 mins.; observed ion = 672.07 (M+H); LCMS Purity = 98%; HPLC Purity = 98%; Chiral HPLC Purity = 98%.

Step 3: Preparation of N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide



To a stirred solution of (S)-N-((6P)-7-((3P)-2-(1-amino-2-(3,5-difluorophenyl)ethyl)-4-oxo-7-(3,3,3-trifluoropropoxy)pyrido[2,3-d]pyrimidin-3(4H)-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (55 g, 82 mmol) and 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (22.70 g, 86 mmol) in ethyl acetate (818 ml) was added 2,6-lutidine (23.83 ml, 205 mmol). To the mixture was added drop-wise 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide ("T3P", 50% wt. in ethyl actate) (97 mL, 164 mmol) upon which the internal temperature rose from 17 °C to 24 °C. The mixture was stirred for 2 hrs at room temperature. The reaction was quenched by the addition of water (500 mL). The phases were partitioned and the organic phase was washed with water (500 mL), then dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated to 1/4 of the original volume to afford the crude product as a solution in ethyl acetate.

A second batch of product was prepared following the same procedure modified as follows: the reaction was conducted using (S)-N-((6P)-7-((3P)-2-(1-amino-2-(3,5-difluorophenyl)ethyl)-4-oxo-7-(3,3,3-trifluoropropoxy)pyrido[2,3-d]pyrimidin-3(4H)-yl)-4-chloro-1-methyl-1H-indazol-3-yl)methanesulfonamide (53.4 g, 79 mmol) and the amounts of all other reagents were adjusted accordingly. The workup concluded with a brine (300 mL) wash before drying over $MgSO_4$.

The crude products were combined and then adsorbed onto Celite. The resulting powder was subjected to silica gel chromatography (3 kg RediSep Gold column) eluting with 30-85% ethyl acetate in hexanes. Fractions containing the desired product were pooled and concentrated under reduced pressure to afford a yellow foam. The material was placed under high vacuum for 18h. The material was converted to a fine powder using a mortar and pestle and the solids were placed in vaccum oven at 50 °C for 48 h to afford N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide as a yellow powder (134.1 g, 90% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.84 - 9.91 (1 H, m) 9.49 (1 H, d, J=8.34 Hz) 8.47 (1 H, d, J=8.35 Hz) 7.79 (1 H, d, J=7.75 Hz) 7.49 (1 H, d, J=8.05 Hz) 7.11 (1 H, d, J=8.64 Hz) 6.80 - 7.09 (2 H, m) 6.66 (2 H, dd, J=8.20, 2.24 Hz) 4.69 - 4.75 (3 H, m) 4.57 (1 H, d, J=16.39 Hz) 4.48 (1 H, ddd, J=11.03, 8.35, 2.68 Hz) 3.51 (3 H, s) 3.42 (1 H, dd, J=14.01, 2.38 Hz) 3.20 (3 H, s) 3.05 (1 H, dd, J=14.01, 11.03 Hz) 2.89 - 2.99 (2 H, m) 2.42 - 2.48 (2 H, m) 1.32 - 1.40 (1 H, m) 0.81 - 0.86 (1 H, m). LCMS Method: Column = Acquity UPLC BEH C18 (2.1 x 100 mm, 1.7 um particles); Solvent A = Water:MeCN (95:5) with 0.1% v/v Formic Acid; Solvent B = MeCN:Water (95:5) with 0.1% v/v Formic Acid; Gradient = Time (min)/%B: 0/0, 3.5/100, 4.5/100; Flow rate = 0.8 mL/min. LCMS Result: retention time = 3.173 min; observed mass = 917.95 (M+H). UPLC purity = 99.8%.

Naming of Example 1:

The compound of Example 1 as prepared above is a homochiral material that contains axial chirality. Axial chirality can be described using P/M nomenclature as detailed in the IUPAC Gold Book (doi:10.1351/goldbook.A00547). However, at this time only a limited number of software tools are available which are capable of generating chemical names containing P/M nomenclature, and even fewer options are available to convert chemicals names using this nomenclature to structural representations of the molecules. Therefore, for clarity and convenience several names for Example 1 are provided below:

The name of Example 1 as generated by ChemDraw Ultra 12 (absent P/M nomenclature) is:

N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide

The chemical name of Example 1 as generated by JChem for Excel (including P/M nomenclature) is:

N-[(1S)-1-[(3P,3P)-3-(4-chloro-3-methanesulfonamido-1-methyl-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3H,4H-pyrido[2,3-d]pyrimidin-2-yl]-2-(3,5-difluorophenyl)ethyl]-2-[(2S,4R)-9-(difluoromethyl)-5,5-difluoro-7,8-diazatricyclo[4.3.0.0^{2,4}]nona-1(6),8-dien-7-yl]acetamide

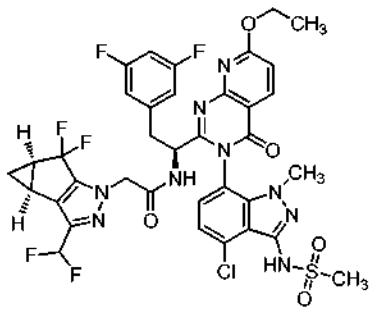
The chemical name generated by ChemDraw Ultra 12 with manually added P/M nomenclature is:

N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide

Comparative Tests:

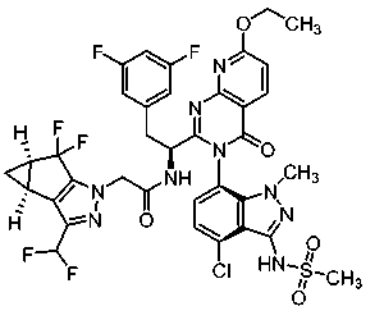
The compound of Example 1 was compared to the compound of Example 60.2 described in WO2018203235 (Scheme 1) in a number of tests. For the purposes of these comparisons we elected to use homochiral material of each compound as this level of purity is most representative of what would be used in human clinical trials. Specifically, restricted rotation about the indicated C-N bond of the indazole gives rise to atropisomers (diastereomers) in both Example 1 and Example 60.2 which can be separated by chromatography and are non-interconverting at room temperature. Thus, using chromatography we isolated in pure form the stereoisomers depicted in Scheme 2.

Scheme 1

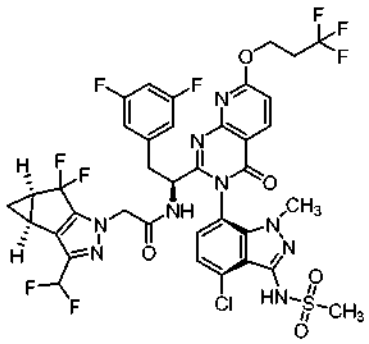


Example 60.2 as depicted in WO2018203235

Scheme 2



Example 60.2 depicting the stereochemistry of the homochiral material used in the described comparative tests.



Example 1 of the present patent depicting the stereochemistry of the homochiral material used in the described comparative tests.

General procedure for quantifying compound via LC-MS/MS:

All *in vitro* samples were injected on an Exion LC 4500 Triple Quad™ LC-MS/MS system. The analytical column used was a Phenomenex C18 (C18, 4.6 mm x 50 mm, 5 µm) maintained at room temperature. Mobile Phase A consisted of 0.1% (v/v) formic acid in MilliQ water. Mobile Phase B consisted of 100% methanol. The flow rate was 1 mL/min. The gradient was as follows: Mobile B was linearly increased from 5% to 90% over 0.7 min, maintained at 90% for 1.4 min, and maintained at 5% for 0.7 min.

All *in vivo* samples were injected on a Triple Quad™ 6500 LC-MS/MS system with columns maintained at 60°C. Mobile Phase A consisted of H_2O, 1 mM NH_4OAc, 0.025% Formic Acid. Mobile Phase B consisted of MeOH, 5mM NH_4OAc. The flow rate was 0.6 mL/min. The column and elution gradient was selected from one of the general analysis methods described below.

General Analysis Method A:

Column = Waters X-Bridge BEH C18 (2.1 x 50 mm, 1.7 µm particles); Gradient: Time(min.)/%B = 0.0/10, 0.2/10, 0.8/90, 1.3/90, 1.31/10, 2.0/10.

General Analysis Method B:

Column = Waters BEH C18 (2.1 x 50mm, 2.5 µm particles); Gradient: Time(min.)/%B = 0.0/10, 0.2/10, 0.8/90, 1.3/90, 1.31/10, 2.0/10.

General Analysis Method C:

Column = Waters BEH C18 (2.1 x 50mm, 1.7 µm particles); Gradient: Time(min.)/%B = 0.0/2, 0.40/2, 0.7/65, 1.3/90, 1.9/90, 1.91/2, 2.5/2.

Procedure to measure potency and cytotoxicity:

MT-2 cells, 293T cells and the proviral DNA clone of NL_{4-3} virus were obtained from the NIH AIDS Research and Reference Reagent Program. MT-2 cells were propagated in RPMI 1640 media supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 mg/ml penicillin G and up to 100 units/mL streptomycin. The 293T cells were propagated in DMEM media supplemented with 10% heat inactivated FBS, 100 mg/mL penicillin G and 100 mg/mL streptomycin. A recombinant NL_{4-3} proviral clone, in which a section of the nef gene was replaced with the Renilla luciferase gene, was used to make the reference virus used in these studies. The recombinant virus was prepared through transfection of the recombinant NL_{4-3} proviral clone into 293T cells using Transit-293 Transfection Reagent from Mirus Bio LLC (Madison, WI). Supernatant was harvested after 2-3 days and the amount of virus present was titered in MT-2 cells using luciferase enzyme activity as a marker by measuring luciferase enzyme activity. Luciferase was quantitated using the EnduRen Live Cell Substrate from Promega (Madison, WI). Antiviral activities of compounds toward the recombinant virus were quantified by measuring luciferase activity in MT-2 cells infected for 4-5 days with the recombinant virus in the presence of serial dilutions of the compound.

The 50% effective concentration (EC_{50}) was calculated by using the exponential form of the median effect equation where (Fa) = 1/[1+ (ED_{50}/drug conc.)m] (Johnson VA, Byington RT. Infectivity Assay. In Techniques in HIV Research. ed. Aldovini A, Walker BD. 71-76. New York: Stockton Press.1990). The 50% inhibitory concentration (EC_{50}) was calculated by using the exponential form of the median effect equation where percent inhibition = 1/[1 + (EC_{50}/drug concentration)^m], where m is a parameter that reflects the slope of the concentration-response curve.

Compound cytotoxicity and the corresponding CC_{50} values were determined using the same protocol as described in the antiviral assay except that uninfected cells were used. Cytotoxicity was assessed on day 4 in uninfected MT2 cells by using an XTT (2,3-bis[2-Methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide inner salt)-based colorimetric assay (Sigma-Aldrich, St Louis, Mo).

Results:

The potencies of Example 1 and Example 60.2 are within the error of the initial anti-HIV virology assay (EC_{50} Example 1 = 25 ±8 pM, EC_{50} Example 60.2= 18 ±13 pM). Note that the EC_{50} of Example 1 was 0.034 nM when initially tested, however, further tested resulted in a revised average of 25 ±8 pM. The cytotoxicy CC_{50} measured is >0.5 μM and >10 μM for Example 1 and Example 60.2, respectively.

Procedure to measure metabolism in liver microsomes:

Liver microsomes from human, rat dog and monkey were thawed and diluted to a final concentration of 1 mg/mL in 100 mM potassium phosphate buffer (pH 7.4). Test compounds and controls were prepared at 100x final concentration of 1 µM in 1:1 acetonitrile:water (v/v) and aliquoted into microsomal mixture. The mixture was preincubated at 37°C in a shaking water bath for 10 minutes. The incubations were performed in duplicate. Three controls were included in the incubations; warfarin, phenacetin, and verapamil. After the preincubation, the reaction was initiated with NADPH at a final concentration of 1 mM. At 0, 5, 15, 30, 45 and 60 minutes, 25 µL of sample was removed and quenched with 300 µL of acetonitrile containing internal standard (Telmisartan). The samples were vortexed for 5 minutes at 1200 rpm and then centrifuged at 4000 rpm for 10 min. A 100 µL aliquot of supernatant was diluted three-fold with water and injected on an Exion LC 4500 Triple Quad LC-MS/MS system. Results were reported as a percentage of parent remaining and was calculated from peak area ratios of test compound remaining after at each time point and compared to time zero incubation.

Results:

Example 1 is six times more stable in dog liver microsomes than Example 60.2, and Example 1 is at least two times more stable in monkey liver microsomes than Example 60.2. This data suggest that Example 1 should be significantly more stable than Example 60.2 to metabolism in vivo in dog and monkey.

Table 1.

Liver microsome stability	**Example 1**	**Example 60.2**
Human liver microsome $T_{1/2}$	> 120 min.	> 120 min.
Rat liver microsome $T_{1/2}$	> 120 min.	> 120 min.
Dog liver microsome $T_{1/2}$	105 min.	17 min.
Monkey liver microsome $T_{1/2}$	> 120 min.	55 min.

Procedure to measure metabolism in human hepatocytes:

Cryopreserved hepatocytes in suspension from human, monkey, dog, rat and mouse were thawed and diluted in pre-warmed William's Medium E (pH 7.4). Aliquots of the hepatocyte suspension were added to test compound working solutions prepared in pre-warmed William's Medium E (pH 7.4) to achieve final concentrations of 0.5 µM in 0.5×10^6 cells per milliliter and ≤0.25% DMSO. These samples were incubated at 37°C with 5% carbon dioxide and shaking at 200 rpm. The incubations were performed in singlet. At time points 0, 10, 30, 60, 120 and 240 minutes, a 50 µL aliquot of the incubation mixtures was removed and

added to a 100 µL solution of acetonitrile containing internal standard and the mixture was vortexed and then centrifuged at 4°C and 3500 rpm for 15 minutes. Following completion of the experiment, samples were analyzed by LC-MS/MS. Metabolic stability results were reported as a percentage of parent test compound remaining. This percentage is calculated by dividing the peak area ratio of test compound following incubation (t_x) by the peak area ratio of test compound at time-zero (t_0) just prior to incubation.

The elimination rate constant (k, min^{-1}) is calculated using nonlinear regression fitting with the following equation:

$$C_t = C_0 \times e^{(-k \times t)}$$

where:

C_0 is the initial concentration represented as the peak area ratio (test compound peak area/ internal standard peak area);

C_t is the concentration at t represented as the area ratio (test compound peak area / internal standard peak area);

e is the base of the natural logarithm

t is the time (min);

k is the elimination rate constant (min^{-1}).

The half-life ($t_{1/2}$, min) is calculated using the following equation:

$$t_{1/2} = \frac{0.693}{k}$$

where:

k is the elimination rate constant (min^{-1}).

The in vitro intrinsic clearance (CL_{int}, mL/min/million cells) is calculated using the following equation:

$$CL_{int} = 0.693 / t_{1/2} / n$$

where:

$t_{1/2}$ is the half-life;

n is the number of cells per mL.

Results:

The half-life of Example 1 in human hepatocytes was calculated to be >480 minutes while the half-life of Example 60.2 in human hepatocytes was calculated to be 350 minutes. The intrinsic clearance of Example 60.2 in human hepatocytes is 0.465 mL/min/g liver which is 1.5 times more rapid than the 0.312 mL/min/g liver clearance found with Example 1.

Procedure for measuring pharmacokinetic parameters (PK) in vivo:

PK was investigated in male CD1 mice, Wistar Han Rats, Cynomolgus monkeys, and Beagle Dogs. Two groups of animals (N = 3 per group) received test compound either as an intravenous (IV) dose (1 mg/kg) or by oral gavage (5 mg/kg solution and suspension). Drug was formulated in 90% PEG 400, 10% ethanol for IV administration and in 90% PEG400, 5% ethanol for PO administration. Blood samples were collected at 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 24, 48, 72 and 96 h post dose for IV; 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 24, 48, 72 and 96 h post dose for oral. Blood samples were collected into K_3EDTA tubes and centrifuged at 1500 to 2000 x g to obtain plasma. Plasma samples were stored at -20°C until analysis by LC-MS/MS. All *in vivo* samples were injected on an Exion LC 4500 Triple Quad™ LC-MS/MS system where the column was maintained at 60 °C and the flow rate was 0.6 mL/min. All LC-MS/MS analysis parameters are captured electronically in the raw data files. Rat IV, Dog IV, Monkey IV, and Monkey PO PK samples were analyzed by General Analysis Method A. Mouse IV, Mouse PO, and Dog PO PK samples were analyzed by General Analysis Method B. Rat PO samples were analyzed by General Analysis Method C.

The PK parameters were obtained by non-compartmental analysis of plasma concentration vs time data (Phoenix WinNonlin v8.1). The peak concentration (C_{max}) and time for C_{max} (T_{max}) were recorded directly from experimental observations. The area under the curve from time zero to the last sampling time [AUC_{0-T}] and the area under the curve from time zero to infinity [AUC_{INF}] were calculated using the linear-log trapezoidal rule. The total plasma clearance (CL_{Tp}), steady-state volume of distribution (V_{ss}), apparent elimination half-life (T-HALF), and mean residence time (MRT) were estimated after IV administration. Estimations of AUC and T-HALF were made using a minimum of three timepoints with quantifiable concentrations. The absolute oral bioavailability (F) was estimated as the ratio of dose-normalized AUC values following oral and IV doses.

Results:

The IV pharmacokinetic (PK) parameters of Example 1 and Example 60.2 were measured in four pre-clinical species: mouse, rat, dog and monkey. Example 1 exhibited improved clearance in all four species relative to Example 60.2. Consistent with the results of liver microsome assay mentioned above, the differences in clearance was most significant for dog and monkey where clearance was improved 4.9-fold and 2.6-fold, respectively. Likewise, the half-life of Example 1 in circulation in dog and monkey was 3.4-fold and two-fold higher than Example 60.2, respectively.

Table 2.

Example 1 *PK Parameters*	**Unit**	**Mouse**	**Rat**	**Monkey**	**Dog**
CL	mL/min/kg	0.50	2.64	8.50	1.68
Vss	L/kg	0.24	3.34	1.18	0.83
$T_{1/2}$	h	7.6	17.4	3.0	8.6

Table 3.

Example 60.2 *PK Parameters*	**Unit**	**Mouse**	**Rat**	**Monkey**	**Dog**
CL	mL/min/kg	5.20	5.89	22.2	8.21
Vss	L/kg	2.14	2.86	1.34	0.96
$T_{1/2}$	h	5.2	11.0	1.4	2.5

Before a prospective medicine can enter human clinical trials, the safety of the compound typically should be assessed in two pre-clinical species: one rodent and one non-rodent. These species are commonly rat, and either dog or monkey. One objective of an in vivo safety study is to achieve concentrations of drug in circulation that are many times higher than what would be expected if a human were given an efficacious dose of the drug. The fold-difference between the drug concentrations achieved in the safety study versus the drug concentrations that would be expected in a person taking an efficacious dose of the drug is termed the "margin". Achieving high margins in a safety study is important because as margins increase so does the confidence that if a drug-related adverse event were possible it would be observed during the pre-clinical safety assessment.

Improved PK parameters in rat, dog or monkey mean that a lower dose of compound would be required to achieve a high concentration of drug in circulation for these pre-clinical species. Therefore, a monkey or dog given a dose of Example 1 would achieve higher margins than if given the same size dose of Example 60.2. Due to practical limitations of dose size, the margin (and therefore the confidence) that could be achieved with Example 1 in a non-rodent safety assessment study is higher than the margin that could be achieved with Example 60.2.

Procedure for allometric scaling of pre-clinical PK parameters to provide a prediction of dose in human:

Human dose predictions were performed using Phoenix WinNonlin (v 8.0) software and Microsoft Excel using the ModelRisk add-in for population modeling. Human estimates for each compound's CL_{Tp} were obtained based on average allometric scaling of mouse, rat, monkey and dog IV data (body weight scaling factor of 0.75) and an average (body weight

scaling factor of 1.0) from all species for Vss. Human IV parameters (Vc, Ka, K12, K21, Kel) were determined using Mean Residence Time (MRT) scaling from preclinical species (mouse, rat, dog and cyno) using the human Vss and CL_{Tp} estimates. Absorption (Ka) was determined by deconvolution (PO) or from the half-life (SC) in preclinical species (Ka = LN(2)/t1/2). The predicted human dose for PO and SC is calculated with consideration of human variability and is calculated to cover 95% of the human population.

Results:

Pre-clinical species PK parameters are commonly used to predict human PK parameters prior to human-clinical trials. The methods used for this predication are called "allometric scaling" and are generally discussed and practiced in the literature. Using allometric scaling, the predicted once-daily oral dose required to maintain an efficacious plasma concentration of drug in human is 7-fold lower for Example 1 than for Example 60.2. Specifically, the predicted human QD PO dose of Example 1 is less than 10 mg while the predicted human QD PO dose of Example 60.2 is greater than 30 mg.

While idiosyncratic drug reactions (i.e., hypersensitivity reactions) are unpredictable and serious in nature, and thus represent a significant clinical problem, it has been stated that drugs given at a daily dose of 10 mg or less are rarely if ever associated with a high incidence of idiosyncratic drug reactions (Uetrecht, J. P. New Concepts in Immunology Relevant to Idiosyncratic Drug Reactions: The "Danger Hypothesis" and Innate Immune System. Chem. Res. Toxicol. 1999, 12(5), 387-395, DOI:10.1021/tx980249i).

Procedure for measuring pharmacokinetic parameters in a subcutaneous in vivo experiment:

Drug was formulated in 1% Kolliphor P188/1% PEG3350/3.5% Mannitol/94.5% Water and then administered to Wistar Han Rats as a subcutaneous injection at a dose of 20 mg/kg. Blood samples were collected at 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 24, 48, 72, 96 h, and then every 3 days for up to 122 days. Blood samples were collected into K_3EDTA tubes and centrifuged at 1500 to 2000 x g to obtain plasma. Plasma samples were stored at -20°C until analysis by LC-MS/MS.

Results:

The suitability of each compound for subcutaneous (SC) administration was evaluated in a rat SC PK experiment. As determined by this experiment, the apparent half-life of compound in plasma was 13 days for Example 1 and 11.5 days for Example 60.2. The $AUC_{0\text{-}Infinity}$ for Example 1 was 4,941 days*ng/mL (2.89% of the AUC extrapolated). The $AUC_{0\text{-}infinity}$ for Example 60.2 was 609 days*ng/mL (12.8% of the AUC extrapolated). The bioavailability was 93% for Example 1 and 25% for Example 60.2. Drug concentrations were maintained

above 7 ng/mL for all animals for 73 days with Example 1, and 24 days with Example 60.2 (Figure 1). Predicted once-monthly subcutaneous (Q1M SC) doses for human were calculated using the apparent half-lives and bioavailabity derived from SC rat PK in conjunction with the predicted human clearance values derived from allometric scaling. The predicted Q1M SC dose required to maintain an efficacious plasma concentration of drug in human is 15-fold lower for Example 1 than for Example 60.2.

Procedure for measuring cytochrome P450 induction in cryopreserved human hepatocytes:

Following the guidance of the FDA ("In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry"), the potential of Example 1 and Example 60.2 to induce CYP2B6 expression was tested using hepatocytes from the same three individual donors (rather than pooled donors), and changes in enzyme mRNA levels were evaluated using the "fold-change method". In this test a fold-change in mRNA levels less than 2-fold is considered a negative finding, while a change ≥ 2-fold is considered a positive finding.

Compounds were tested in a CYP induction assay using inducible cryopreserved human primary hepatocytes from three donors to determine the potential to cause induction (as measured by an increase in mRNA transcription) of CYP2B6. Test compounds (0.12 to 30 µM final concentration) were incubated for 48 hours with primary human hepatocytes naturally expressing all nuclear receptors involved in regulation of expression levels of various CYP enzymes. Fresh solutions of test compounds and controls were diluted in assay media and added every 24 hours for two consecutive days, with a final DMSO concentration of 0.1%. At the end of the incubation, the integrity of cell monolayers, cell density and viability were evaluated to assess cytotoxicity effects. The cells were then solubilized in cell lysis buffer and total RNA was purified from each assay sample. Samples were then used in reverse transcription polymerase chain reactions (RT-PCR) to quantify the amount of specific mRNA species encoding the human CYP2B6 gene.

The induction potential of test compounds and controls was compared to known CYP2B6 inducer Phenobarbital (1000 µM). The results of this assay are expressed as fold induction. Fold induction was calculated as a ratio of mRNA level in cells treated with test compound over that in cells treated with DMSO (solvent control) alone, the basal mRNA level, and thus represents the induction potential of the test compound. Fold induction values were used to calculate percent of control activity values, which were then fitted to a 4-parameter logistic regression model to determine the EC_{50} and E_{max} values (if there is induction observed). The cytotoxicity was also assessed in parallel to avoid false positive CYP induction results due to cytotoxicity. Assessment and interpretation of CYP induction potential at cytotoxic concentrations should be avoided.

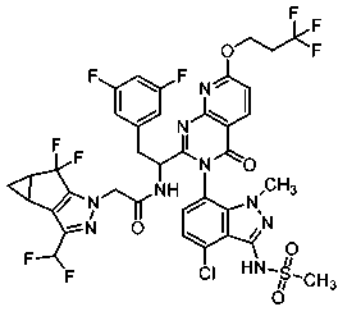
Results:

No cytotoxicity was observed with either compound at any of the concentrations tested (up to 30 μM). For Example 1, a negative finding (no induction) was found with all three donors. For Example 60.2, a positive finding (induction) was found with 2 of 3 donors (EC_{50} values of 1.5 μM and 1.8 μM).

Induction of CYP enzyme expression is recognized as a root cause of drug-drug interactions, leading to increased clearance of the victim drug whose metabolism is governed by the induced CYP isoform. Among the CYP isoforms, CYP2B6 is of particular importance in the context of HIV treatment because efavirenz (EFV), a medicine widely used to treat HIV (included on the 2019 World Health Organization list of essential medicines), is primarily metabolized by CYP2B6 (Ward, B. A., Gorski, J. C., Jones, D. R., Hall, S. D., Flockhard, D. A., Desta, Z. The Cytochrome P450 2B6 (CYP2B6) Is the Main Catalyst of Efavirenz Primary and Secondary Metabolism: Implication for HIV/AIDS Therapy and Utility of Efavirenz as a Substrate Marker of CYP2B6 Catalytic Activity, J. Pharmacol. Exp. Ther., 2003, 306, 287-300, DOI: 10.1124/jpet.103.049601

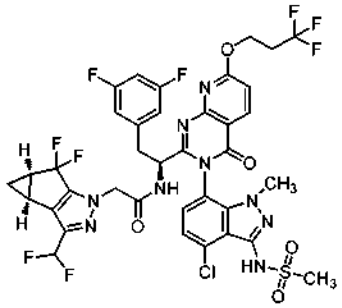
What is claimed is:

1. The compound:



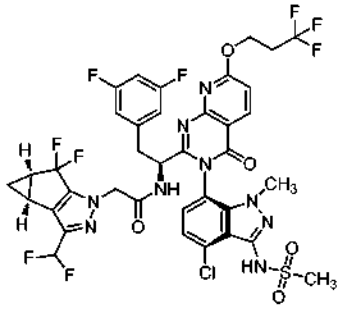
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 having the stereochemistry depicted below



or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2 having the stereochemistry depicted below



or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound or salt according to any of Claims 1-3.

5. A composition according to Claim 4 further comprising a pharmaceutically acceptable excipient.

6. A composition according to Claim 4 or Claim 5 suitable for oral administration, for intramuscular injection, or for subcutaneous injection.

7. A method of treating HIV infection in a human comprising administration of a compound or salt according to any of Claims 1-3.

8. The method of Claim 7 wherein said administration is oral.

9. The method of Claim 7 wherein said administration is intramuscular injection or subcutaneous injection.

10. The method of Claim 7 wherein said method further comprises administration of at least one other agent used for treatment of HIV infection in a human.

11. The method of Claim 10 wherein at least one other agent is selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, darunavir, doravirine, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil,, tenofovir, tenofovir afenamide, S-648414, GSK3640254, the antibody N6LS, and GSK3739937/VH3739937.

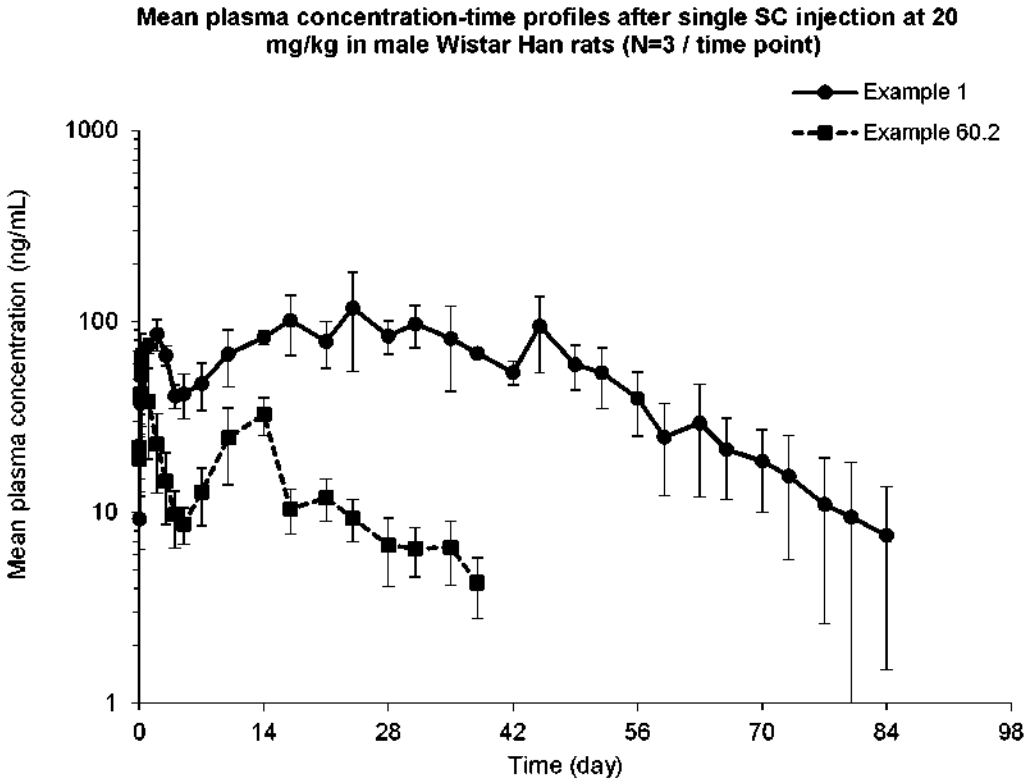
12. The method of Claim 11 wherein at least one other agent is selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, the antibody N6LS, and GSK3739937/VH3739937.

13. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-3 for use in therapy

14. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-3 for use in treating HIV infection.

15. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-3 for use in the manufacture of a medicament for the treatment of HIV infection.

Figure 1.


Mean plasma concentration-time profiles after single SC injection at 20 mg/kg in male Wistar Han rats (N=3 / time point)
Example 1
Example 60.2
Mean plasma concentration (ng/mL)
1000
100
10
1
0
14
28
42
56
70
84
98
Time (day)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/055653

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P31/18 C07D471/04 A61K31/519
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/203235 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 8 November 2018 (2018-11-08) page 478 - page 502; claims; example 60	1-15
E	WO 2020/157692 A1 (VIIV HEALTHCARE UK LTD [GB]) 6 August 2020 (2020-08-06) claims	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2020	10/09/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/055653

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018203235 A1	08-11-2018	EP 3619205 A1	11-03-2020
		JP 2020518601 A	25-06-2020
		TW 201906834 A	16-02-2019
		UY 37710 A	30-11-2018
		WO 2018203235 A1	08-11-2018
WO 2020157692 A1	06-08-2020	NONE	

ANNEXURE-3

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

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

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CABOTEGRAVIR

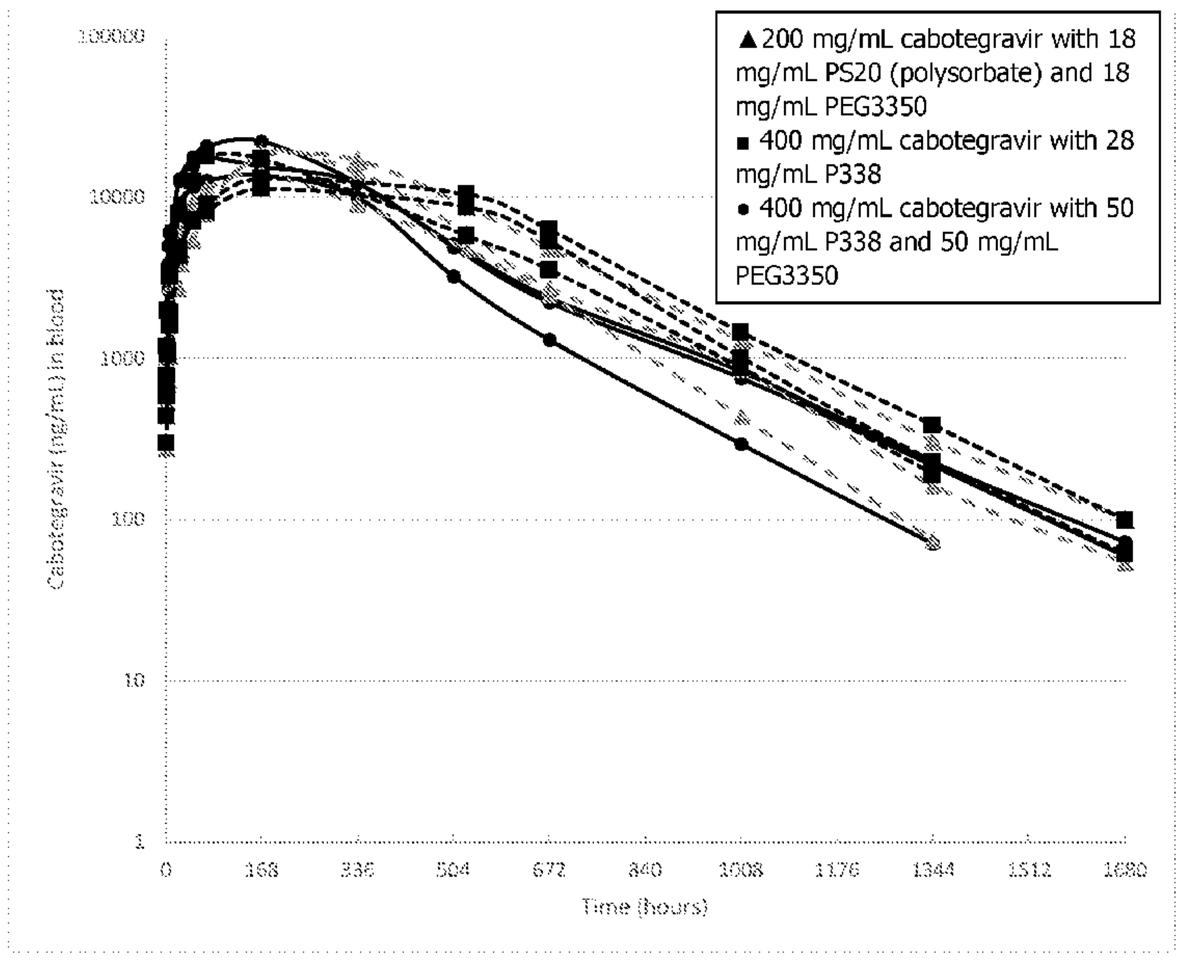


Figure 2

(57) Abstract: The present invention relates to Human Immunodeficiency Virus (HIV) treatment. In particular, the invention relates to a pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer useful as a long acting HIV treatment.

[Continued on next page]

WO 2021/116872 A1

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

PHARMACEUTICAL COMPOSITIONS COMPRISING CABOTEGRAVIR

FIELD OF THE INVENTION

The invention relates to Human Immunodeficiency Virus (HIV) treatment. In particular, the invention relates to long acting treatment of HIV.

BACKGROUND TO THE INVENTION

Patients with HIV infection commonly undergo complex treatment regimens which involve taking multiple pills at regular intervals each day. Patient non-compliance is a known problem accompanying these complex HIV treatment regimens and can lead to the emergence of multiple-drug resistant strains of HIV.

The application of long-acting parenterals has been established in clinical practice for decades, notably in the areas of contraception, anti-psychotics and opiate addiction. More recently, long-acting parenterals have been explored for use in the treatment and prevention of HIV. Long-acting injectables have been proposed as a way of overcoming the non-compliance problem with HIV treatment regimens. Long-acting injectable formulations are in clinical development and clinical studies have demonstrated prolonged exposures (≥30 days) following injection, enabling dosing at once-monthly intervals.

Achieving an injectable suspension with a high concentration of anti-HIV drug in order to dose less frequently and overcome the non-compliance problem with HIV treatment regimens, whilst keeping the same injection volume as previous HIV treatment regimens in order to maintain patient experience is desirable. High concentration suspensions typically suffer from difficulty in resuspension and particle size growth.

There is a need in the art for a long acting injectable to treat HIV that can be dosed at fewer intervals whilst still achieving the same patient experience and overcoming know difficulties with high concentration suspensions.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a pharmaceutical composition comprising cabotegravir, or a pharmaceutically acceptable salt thereof, polyethylene glycol (PEG) and poloxamer.

According to a second aspect of the invention, there is provided a method for the treatment or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising administering to said human a therapeutically effective amount of the pharmaceutical composition as defined herein.

According to a third aspect of the invention, there is provided a pharmaceutical composition as defined herein for use in the treatment or prevention of HIV.

According to a further aspect of the invention, there is provided a kit comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and a poloxamer.

The compositions of the invention may be advantageous in a number of respects. The compositions of the invention allow a high concentration of cabotegravir to be present in the composition. Currently there are no marketed suspensions with drug concentration higher than 312 mg/mL. When considering marketed suspensions for any pharmaceutical use, the suspensions with the highest drug concentrations are ARISTADA INITIO (aripipazole lauroxil, used to treat adults with schizophrenia) and INVEGA TRINZA (paliperidone palmitate, used to treat adults with schizophrenia) which have solid drug concentrations of 281.25 mg/mL and 312 mg/mL

respectively. The compositions of the present invention enable up to 600 mg/mL of cabotegravir to be present in the composition (for example about 400 mg/mL).

The high concentration of cabotegravir allowed by the compositions of the present invention allows the concentrations to be administered to a patient less frequently than known HIV treatments. Compositions of the present invention also exhibit particle size stability and are able to achieve resuspension after storage.

DESCRIPTION OF DRAWINGS/FIGURES

Figure 1 shows a comparison of resuspension of two suspensions, Figure 1 A shows a suspension comprising cabotegravir, P338 (poloxamer) and PEG3350 (left) and Figure 1 B shows a suspension comprising cabotegravir, P338 and Kollidon 12 (polyvinylpyrrolidone) (right). The left vial shows a mostly clear vial bottom indicating that the suspension was resuspended and decanted. The right vial shows a vial bottom with suspension adhered to the bottom of the vial, indicating that resuspension was not achieved.

Figure 2 shows cabotegravir concentrations in blood of individual rats after a 10 mg/kg intramuscular administration of: a 200 mg/mL cabotegravir with 18 mg/mL PS20 (polysorbate) and 18 mg/mL PEG3350 (▲); 400 mg/mL cabotegravir with 28 mg/mL P338 (■); or 400 mg/mL cabotegravir with 50 mg/mL P338 and 50 mg/mL PEG3350 (●). Formulations also contained mannitol (14 to 30 mg/mL) for tonicity adjustment. 3 rats were used per formulation.

Figure 3 shows cabotegravir concentrations in blood of individual rats after a 10 mg/kg subcutaneous administration of 400 mg/mL cabotegravir with 50 mg/mL P338, 50 mg/mL PEG3350 and 30 mg/mL mannitol (●). 3 rats were used.

Figure 4 shows microscopy images of suspensions. Figure 4A (left) shows suspension 3a which was fully resuspended after storage for 6 months upright at 30°C/65%RH. Figure 4B (right) shows suspension 2a which was not resuspended after storage for 6 months upright at 30°C/65%RH.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term 'pharmaceutical composition' means a composition that is suitable for pharmaceutical use.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 1977, 66, 1-19, or those listed in P H Stahl and C G Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley-VCH/VHCA, 2011 (see http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html). Suitable pharmaceutically acceptable salts can include acid or base addition salts. Suitable pharmaceutically acceptable salts of the invention include base addition salts.

Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolildine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

As used herein, the term "treatment" or "treating" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression, invasion, or spread of the condition and reducing or delaying the reoccurrence of the condition in a previously afflicted subject.

As used herein, the term "prevention" or "preventing" refers to precluding the specified condition or symptoms of the condition.

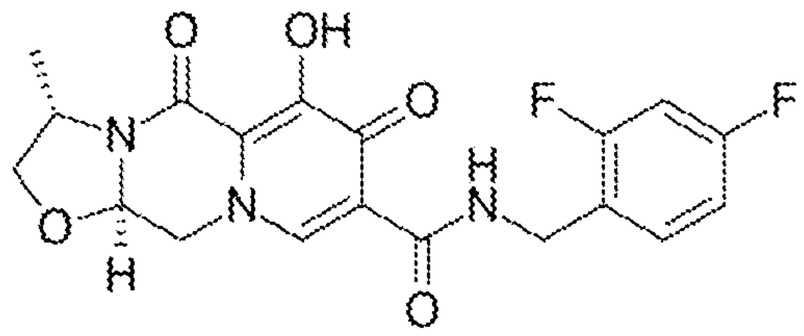
STATEMENT OF THE INVENTION

The present invention provides a pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

The pharmaceutical compositions described herein may be administered by any appropriate route. In a preferred embodiment, the compositions are administered parenterally (including subcutaneous, intramuscular, intravenous, or intradermal). In one embodiment the composition is administered intramuscularly. In another embodiment the composition is administered subcutaneously.

Cabotegravir (*N*-((2,4-Difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide) is described in US 8,129,385 in example Z-1, which example is incorporated herein by reference. Cabotegravir is an integrase strand transfer inhibitor (INSTI) that exhibits subnanomolar potency and antiviral activity against a broad range of HIV-1 strains. Oral administration of Cabotegravir has exhibited acceptable safety and tolerability profiles, a long half-life, and few drug-drug interactions. Cabotegravir has been demonstrated to be efficacious in treatment and prevention of HIV both in oral and parenteral dosage forms, see for instance, Margolis DA, Brinson CC, Eron JJ, et al. 744 and Rilpivirine as Two Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results. 21st Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA, Margolis DA, Podzamczer D, Stellbrink H-J, et al. Cabotegravir + Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 48 Results. 21st International AIDS Conference; July 18-22, 2016; Durban, South Africa, Abstract THAB0206LB. Levin: Conference reports for National AIDS Treatment Advocacy Project (NATAP); 2016, and Markowitz M, Frank I, Grant R, et al. ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Abstract presented at: 23rd Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2016; Boston, MA.

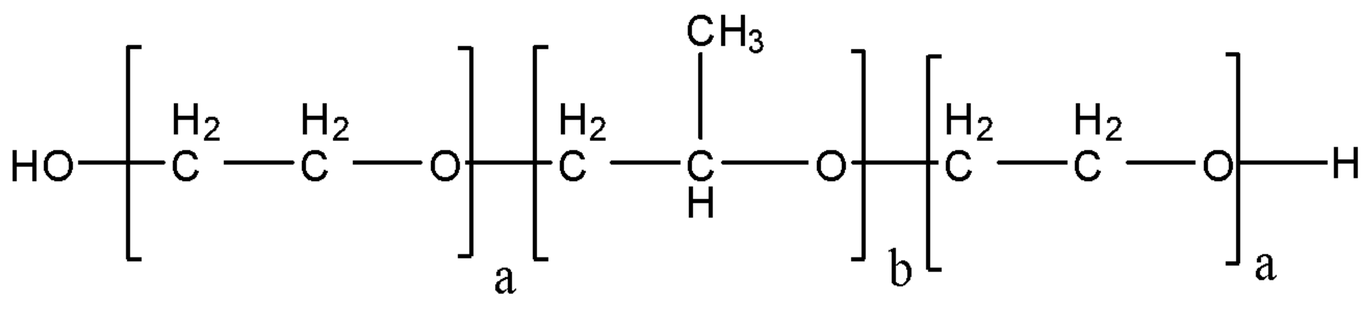
Cabotegravir is represented by formula (I):



(I)

In an embodiment of the invention, cabotegravir is present in the pharmaceutical composition as the free acid.

The pharmaceutical compositions of the invention comprise a poloxamer. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (polyethylene glycol). Poloxamers are represented by Formula II. Poloxamers are also known by the trade names Synperonics, Pluronics, and Kolliphor. Poloxamers are commonly named with the letter "P" followed by three digits, the first two digits x 100 give the approximate molecular mass of the polyoxypropylene core, and the last digit x 10 gives the percentage polyoxyethylene content (e.g., P407 = Poloxamer with a polyoxypropylene molecular mass of 4,000 g/mol and a 70% polyoxyethylene content).



(II)

In an embodiment of the invention, the poloxamer may have a molecular mass of polyoxypropylene from 2000 to 5000 g/mol, and a polyoxyethylene content of 60% to 90%.In an embodiment of the present invention, the poloxamer may be P237, P338 or P407 (a and b values for these poloxamers can be seen in Table 1). P237, P338 and P407 are commercially available.

Poloxamer	**a**	**b**
P237	64	37
P338	141	44
P407	101	56

Table 1

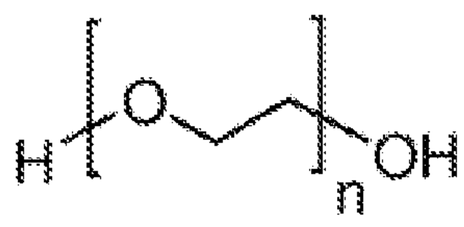
In an embodiment of the invention, the poloxamer is P237. In an embodiment the poloxamer is P407. In an embodiment the poloxamer is P338.

It is desirable to have a high concentration of cabotegravir in the composition (for example a cabotegravir concentration of around 400 or around 500 mg/mL). The inventors have found that the use of poloxamer in the composition allows a high concentration of cabotegravirto be present in the pharmaceutical composition. Cabotegravir is present in the composition in particle form. The inventors have found that at high particle concentrations, there are more particle to particle interactions. These particle to particle interactions can lead to an unstable suspension. Poloxamer has both hydrophobic and hydrophilic chains. It is thought that the hydrophobic polyoxypropylene

chains of poloxamer adsorb onto the surface of the cabotegravir particles and thus provide steric hinderance between particles. This provides stabilization against particle aggregation or flocculation. It is thought that the polyethylene glycol chains provide stabilisation through steric hinderance, thus allowing a higher concentration of cabotegravir to be present in the overall composition and minimising the particle to particle interactions usually associated with high particle concentrations.

The inventors have found that the use of poloxamer P237, P407 or P338 gives enhanced physical stability to the pharmaceutical compositions of the invention. Without wishing to be bound by theory, it is thought this enhanced stability comes from the fact that P237, P407 and P338 comprise more polyethylene glycol chains than other commercially available poloxamers.

The pharmaceutical compositions of the invention also comprise polyethylene glycol (PEG). PEG is a polymer of ethylene oxide and is represented by formula (III):



(III)

In embodiments of the invention, n may be any suitable number. In an embodiment of the invention PEG has a number average mean molecular weight (M_n) of from 1000 to 8000 g/mol. In an embodiment of the invention PEG has an M_n of from 2500 to 5000 g/mol. In an embodiment of the invention PEG has an M_n of from 3000 to 4000 g/mol. In an embodiment of the invention PEG has an M_n of 3100 to 3700 g/mol. In an embodiment of the invention, PEG is PEG 3350 *i.e.* PEG has an M_n of 3350 g/mol. PEG3350 is commercially available.

Without wishing to be bound by theory, the inventors believe that PEG acts as a stabilizer in the compositions of the present invention, further stabilizing the cabotegravir alongside the PEG chains that are present in the poloxamer. As a non-adsorbing polymer, it is thought that PEG stabilizes the compositions of the present invention through increase in viscosity and providing steric repulsions between particles in the suspension.

The combination of PEG and poloxamer enables the high cabotegravir concentration described above to be achieved. This enables the composition of the invention to treat HIV in a patient for up to 6 months. In an embodiment the composition of the invention can treat HIV in a patient for up to 3 months, therefore enabling dosing once every month, 2 months or 3 months. In an embodiment about 1 mL to 3 mL of the pharmaceutical composition is delivered to a patient. In comparison with known and proposed cabotegravir compositions, the present invention allows for a higher dose to be delivered to the patient with less frequent dosing while keeping injection volume the same as for previous products.

In an embodiment of the invention the composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 407. In an alternative embodiment of the invention, the pharmaceutical composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 338. In an alternative embodiment of the invention, the pharmaceutical composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 237.

In an embodiment of the invention, the pharmaceutical composition comprises from 350 to 600 mg/mL of cabotegravir. In an embodiment of the invention, the pharmaceutical composition comprises from 350 to 500 mg/mL of cabotegravir. In another embodiment, the pharmaceutical composition comprises 380 to 420 mg/mL of cabotegravir. In another embodiment, the pharmaceutical composition comprises about 400 mg/mL of cabotegravir. In an alternative embodiment the pharmaceutical composition comprises about 500 mg/mL of cabotegravir

In an embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 4 to 50 mg/mL. In another embodiment the pharmaceutical composition comprises a poloxamer concentration of from 20 to 50 mg/mL. In an embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 30 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 35 to 40 mg/mL.

As described above, the PEG chains in poloxamer provide stabilisation by steric hinderance, therefore it is possible that 0 mg/mL of PEG may be present in the composition. However, a composition comprising poloxamer and PEG provides additional stability to the composition, particularly particle size stability, and is preferred. A pharmaceutical composition comprising a polyethylene glycol concentration of 0 to 50 mg/mL. is disclosed herein.

In an embodiment of the invention, the pharmaceutical composition comprises a polyethylene glycol concentration of from more than 0 to 75 mg/mL. In another embodiment, the pharmaceutical composition comprises a PEG concentration of 5 to 50 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 20 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 30 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 32 to 38 mg/mL.

In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer.

In an embodiment of the invention the pharmaceutical composition is as described in Table 2a:

Ingredient	**Concentration (mg/mL)**
Cabotegravir	About 400.0
Poloxamer 338	4 – 50
Polyethylene Glycol 3350	>0 – 75
Mannitol	20 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)

Table 2a

In an embodiment, the pharmaceutical composition is as described in Table 2b:

Ingredient	**Concentration (mg/mL)**	**Lower allowed Concentration (mg/mL)**	**Higher allowed Concentration (mg/mL)**
Cabotegravir	400	320	500
Poloxamer 338	38	30	47.5
Polyethylene Glycol 3350	35	28	43.7
Mannitol	20	16	25

Table 2b

In a further embodiment, the composition is as described in Table 2c:

Ingredient	Concentration (mg/mL)	
Cabotegravir	About 500.0	About 500.0
Poloxamer 338	35 – 50	--
Poloxamer 407	--	35 – 50
Polyethylene Glycol 3350	>0 – 75	>0 – 75
Mannitol	40 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)	40 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)

Table 2c

The pharmaceutical composition of the present invention comprises particles of crystalline cabotegravir. In an embodiment the median particle diameter is from 0.1 µm to 10.0 µm. In another embodiment the median particle diameter is between 0.1 µm and 0.4 µm. In another embodiment the median particle diameter is from 0.15 µm to 0.25 µm. In another embodiment the median particle diameter is about 0.2 µm. The inventors have found that compositions with a median particle diameter of from 0.15 µm to 0.25 µm *e.g.* of about 0.2 µm have improved resuspension over compositions with larger particle sizes (as used here 'resuspension' means dispersion of sedimented product to a free-flowing suspension). The median particle diameter may be measured by any suitable method, for example, median particle diameter may be measured by laser diffraction (Malvern Mastersizer 3000) as described in the Examples section herein.

Pharmaceutical compositions of the present invention may retain their particle size over time. This is advantageous as increase in particle size can lead to poor resuspension. Poor resuspension can, for example, make it difficult for healthcare professionals to withdraw a pharmaceutical composition from, for example, a vial or flask. Particle size stability is believed to be important for resuspension of the composition over time and reduces the risk of changing pharmacokinetics.

In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer, wherein the median particle diameter of cabotegravir is from 0.1 µm to 10.0 µm.

In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer, wherein the median particle diameter of cabotegravir is from 0.15 µm to 0.25 µm.

In an embodiment the composition of the invention further comprises a tonicity adjuster. The tonicity adjuster may be selected from any suitable tonicity adjuster. In an embodiment of the invention, the tonicity adjuster adjusts tonicity to be within 250 to 350 mOsmol/kg. In another embodiment the tonicity adjuster adjusts tonicity to be within 285 to 310 mOsmol/kg. In an embodiment mannitol is used as the tonicity adjuster. In an embodiment of the invention, the mannitol adjusts tonicity to be within 250 to 350 mOsmol/kg. In another embodiment the mannitol

adjusts tonicity to be within 285 to 310 mOsmol/kg. In an embodiment of the invention mannitol is present in the pharmaceutical composition at a concentration of 15 to 30 mg/mL.

In an embodiment the composition of the invention has a pH of about 4 or greater. A pH of about 4 or more reduces pain to the patient if the composition is administered via injection.

In an embodiment the pharmaceutical composition of the present invention further comprises at least one hyaluronidase. As used herein, the term 'hyaluronidase' refers to any enzyme of the family of hyaluronidases that catalyse the degradation of hyaluronic acid, a constituent of the extracellular matrix. Degradation of hyaluronic acid causes subcutaneous and intramuscular tissues to become more permeable allowing fluid or medication to diffuse into the extracellular matrix and be taken up by the surrounding tissue more quickly. Without wishing to be bound by theory, it is thought that administrating a pharmaceutical composition of the present invention in combination with a hyaluronidase may allow administration of a larger volume of the pharmaceutical composition thus allowing dosing frequency to be reduced. In addition, it is believed that the use of at least one hyaluronidase will provide an improved tolerability for the pharmaceutical composition at the site of administration.

In a second aspect, the present invention provides a method for the treatment or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising administering to said human a therapeutically effective amount of a pharmaceutical composition as defined herein.

In one embodiment the method comprises administering the pharmaceutical composition parenterally. In an embodiment the pharmaceutical composition is administered intramuscularly. In an embodiment the pharmaceutical composition is administered subcutaneously.

In an embodiment around 1mL to around 3 mL of the pharmaceutical composition is administered to the human. In an embodiment around 1mL of the pharmaceutical composition is administered to the human. In another embodiment around 2 mL of the pharmaceutical composition is administered to the human. In an embodiment around 3 mL of the pharmaceutical composition is administered to the human.

In an embodiment the pharmaceutical composition is administered to the human once every 1, 2 or 3 months. In an embodiment the pharmaceutical composition is administered to the human once every month. In an alternative embodiment, the pharmaceutical composition is administered once every 2 months. In an alternative embodiment the pharmaceutical composition is administered once every 3 months.

In one embodiment, the pharmaceutical composition is delivered to a patient once every month. The pharmaceutical composition may be administered by any suitable means. In one embodiment, the pharmaceutical composition is self-administered by a patient. The term "self-administered", as used herein, means administration by someone other than a healthcare professional, for example, a patient may administer the pharmaceutical composition to themselves, or someone else, other than a healthcare professional may administer the pharmaceutical composition to the patient. In this embodiment the pharmaceutical composition may be administered subcutaneously via injection. The subcutaneous injection may comprise 1 to 1.5 mL of the pharmaceutical composition. In one embodiment of the invention the pharmaceutical composition is self-administered once monthly by subcutaneous injection.

In an alternative embodiment the pharmaceutical composition is delivered to a patient once every three months. The pharmaceutical composition may be administered by any suitable means. In one embodiment the pharmaceutical composition is administered intramuscularly via injection. In an embodiment the intramuscular injection is administered by a healthcare professional. The intramuscular injection may comprise 1 to 3 mL of the pharmaceutical

composition. In an embodiment of the invention the pharmaceutical composition is administered once every 3 months via intramuscular injection.

In an embodiment the pharmaceutical compositions of the present invention are administered in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

In an embodiment a pharmaceutical compound described herein is administered in combination with a broadly neutralising antibody. In an embodiment the neutralising antibody is N6-LS. N6-LS is a broadly neutralising antibody, which comprises (a) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region (HCDR)1, a HCDR2, and a HCDR3 of the VH set forth as SEQ ID NO: 1; (b) a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1, a LCDR2, and a LCDR3 of the VL set forth as SEQ ID NO: 2 or a VL comprising an amino acid sequence at least 90 percent identical to one of SEQ ID NO: 2; or (c) a combination of (a) and (b); further comprising an IgGl constant domain comprising M428L and N434S mutations; and wherein the antibody or antigen binding fragment specifically binds to HIV-1 gpl20 and neutralizes HIV-1 infection.

SEQ ID NO: 1 is the amino acid sequence of the VH of the N6 mAb disclosed in patent application PCT/US2016/023145. SEQ ID NO: 2 is the amino acid sequence of the VL of the N6 mAb disclosed in patent application PCT/US2016/023145. SEQ ID NO: 1 and SEQ ID NO: 2 are described below:

SEQ ID NO 1:

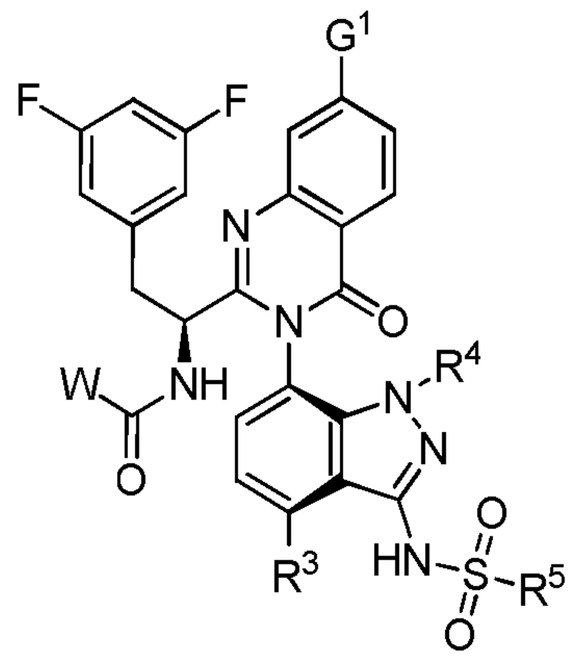
RAHLVQSGTAMKKPGASVRVSCQTSGYTFTAHILFWFRQAPGRGLEWVGWIKPQYGAVNFGGGFRDRVTL TRDVYREIAYMDIRGLKPDDTAVYYCARDRSYGDSSWALDAWGQGTTVWSA

SEQ ID NO: 2:

YIHVTQSPSSLSVSIGDRVTINCQTSQGVGSDLHWYQHKPGRAPKLLIHHTSSVEDGVPSRFSGSGFHTS FNLTISDLQADDIATYYCQVLQFFGRGSRLHIK

In an embodiment, a pharmaceutical composition described herein is administered in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI).

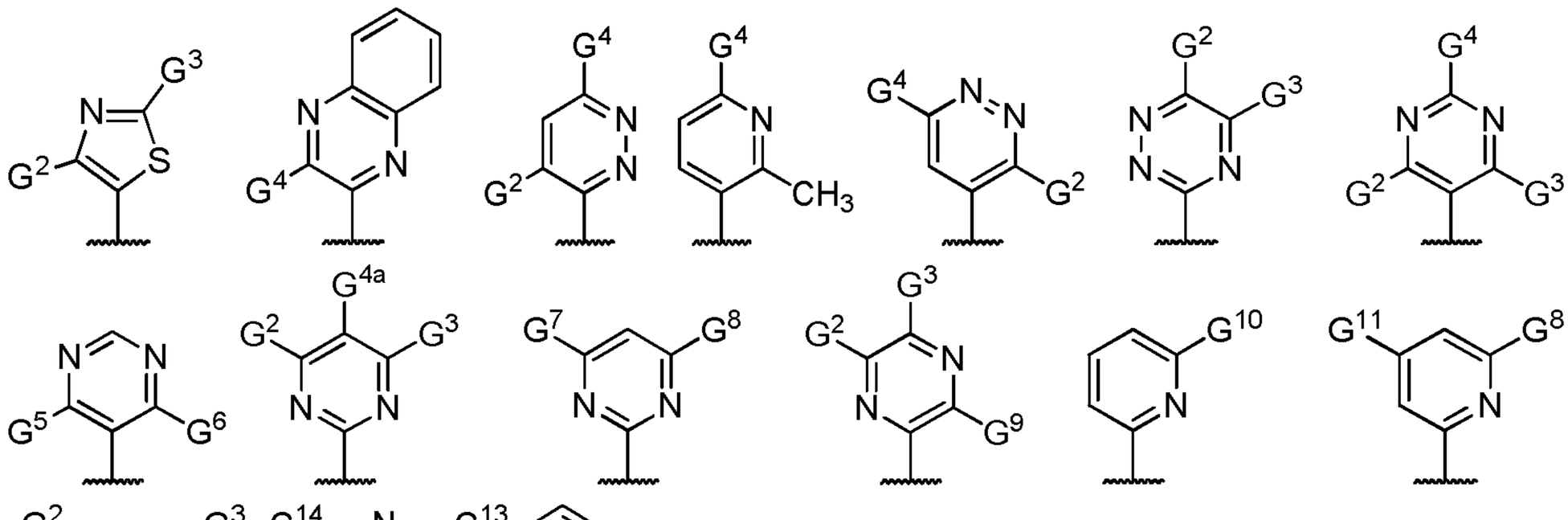
The pharmaceutical composition may be administered in combination with a capsid inhibitor. In an embodiment the capsid inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof:

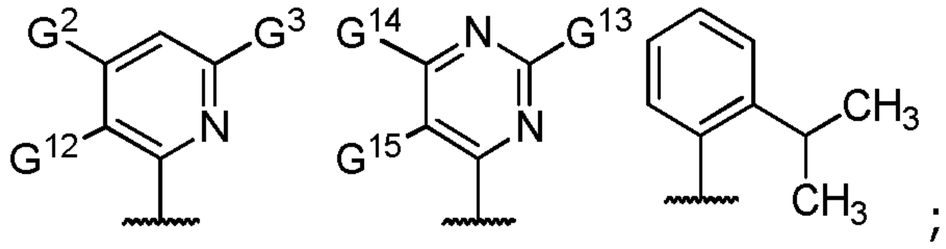


Formula I

wherein:

G1 is phenyl substituted once with -N(CH3)S(O2)CH3, -S(O2)C(CH3)3, -CHF2, -CF3, -OCHF2, -OCF3, or -C(CH3)2OH, with the proviso that when G1 is -CHF2 or CF3, G1 is not in the para position or G1 is one of the following:





;

G^2 and G^3 are independently selected from is H or -CH_3;

G^4 is H, -CH_3, or -OCH_3;

G^{4a} is -CH_3, or -OCH_3;

G^5 is -CH_3, or CH_2CH_3;

G^6 is H, -CH_3, or CH_2CH_3;

G^7 is ethyl, isopropyl, *tert*-butyl, -CHF_2, or -CF_3;

G^8 is H, methyl, ethyl, -CHF_2, -CF_3, -OCH_3, or -OCH_2CH_3;

G^9 is ethyl, isopropyl, cyclopropyl, -CH_2OH, -OCH_3;

G^{10} is ethyl, isopropyl, cyclopropyl, *tert*-butyl, -CHF_2, or -CF_3;

G^{11} is methyl, -OCH_3, -CHF_2, -CF_3, -$S(O_2)CH_3$;

G^{12} is F, -CH_3, -CHF_2, -CF_3, -OCH_3, -$S(O_2)CH_3$;

G^{13} is C_1-C_4alkyl, C_1-C_6cycloalkyl, -$CH_2O(C_1$-C_3alkyl);

G^{14} is H, C_1-C_4alkyl, -CHF_2, -CF_3, -$O(C_1$-C_3alkyl);

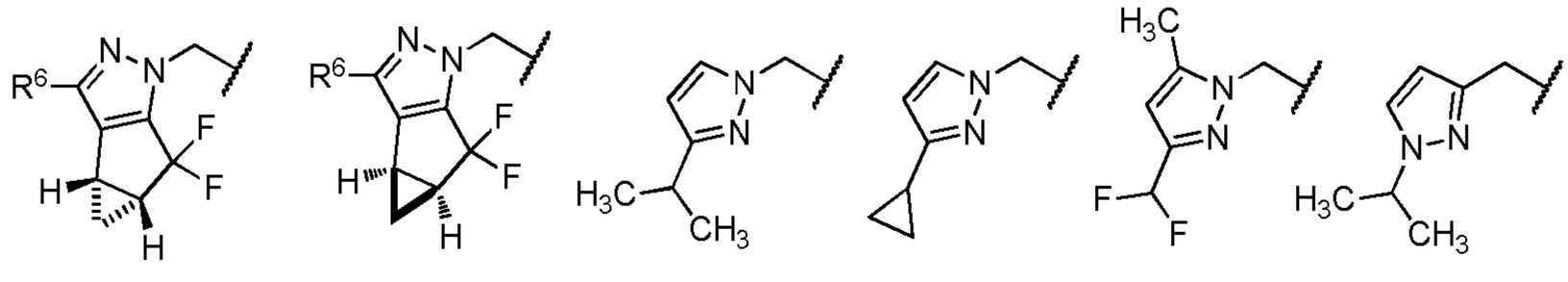
G^{15} is H, F, -CH_3, or OCH_3;

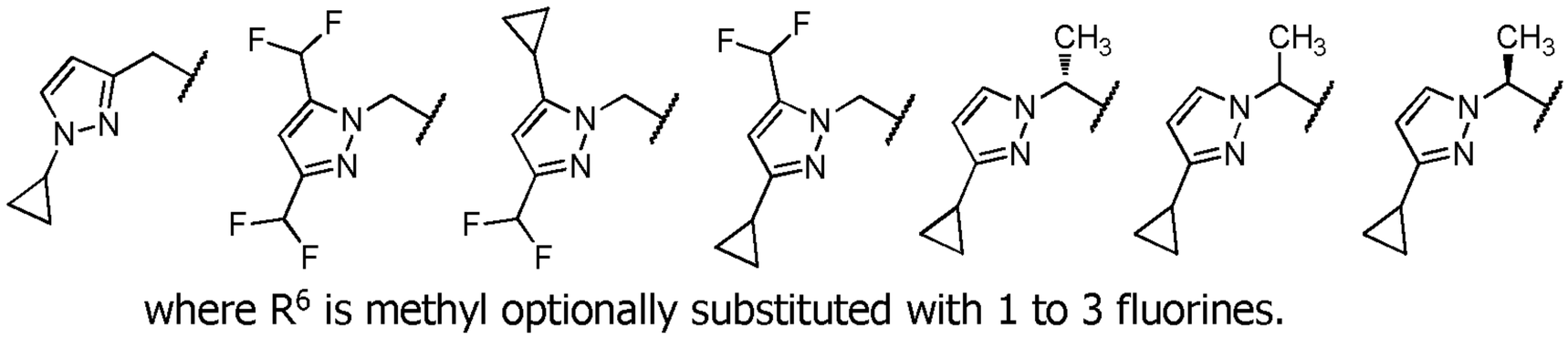
R^3 is H, F, Cl, -CH_3, or -OCH_3;

R^4 is H or C_1-C_3alkyl wherein C_1-C_3alkyl is optionally substituted with 1-3 fluorines;

R^5 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

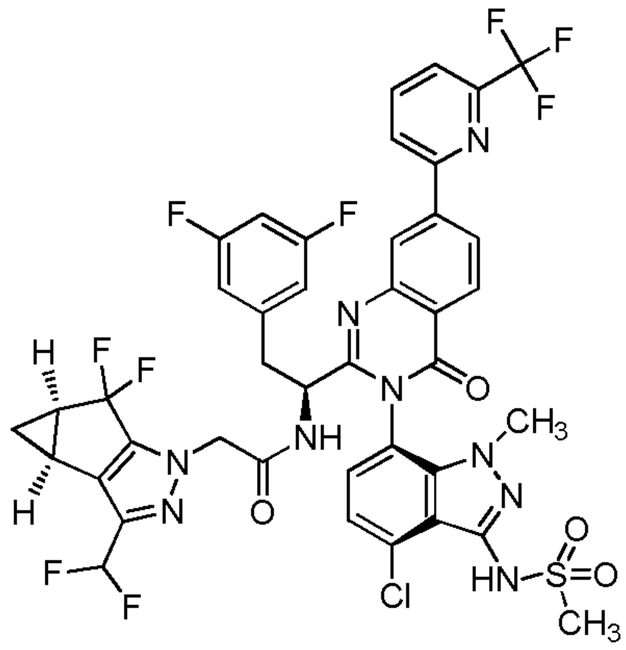
W is selected from:





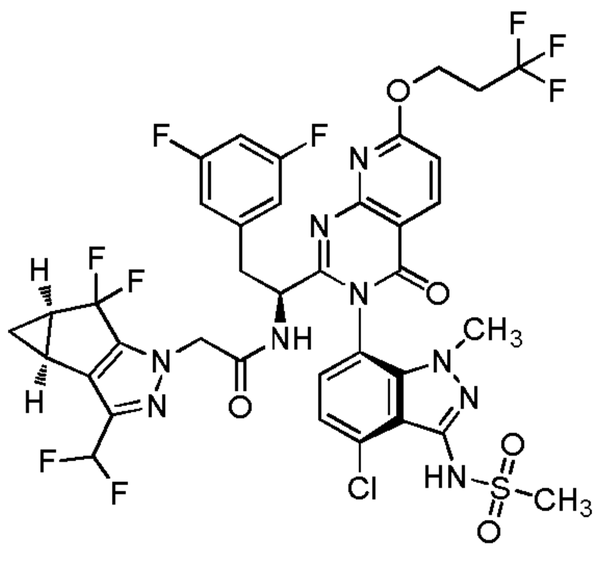
where R^6 is methyl optionally substituted with 1 to 3 fluorines.

Compounds of Formula I are described in WO2020/084492 which is incorporated by reference. In an embodiment the capsid inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is described in WO 2020/084492 as Example 59 which example is incorporated herein by reference.



Compound 1.

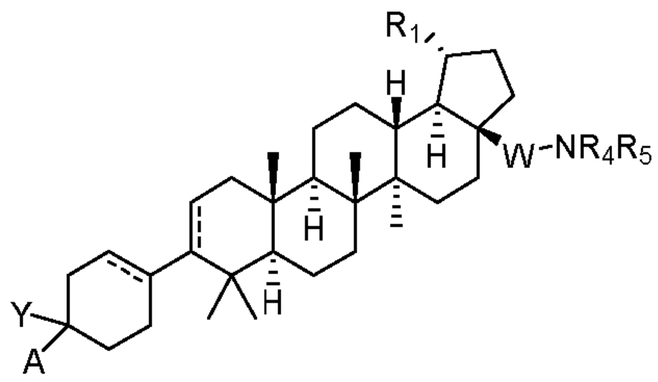
In an embodiment the capsid inhibitor is Compound 2 pharmaceutically acceptable salt thereof. Compound 2 is described in patent application number PCT/IB2020/055653 as Example 1, which example is incorporated herein by reference.



Compound 2.

In an alternative embodiment, the capsid inhibitor is Lenacapravir.

The pharmaceutical composition may be administered in combination with a maturation inhibitor. In an embodiment the maturation inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof:



Formula II

wherein R_1 is isopropenyl or isopropyl;

A is -C_{1-6} alkyl-OR_0;

wherein R_0 is heteroaryl-Q_0;

Q_0 is selected from the group of -H, -CN, -C_{1-6} alkyl, -COOH, -Ph, -OC_{1-6} alkyl, -halo, -CF_3,

Y is selected from the group of -$COOR_2$, -$C(O)NR_2SO_2R_3$, -$C(O)NHSO_2NR_2R_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,

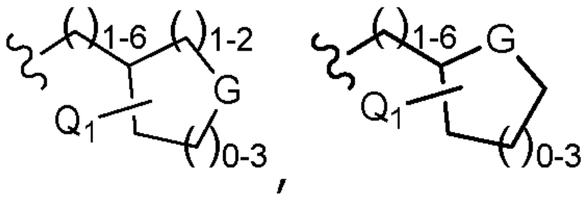
wherein n = 1-6;

R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

W is absent, or is -CH_2- or -CO-;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} substituted -C_{1-6} alkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -SO_2R_7, -$SO_2NR_2R_2$, and



wherein G is selected from the group of –O-, -SO_2- and -NR_{12}-;

wherein Q_1 is selected from the group of -C_{1-6} alkyl, - C_{1-6} fluoroalkyl, heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_8R_9$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_3, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 is not -COR_6 when W is -CO-;

with the further proviso that only one of R_4 or R_5 is selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

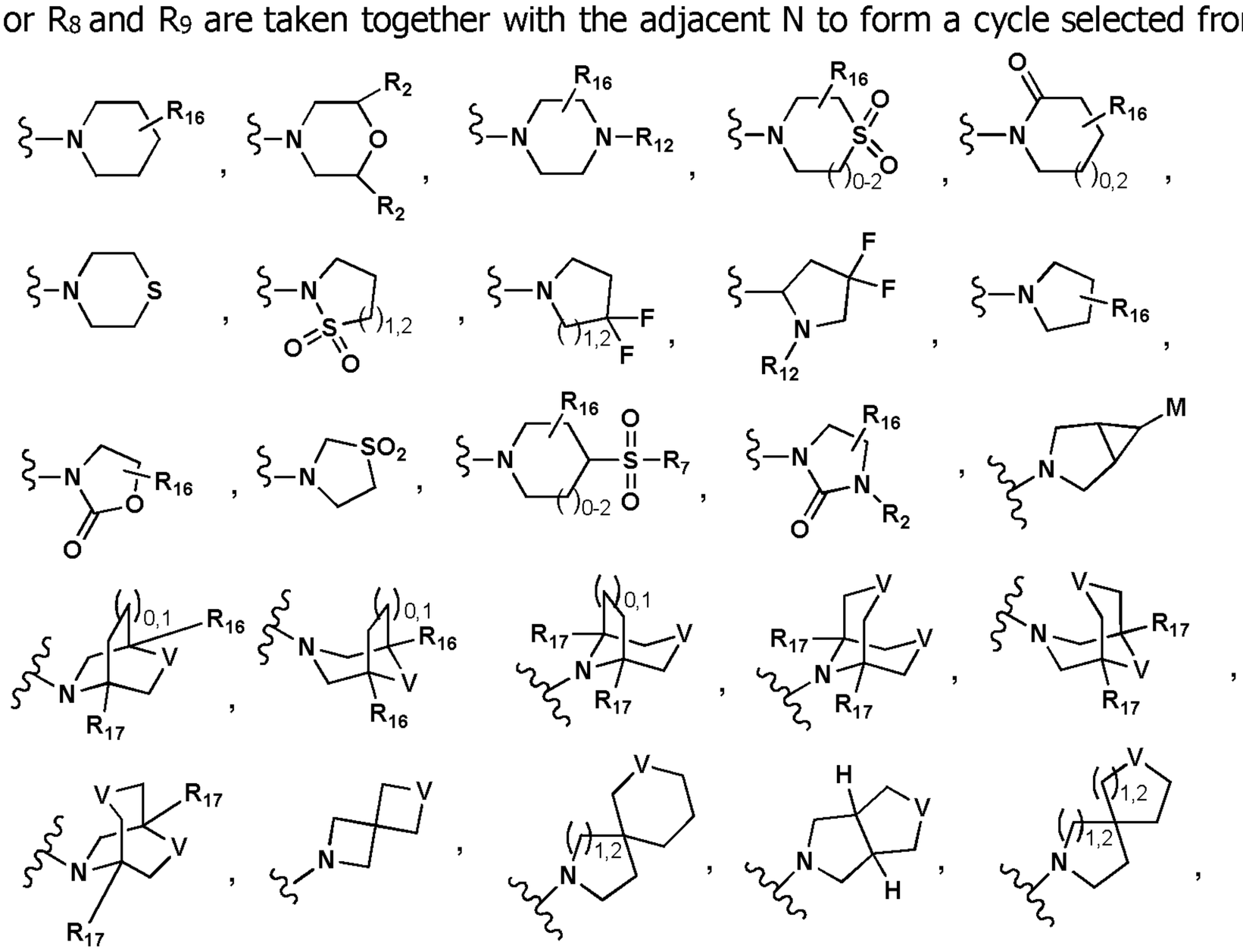
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

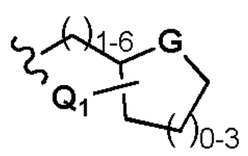
R_7 is selected from the group of –H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, -CF_3, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



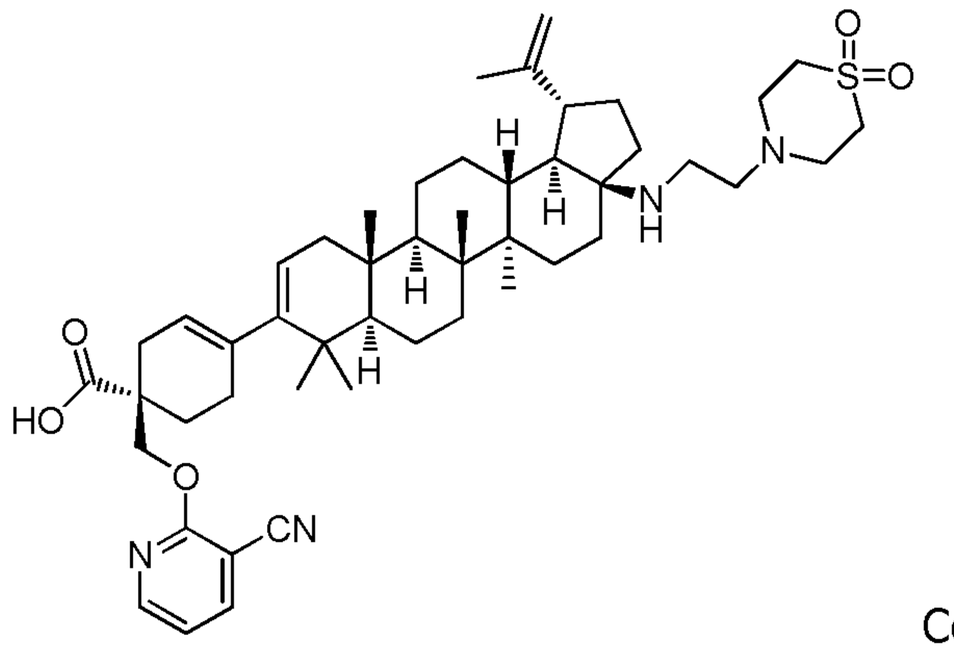
and



;

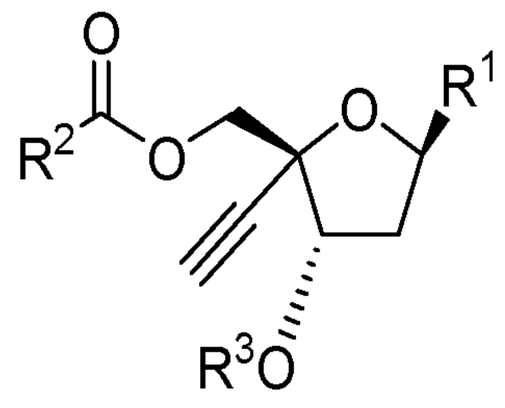
M is selected from the group of –R_{15}, -SO_2R_2, -$SO_2NR_2R_2$, -OH and –NR_2R_{12};
V is selected from the group of –$CR_{10}R_{11}$-, -SO_2-, -O- and –NR_{12}-;
with the proviso that only one of R_8 or R_9 can be -$COOR_3$;
R_{10} and R_{11} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl and -C_{3-6} cycloalkyl;
R_{12} is selected from the group of -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl, -$CONR_2R_2$, -SO_2R_3, and -$SO_2NR_2R_2$;
R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, and C_{1-6} substituted alkyl-Q_3;
Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -NR_2R_{12}, -$CONR_2R_2$, -$COOR_2$, -OR_2, and -SO_2R_3;
R_{15} is selected from the group of -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3 and -C_{1-6} substituted alkyl-Q_3;
R_{16} is selected from the group of -H, -C_{1-6} alkyl, -NR_2R_2, and –$COOR_2$;
with the proviso that when V is –NR_{12}-; R_{16} is not –NR_2R_2; and
R_{17} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl.

Compounds of Formula II are described in WO 2017/134596 which is incorporated herein by reference. In an embodiment the maturation inhibitor is Compound 3. Compound 3 is described in WO 2017/134596 as Example 25 which example is incorporated herein by reference.



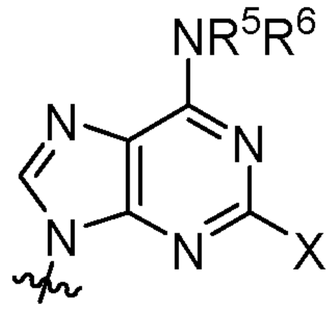
Compound 3.

The pharmaceutical composition may be administered in combination with an NRTTI. In an embodiment the NRTTI is a compound of the formula 3:



Formula 3

wherein:
R^1 is:



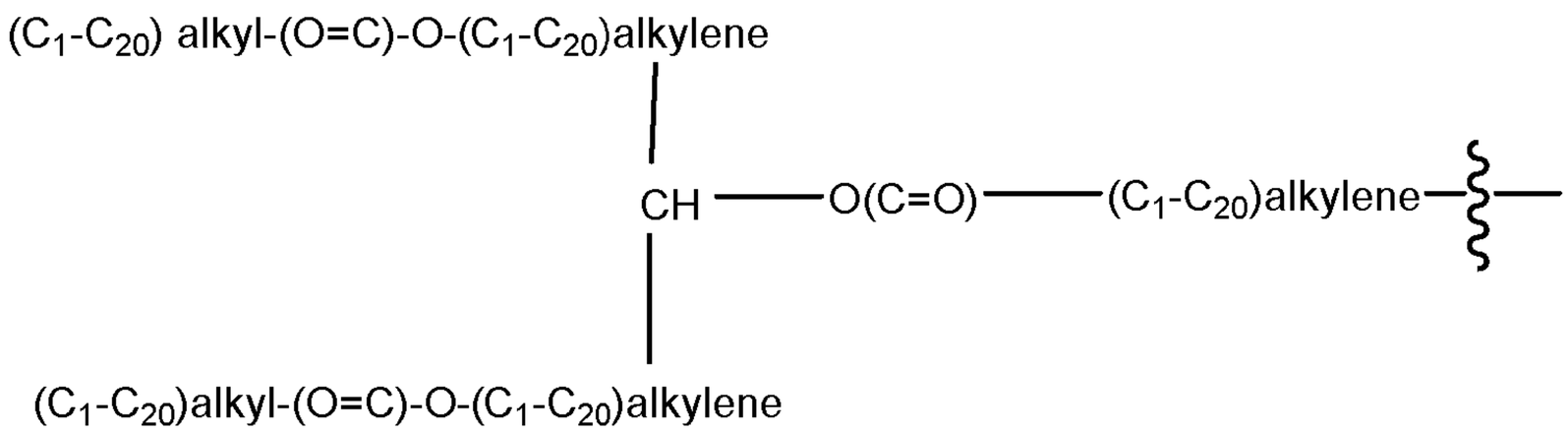
wherein:

X is selected from the group consisting of NH_2, F and Cl;

R^5 is selected from the group consisting of H and (C_1-C_{14}) alkyl;

R^6 is selected from the group consisting of H and -(C=O)-(C_1-C_{14}) alkyl;

R^2 is selected from the group consisting of (C_1-C_{24}) alkyl; $(CH_2)_{n1}$-O-$(CH_2CH_2O)_{n2}$-(C_1-C_{14} alkyl) where n1 and n2 are integers independently selected from 1-4; -R^7-NH-(C=O)-R^8 wherein R^7 may be (C_1-C_{14}) alkyl and R^8 may be independently selected from H and (C_1-C_{14}) alkyl; -R^9-(C_6-C_{14}) aryl, wherein R^9 is a bond or (C_1-C_6) alkyl; -R^{10}-(C_3-C_{14}) cycloalkyl, wherein R^{10} is a bond or (C_1-C_6) alkyl; -(C_1-C_{20}) alkylene-(C=O)-O-R^{11} wherein R^{11} may be selected from H and (C_1-C_{20})alkyl;



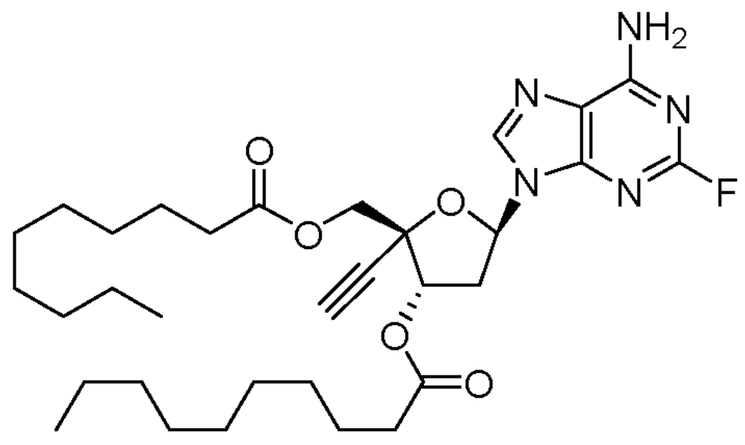
and;

R^3 is selected from the group consisting of H, -(C=O)-(C_1-C_{24}) alkyl; -(C=O)-O-(C_1-C_{24}) alkyl; and C_3-C_{14} cycloalkyl; or

R^2 and R^3 join together to form a C_3 to C_{28} cyclic structure; and

with the proviso that when R^2 is (C_1-C_{14} alkyl) at least one of R^3, R^5 and R^6 is not H.

Compounds of Formula 3 are disclosed in WO 2020/178767 which is incorporated by reference herein. In an embodiment a pharmaceutical composition of the invention is combined with Compound 4. Compound 4 is described in WO 2020/178767 as Example 18, which example is incorporated by reference herein.



Compound 4

In an alternative embodiment the NRTTI is Islatravir.

In an embodiment of the invention the pharmaceutical compositions of the present invention are administered in combination with hyaluronidase. In one embodiment the pharmaceutical compositions of the present invention and the hyaluronidase are administered sequentially. The hyaluronidase may be administered subcutaneously or intramuscularly via injection. In one embodiment the hyaluronidase is administered prior to the administration of the pharmaceutical composition. In this embodiment the pharmaceutical composition is administered as close as possible to the site of the injection of hyaluronidase. It is thought that the hyaluronidase increases the permeability of the injection site tissues to the pharmaceutical compositions.

In a third aspect, the present invention provides a pharmaceutical composition defined herein for use in the treatment or prevention of HIV.

In one embodiment, the pharmaceutical composition is suitable for use as an injectable composition. In one embodiment the use comprises administering the pharmaceutical composition

parenterally. In an embodiment the use comprises administering the pharmaceutical composition intramuscularly. In another embodiment the use comprises administering the pharmaceutical composition subcutaneously.

In an embodiment the use comprises administering around 1mL to around 3 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 1mL of the pharmaceutical composition to a patient. In another embodiment the use comprises administering around 2 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 3 mL of the pharmaceutical composition to a patient.

In an embodiment the use comprises administering the pharmaceutical to a patient once every 1, 2 or 3 months. In an embodiment the use comprises administering the pharmaceutical composition to a patient once every month. In an alternative embodiment, the use comprises administering the pharmaceutical composition once every 2 months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every 3 months.

In one embodiment, the use comprises delivering the the pharmaceutical composition to a patient once every month. In this embodiment, the pharmaceutical composition may be administered by any suitable means. The pharmaceutical composition may be self-administered by a patient. In this embodiment the pharmaceutical composition may be administered subcutaneously via injection. The subcutaneous injection may comprise 1 to 1.5 mL of the pharmaceutical composition. In one embodiment of the invention the pharmaceutical composition is self-administered once monthly by subcutaneous injection.

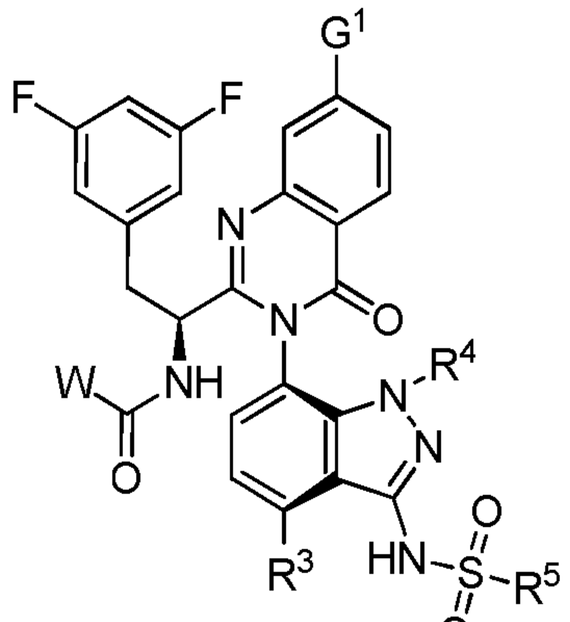
In an alternative embodiment the use comprises delivering the pharmaceutical composition to a patient once every three months. In this embodiment, the pharmaceutical composition may be administered by any suitable means. The pharmaceutical composition may be administered intramuscularly via injection. In an embodiment the intramuscular injection is administered by a healthcare professional. The intramuscular injection may comprise 2.5 to 3 mL of the pharmaceutical composition. In an embodiment of the invention the pharmaceutical composition is administered once every 3 months by intramuscular injection.

In an embodiment of the invention use comprises administering the pharmaceutical compositions of the present invention in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with N6-LS. N6-LS is described above.

In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI).

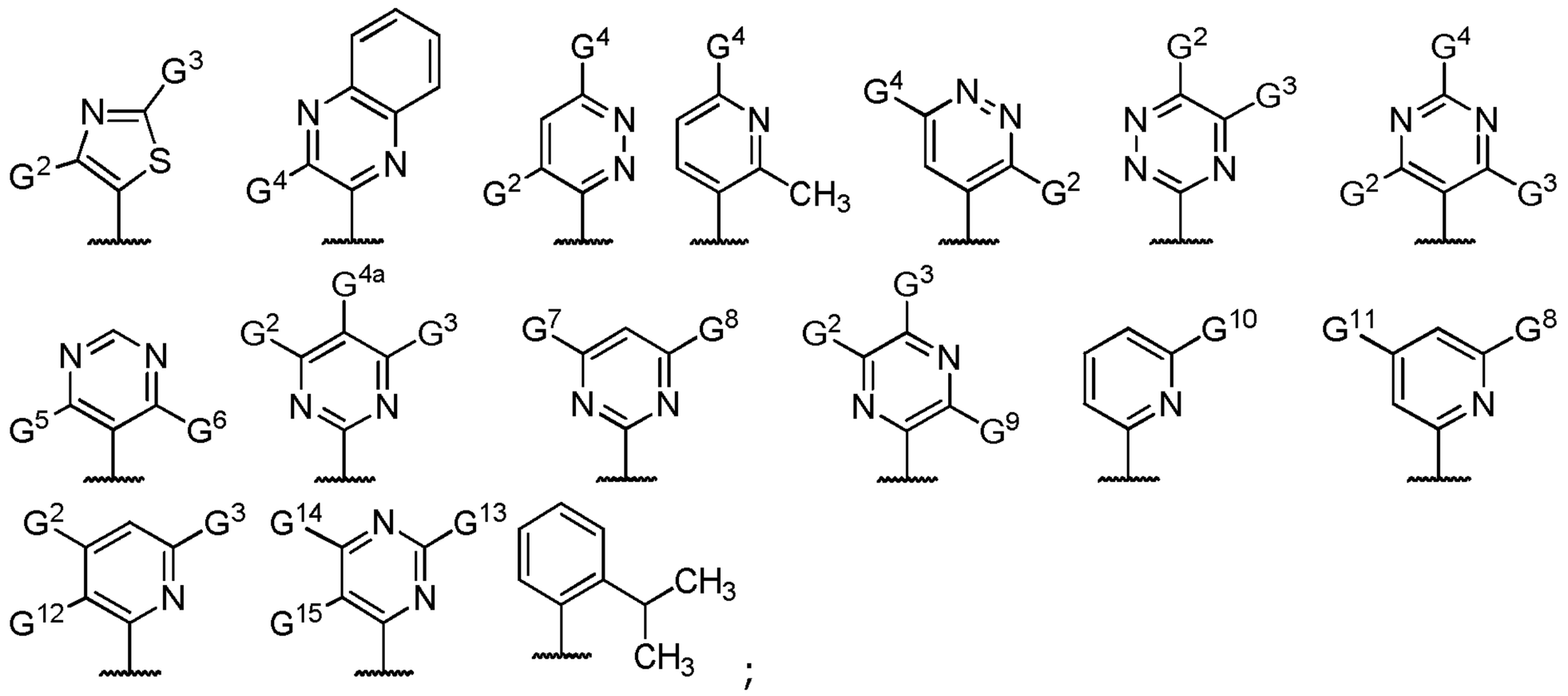
The pharmaceutical composition may be administered in combination with a capsid inhibitor. In an embodiment the capsid inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

G1 is phenyl substituted once with -N(CH3)S(O2)CH3, -S(O2)C(CH3)3, -CHF2, -CF3, -OCHF2, -OCF3, or -C(CH3)2OH, with the proviso that when G1 is -CHF2 or CF3, G1 is not in the para position or G1 is one of the following:



;

G^2 and G^3 are independently selected from is H or -CH_3;

G^4 is H, -CH_3, or -OCH_3;

G^{4a} is -CH_3, or -OCH_3;

G^5 is -CH_3, or CH_2CH_3;

G^6 is H, -CH_3, or CH_2CH_3;

G^7 is ethyl, isopropyl, *tert*-butyl, -CHF_2, or -CF_3;

G^8 is H, methyl, ethyl, -CHF_2, -CF_3, -OCH_3, or -OCH_2CH_3;

G^9 is ethyl, isopropyl, cyclopropyl, -CH_2OH, -OCH_3;

G^{10} is ethyl, isopropyl, cyclopropyl, *tert*-butyl, -CHF_2, or -CF_3;

G^{11} is methyl, -OCH_3, -CHF_2, -CF_3, -$S(O_2)CH_3$;

G^{12} is F, -CH_3, -CHF_2, -CF_3, -OCH_3, -$S(O_2)CH_3$;

G^{13} is C_1-C_4alkyl, C_1-C_6cycloalkyl, -$CH_2O(C_1$-C_3alkyl);

G^{14} is H, C_1-C_4alkyl, -CHF_2, -CF_3, -$O(C_1$-C_3alkyl);

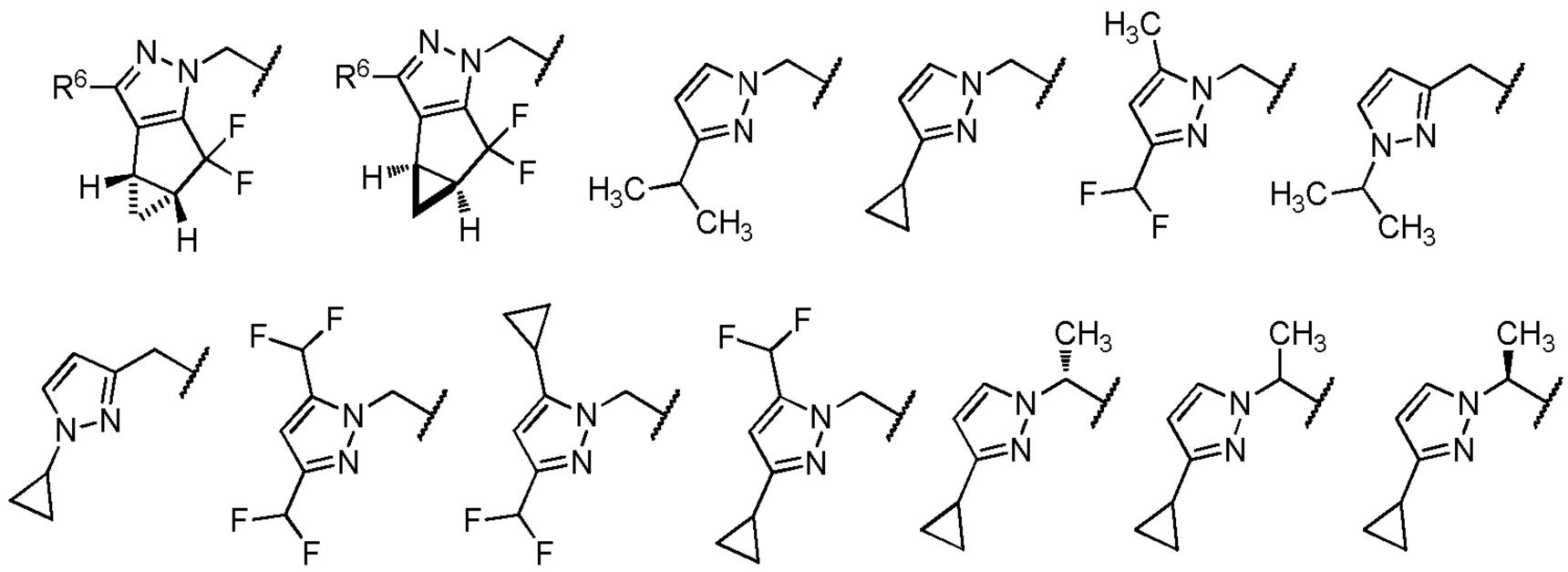
G^{15} is H, F, -CH_3, or OCH_3;

R^3 is H, F, Cl, -CH_3, or -OCH_3;

R^4 is H or C_1-C_3alkyl wherein C_1-C_3alkyl is optionally substituted with 1-3 fluorines;

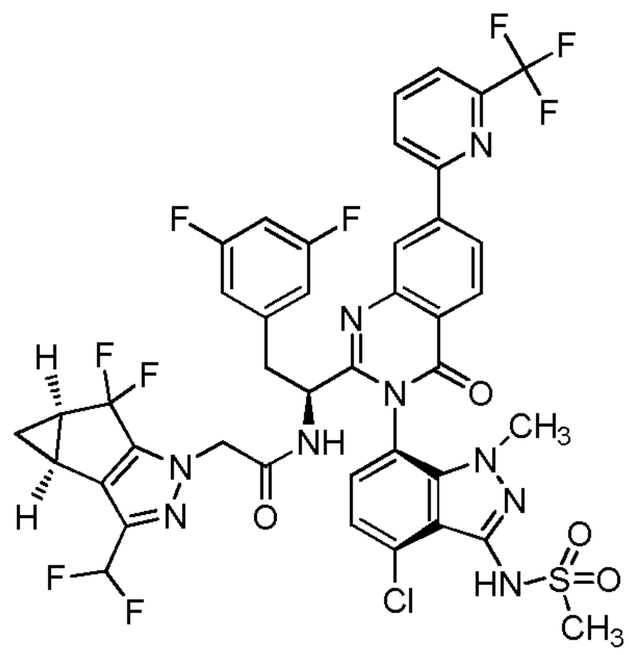
R^5 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

W is selected from:



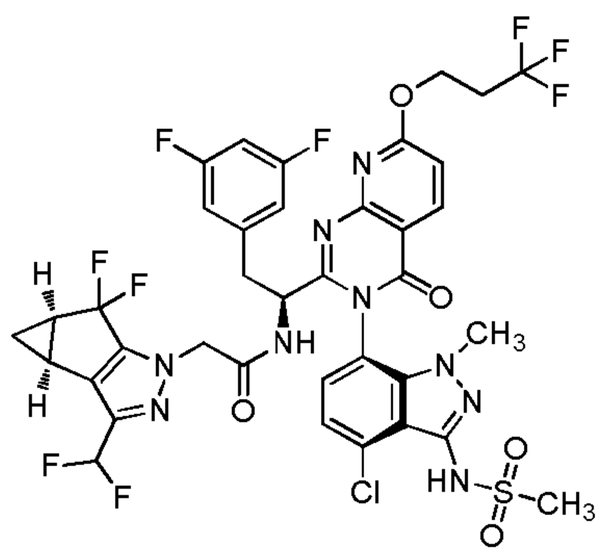
where R^6 is methyl optionally substituted with 1 to 3 fluorines.

Compounds of Formula I are described in WO2020/084492 which is incorporated by reference. In an embodiment the capsid inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is described in WO 2020/084492 as Example 59 which example is incorporated herein by reference.



Compound 1.

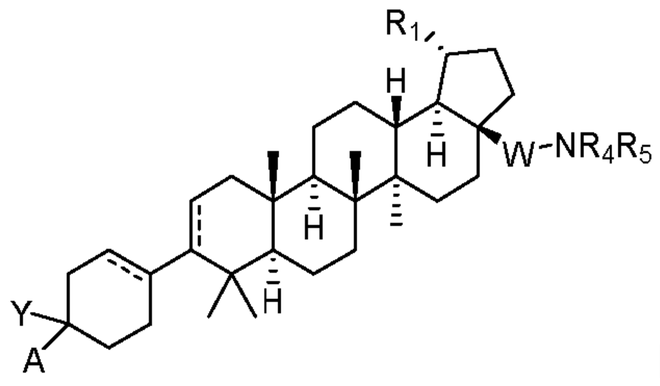
In an embodiment the capsid inhibitor is Compound 2 pharmaceutically acceptable salt thereof. Compound 2 is described in patent application number PCT/IB2020/055653 as Example 1, which example is incorporated herein by reference.



Compound 2.

In an alternative embodiment the capsid inhibitor is lenacapravir.

The pharmaceutical composition may be administered in combination with a maturation inhibitor. In an embodiment the maturation inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof:



Formula II

wherein R_1 is isopropenyl or isopropyl;

A is -C_{1-6} alkyl-OR_0;

wherein R_0 is heteroaryl-Q_0;

Q_0 is selected from the group of -H, -CN, -C_{1-6} alkyl, -COOH, -Ph, -OC_{1-6} alkyl, -halo, -CF_3,

Y is selected from the group of -$COOR_2$, -$C(O)NR_2SO_2R_3$, -$C(O)NHSO_2NR_2R_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,

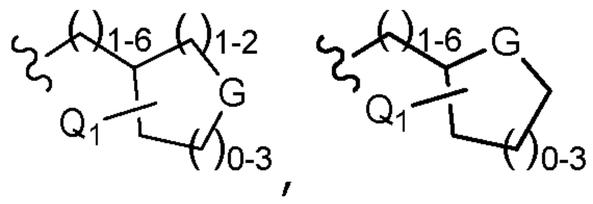
wherein n = 1-6;

R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

W is absent, or is -CH_2- or -CO-;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} substituted -C_{1-6} alkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -SO_2R_7, -$SO_2NR_2R_2$, and



wherein G is selected from the group of –O-, -SO_2- and -NR_{12}-;

wherein Q_1 is selected from the group of -C_{1-6} alkyl, - C_{1-6} fluoroalkyl, heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_8R_9$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_3, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 is not -COR_6 when W is -CO-;

with the further proviso that only one of R_4 or R_5 is selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

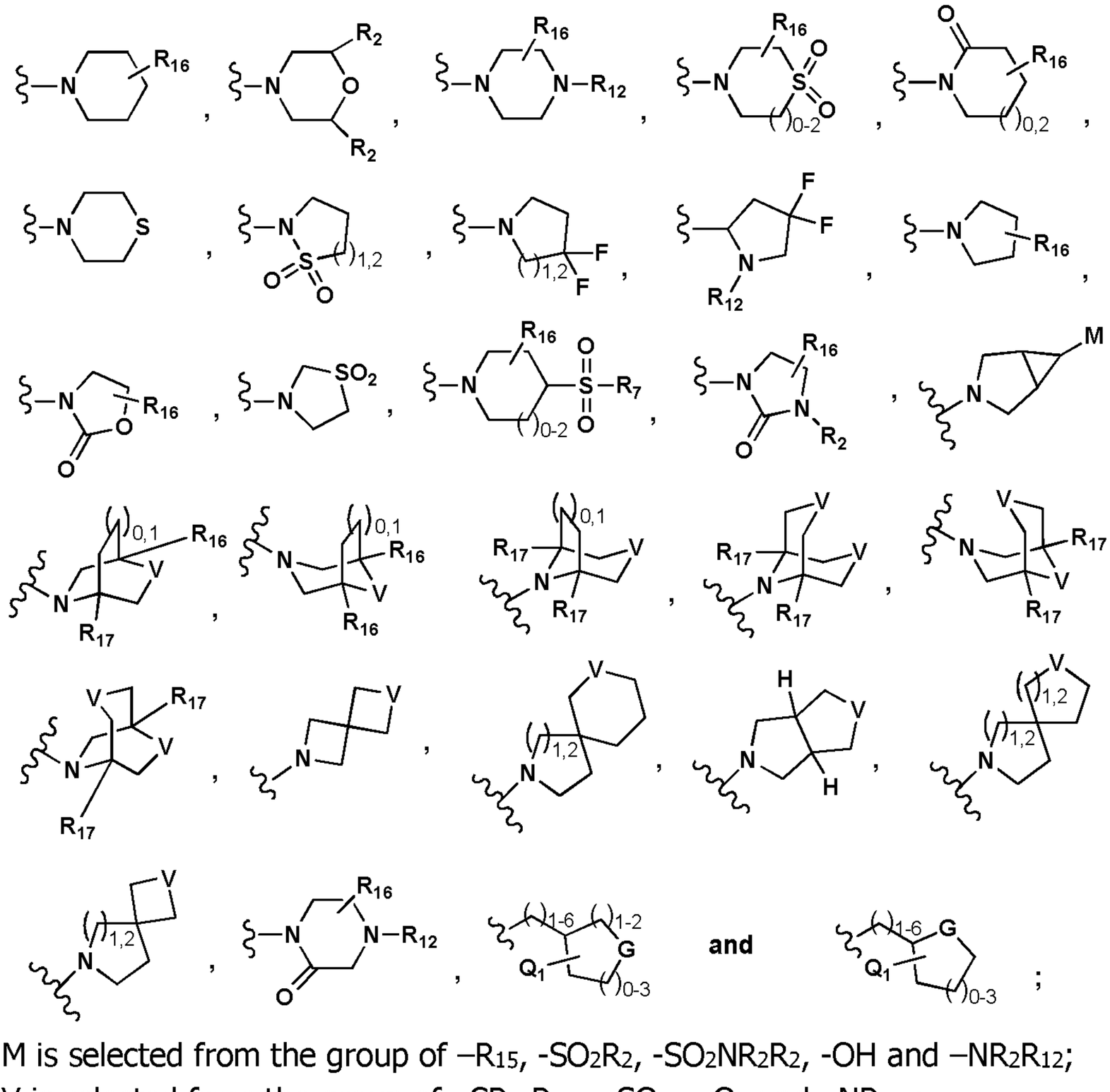
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_7 is selected from the group of –H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, -CF_3, aryl, and heteroaryl;

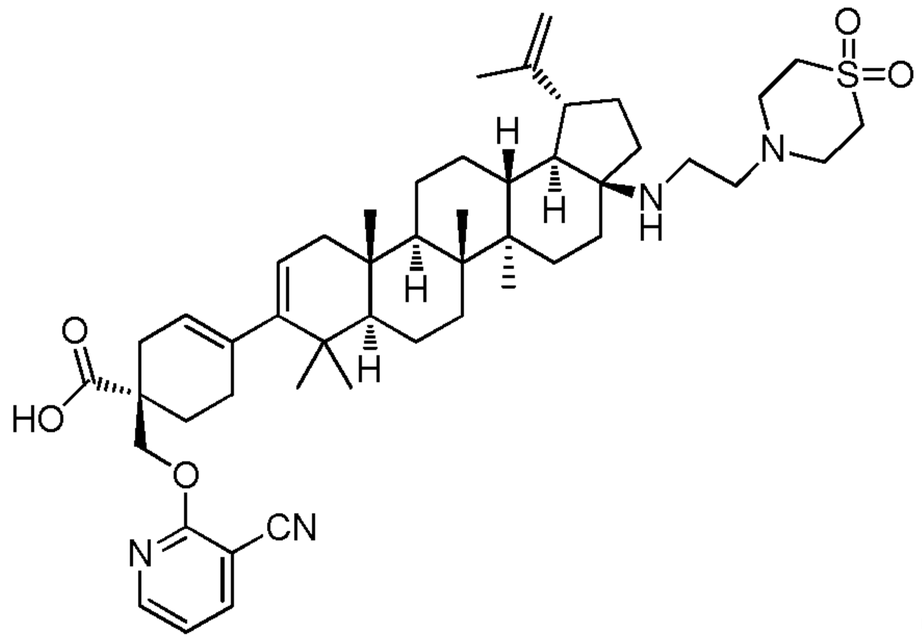
R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



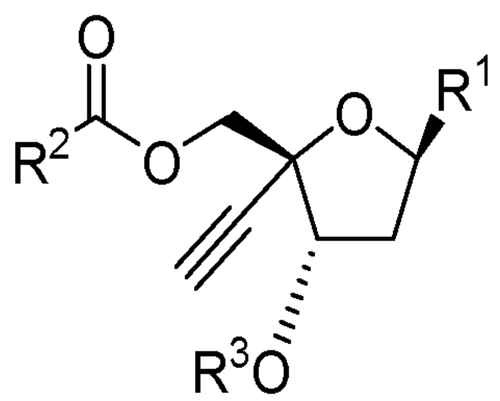
M is selected from the group of $-R_{15}$, $-SO_2R_2$, $-SO_2NR_2R_2$, -OH and $-NR_2R_{12}$;
V is selected from the group of $-CR_{10}R_{11}$-, $-SO_2$-, -O- and $-NR_{12}$-;
with the proviso that only one of R_8 or R_9 can be $-COOR_3$;
R_{10} and R_{11} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl;
R_{12} is selected from the group of -H, $-C_{1-6}$ alkyl, -alkylsubstituted C_{1-6} alkyl, $-CONR_2R_2$, $-SO_2R_3$, and $-SO_2NR_2R_2$;
R_{13} and R_{14} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3, and C_{1-6} substituted alkyl-Q_3;
Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_2R_{12}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;
R_{15} is selected from the group of $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3 and $-C_{1-6}$ substituted alkyl-Q_3;
R_{16} is selected from the group of -H, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_2$;
with the proviso that when V is $-NR_{12}$-; R_{16} is not $-NR_2R_2$; and
R_{17} is selected from the group of -H, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl.

Compounds of Formula II are described in WO 2017/134596 which is incorporated herein by reference. In an embodiment the maturation inhibitor is Compound 3. Compound 3 is described in WO 2017/134596 as Example 25 which example is incorporated herein by reference.



Compound 3.

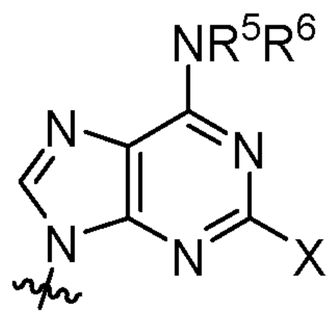
The pharmaceutical composition may be administered in combination with an NRTTI. In an embodiment the NRTTI is a compound of the formula 3:



Formula 3

wherein:

R^1 is:



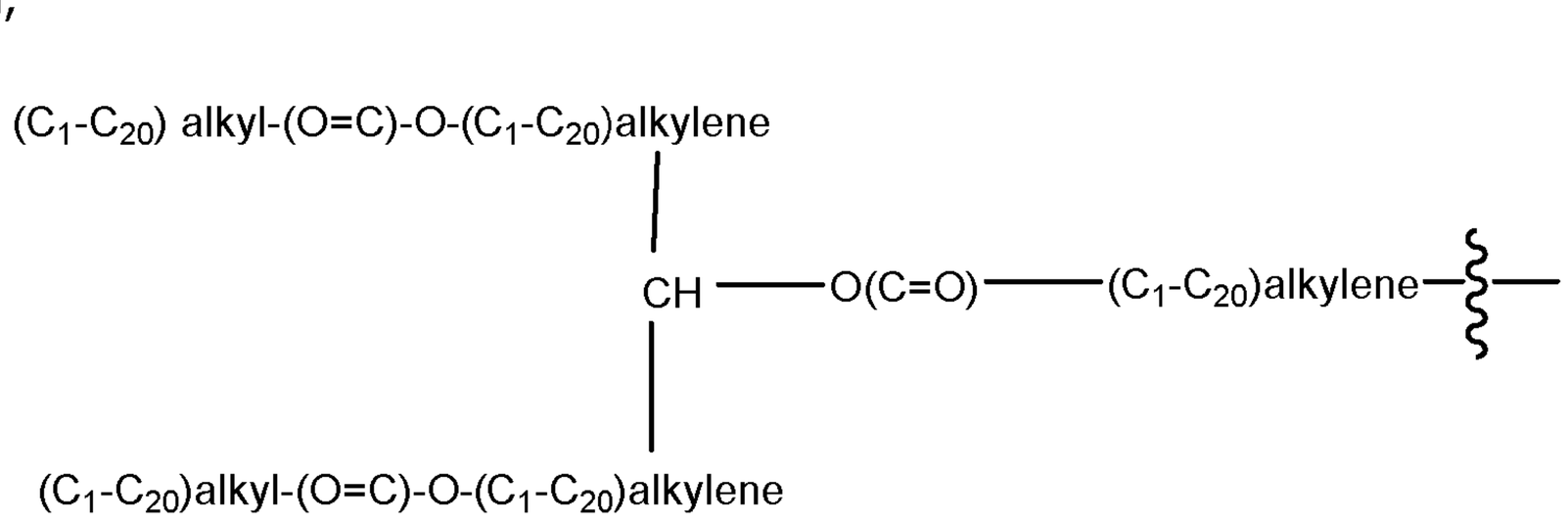
wherein:

X is selected from the group consisting of NH_2, F and Cl;

R^5 is selected from the group consisting of H and (C_1-C_{14}) alkyl;

R^6 is selected from the group consisting of H and -(C=O)-(C_1-C_{14}) alkyl;

R^2 is selected from the group consisting of (C_1-C_{24}) alkyl; $(CH_2)_{n1}$-O-$(CH_2CH_2O)_{n2}$-(C_1-C_{14} alkyl) where n1 and n2 are integers independently selected from 1-4; -R^7-NH-(C=O)-R^8 wherein R^7 may be (C_1-C_{14}) alkyl and R^8 may be independently selected from H and (C_1-C_{14}) alkyl; -R^9-(C_6-C_{14}) aryl, wherein R^9 is a bond or (C_1-C_6) alkyl; -R^{10}-(C_3-C_{14}) cycloalkyl, wherein R^{10} is a bond or (C_1-C_6) alkyl; -(C_1-C_{20}) alkylene-(C=O)-O-R^{11} wherein R^{11} may be selected from H and (C_1-C_{20})alkyl;



(C_1-C_{20}) alkyl-(O=C)-O-(C_1-C_{20})alkylene

CH — O(C=O) — (C_1-C_{20})alkylene

(C_1-C_{20})alkyl-(O=C)-O-(C_1-C_{20})alkylene

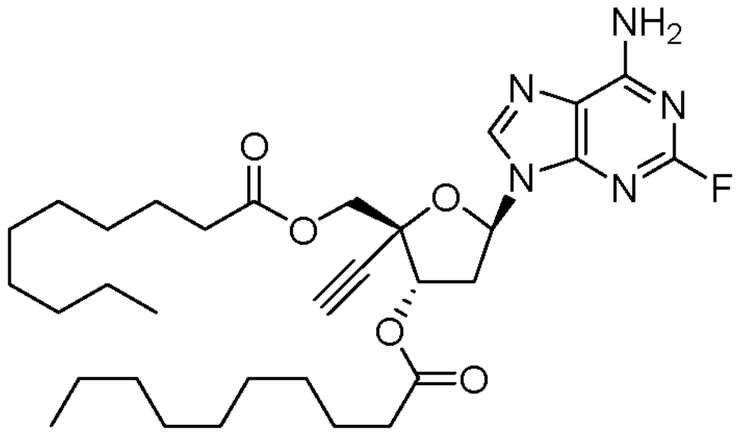
and;

R^3 is selected from the group consisting of H, -(C=O)-(C_1-C_{24}) alkyl; -(C=O)-O-(C_1-C_{24}) alkyl; and C_3-C_{14} cycloalkyl; or

R^2 and R^3 join together to form a C_3 to C_{28} cyclic structure; and

with the proviso that when R^2 is (C_1-C_{14} alkyl) at least one of R^3, R^5 and R^6 is not H.

Compounds of Formula 3 are disclosed in WO 2020/178767 which is incorporated by reference herein. In an embodiment a pharmaceutical composition of the invention is combined with Compound 4. Compound 4 is described in WO 2020/178767 as Example 18, which example is incorporated by reference herein.



Compound 4

In an alternative embodiment the NRTTI is Islatravir.

In a further embodiment the present invention provides a kit comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer. In an embodiment the kit comprises a syringe comprising a composition of the invention as well as a leaflet comprising use instructions.

The following non-limiting Examples illustrate the present invention.

EXAMPLES

Example 1: Composition of the invention

Ingredient	**Concentration (mg/mL)**
Cabotegravir	400.0
Poloxamer 338	38.0
Polyethylene Glycol 3350	35.0
Mannitol	20.0

Table 3

Table 3 shows an exemplary pharmaceutical composition of the invention (pharmaceutical compositions are also described in these examples as "suspensions") which was made using the following method.

A formulation vehicle was prepared by dissolving 9.5g Poloxamer 338 (BASF), 5.0g mannitol (Roquette Freres), and 8.7g PEG3350 (Clariant) in 164.2g water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired median particle diameter of 0.2 to 1.0 µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The resulting suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Example 2: Stability of a composition comprising Cabotegravir, Poloxamer 338 and PEG3350

A formulation vehicle was prepared by dissolving 7.5g Poloxamer 338 (BASF), 5.7g mannitol (Roquette Freres), and 7.5g PEG3350 (Clariant) in 166.7g water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 100g Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until a desired median particle diameter of 0.25µm was reached. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The milled suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy. Table 4 shows the suspension which was made.

Suspension 1	398 mg/mL cabotegravir (measured by HPLC)	30 mg/mL P338	30 mg/mL PEG3350	23 mg/mL mannitol

Table 4

Suspension 1 was stored at ambient laboratory conditions for 3 months and then evaluated for resuspension using an automated vial shaker. Assessment of the time it took the suspension to resuspend was performed by using an automatic shaker to reduce variability in shaking (Glas-Col Benchtop Shaker). The vial comprising the composition was placed into a holder on the shaker and was shaken at 230 to 350 motor speed for 30 second intervals until the bottom of the vial was assessed through visual inspection to be clear of sedimented/caked suspension material. Figure 1 shows a micrograph of the bottom of a vial which contained Suspension 1 after 30 seconds of shaking by the automated shaker. Based on the microscopy images, Suspension 1 (left image in Figure 1) was superior in resuspension compared to Suspension 2 which is the same formulation, made using the method described above, but comprising Kollidon 12 (polyvinylpyrrolidone) instead of PEG3350. Suspension 1 (left image in Figure 1) shows a mostly clear vial bottom indicating that the suspension was resuspended and decanted. Suspension 2 shows a vial bottom with suspension (*i.e.* crystalline cabotegravir particles) adhered to the bottom of the vial, meaning that resuspension was not achieved. Both formulations were shaken using the automated shaker for 30 seconds, but Suspension 2 was hand shaken to try to further resuspend the product.

Particle size of Suspension 1 was measured after vials were stored in an upright position at accelerated (40°C/75%RH) and stressed (50°C/ambient) stability conditions. Particle size analysis for the particles in the suspension was performed using laser diffraction (Malvern Mastersizer 3000). This method generates particle size distributions for the samples. The instrument uses a proprietary algorithm to convert the 2-dimensional scattering pattern generated by the interaction of the laser with particles in the sample to a particle size distribution; the scattering pattern is dependent on the size distribution of the particles in the sample. Table 6 explains the definitions used reporting particle size distributions.

	Initial particle size			1 month 40°C/75%RH			1 month 50°C/ambient		
	x10	**x50**	**x90**	**x10**	**x50**	**x90**	**x10**	**x50**	**x90**
Suspension 1	0.07	0.15	0.37	0.07	0.16	0.39	0.08	0.18	0.45

Table 5

x50	Median particle diameter, µm; here used on a volumetric basis, i.e. 50% by volume of the particles is smaller than this diameter and 50% is larger
x10	Particle diameter corresponding to 10% of the cumulative undersize distribution (here by volume), µm
x90	Particle diameter corresponding to 90% of the cumulative undersize distribution (here by volume), µm

Table 6

Table 5 shows minimal change in particle size of Suspension 1 over time and at varying conditions indicating stability of the suspension.

Example 3: 400 mg/mL Cabotegravir with Poloxamer 338 or 407

Injectable suspensions comprising about 400 mg/mL cabotegravir were prepared with Poloxamer 407 or 338. Mannitol was also added as a tonicity agent. The formulation vehicle was prepared by dissolving: 7.0g Poloxamer 338 and 3.5g mannitol in 177.0 g WFI (Suspension 4) or 7.5g P407 (BASF) and 4.7g mannitol (Roquette Freres) in 175.3g WFI (Suspension 3) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 100g Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired mean particle diameter of around 0.2µm was reached. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Table 7 shows the suspensions which were made. Each suspension was stored at 40°C/75%RH in an upright position. Initial particle size and particle size after 1 month was measured as an indicator of suspension stability. Table 8 shows the particle size in each suspension after 1 month. There was no change between initial particle size and particle size after 1 month. The lack of change in particle size is an indicator of stability of the suspensions.

Suspension 3	389 mg/mL cabotegravir (measured by HPLC)	30 mg/mL P407	19 mg/mL mannitol
Suspension 4	393 mg/mL cabotegravir (measured by HPLC)	28 mg/mL P338	14 mg/mL mannitol

Table 7

Suspension	**Initial**			**1 month**		
	X10 (um)	X50 (um)	X90 (um)	X10 (um)	X50 (um)	X90 (um)
Suspension 3	0.059	0.137	0.338	0.06	0.14	0.35
Suspension 4	0.12	0.28	0.74	0.12	0.28	0.75

Table 8

Example 4: Ability of compositions comprising Cabotegravir, Poloxamer 338 and PEG3350 to resuspend

Sixteen suspensions were made varying levels of PEG3350, p338 and particle size as shown in Table 9. All formulations were prepared using the above described methods *i.e.* by dissolving Poloxamer 338 (BASF), mannitol (Roquette Freres), and PEG3350 (Clariant) in water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to cabotegravir (free acid) to prepare an about 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until desired mean particle diameter of 0.2, 0.6 or 1.0 µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The filled suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy. The formulation was selected based on time to resuspension, particle size stability, viscosity and injection force. All suspensions made comprised about 400 mg/mL cabotegravir and about 30 mg/mL mannitol. The concentrations of P338 and PEG338 were varied. The suspensions made are listed below in Table 9.

Suspension	Cabotegravir (mg/mL) by HPLC	pH (duplicate measurements)	P338 (mg/mL)	PEG3350 (mg/mL)	Target x50 (µm)
1a	402	4.6, 4.5	26	20	0.2
2a	404	4.3, 4.5	26	50	0.2
3a	405	5.2, 5.3	38	35	0.2
4a	396	4.4, 4.1	50	0	0.2
5a	406	4.3, 4.3	50	20	0.2
6a	406	4.8, 4.8	50	50	0.2
7a	403	4.9, 4.8	26	35	0.6
8a	397	4.8, 4.7	38	20	0.6
9a	394	4.0, 4.3	38	35	0.6
10a	401	5.0, 4.9	38	50	0.6
11a	398	5.1, 4.7	50	35	0.6
12a	401	4.4, 4.6	26	20	1.0
13a	402	5.0, 5.1	26	50	1.0
14a	400	4.9, 4.8	38	35	1.0
15a	402	4.1,4.4	50	20	1.0
16a	402	5.0, 5.2	50	50	1.0

Table 9

Each suspension was tested for its ability to resuspend. Vials were stored in an upright position prior to testing. The vials were then inserted into the holder of a benchtop shaker (Glas-Col) so that the vials were at an angle of approximately 45° (1 and 2 months) to the ground with the top of the vial facing downwards, or 0° (3 and 6 months) to the ground. The vials were shaken for 30 seconds at a motor speed setting of 230 to 250. After shaking, the samples were visually

inspected to see if the suspension had resuspended. Resuspension was determined visually as absence of product caked to the bottom of the vial. If the bottom of the vial was transparent to light, it was determined that the suspension had resuspended. If the product had not yet resuspended, it was shaken for another 30 seconds and the bottom of the vial was checked again. Shaking and visual inspection were continued until the product visually appeared resuspended after a maximum of 4 shaking increments (up to 3 months) or a maximum of 5 shaking increments at 6 months.

The shaking angle of the test was changed from 45° to 0° after 2 months to improve resuspension because the majority of suspensions did not resuspend after 2 months at 30°C/65%RH. The 45° angle is not as representative of human shaking as the 0° angle when Instruction for Use (IFU) instructions for suspension redispersion prior to administration are followed. At 2 months, samples were noted with an asterisk if the vials were not fully resuspended by visual observation. At 3 and 6 months, microscope images were used to determine whether product was fully resuspended; samples containing residual product on the vial bottom were noted with an asterisk. An example of suspensions considered to be fully resuspended (A) and not resuspended (B) are in Figure 4.

Table 10 shows resuspension data after 2 months upright storage at 30°C/65%RH. The number of 30-second shaking intervals to resuspend 3 vials per suspension is shown. The automated shaker was used to reduce the variability in force and torque experienced by the vial during shaking.

Suspension 3a required the lowest number of shaking intervals to resuspend the vials. The three suspensions which required the least number of shaking intervals were all 0.2 µm formulations indicating that this particle size allows for good resuspension.

Table 11 shows resuspension data after 3 and 6 months upright storage at 30°C/65%RH. The number of 30-second shaking intervals to resuspend 3 vials per suspension is shown. Suspension 3a continued to require a lower number of 30 sec increments of shaking on the benchtop shaker per vial for product resuspension after 6 months compared to most of the other formulations.

Suspension	**P338 (mg/mL)**	**PEG3350 (mg/mL)**	**Target Size (µm)**	**# of 30 second shaking intervals (3 replicates)**			**Total**
3a	38	35	0.2	2	2	2	6
4a	50	0	0.2	3	2	2	7
1a	26	20	0.2	2	3	3	8
6a	50	50	0.2	3	3	3	9
9a	38	35	0.6	4	4	4	12
16a	50	50	1	4	4	4	12
2a	26	50	0.2	4	4	4	*12
5a	50	20	0.2	4	4	4	*12
11a	50	35	0.6	4	4	4	*12
14a	38	35	1	4	4	4	*12
13a	26	50	1	4	4	4	*12
15a	50	20	1	4	4	4	*12

12a	26	20	1	4	4	4	*12
8a	38	20	0.6	4	4	4	*12
7a	26	35	0.6	4	4	4	*12
10a	38	50	0.6	4	4	4	*12

Table 10 - *indicates that suspensions were not fully resuspended after 4 shakes per vial

	3 months 30°C/65%RH		6 months 30°C/65%RH	
Suspension	Total	Avg/Vial	Total	Avg/Vial
1a	5	1.7	6	2.0
2a	12	4.0*	15	5.0*
3a	5	1.7	6	2.0
4a	3	1.0	3	1.0
5a	6	2.0	6^	3.0
6a	7	2.3	9	3.0
7a	6	2.0	7	2.3
8a	6	2.0	7	2.3
9a	8	2.7	15	5.0
10a	6	2.0	15	5.0
11a	6	2.0	15	5.0
12a	12	4.0*	15	5.0*
13a	9	3.0	15	5.0
14a	5	1.7	6	2.0
15a	3	1.0	6	2.0
16a	6	2.0	14	4.7

Table 11 - * indicates that suspensions were not fully resuspended after 4 or 5 shakes per vial via evaluation using a light microscope. ^indicates that only 2 vials were tested. 3 vials were tested for all other conditions.

Example 5: Particle size and viscosity of compositions comprising Cabotegravir, Poloxamer 338 and PEG3350

The viscosity of each of the suspensions made in Table 9 in Example 4 was measured initially after they were made. The particle size of the suspensions was also measured initially after they were made as well as after 2, 3 and 6 months of storage at 40°C/75%RH. Results are shown in Table 12 and 13. Across all suspensions, there was minimal change in particle size after storage under accelerated conditions. Viscosity differed across suspensions. Suspensions with a target x50 of 0.2µm and 50 mg/mL P338 had the highest viscosities. The shear viscosity of the suspensions was measured using a Malvern Kinexus Pro rheometer equipped with a roughened cone and plate. Data was gathered at 20 °C with data collection at 10 points per decade across a shear rate range from 0.1 s-1 to 10 s-1.

			Initial			2 MN 40°C/75%RH		
Suspensions	**Visc @ 0.1 s^{-1} (cP)**	**Visc @ 10 s^{-1} (cP)**	**X10 (µm)**	**X50 (µm)**	**X90 (µm)**	**X10 (µm)**	**X50 (µm)**	**X90 (µm)**
1a	24	18	0.09	0.2	0.5	0.11	0.23	0.54

2a	38	24	0.1	0.23	0.54	0.12	0.26	0.59
3a	116	43	0.07	0.17	0.39	0.08	0.17	0.4
4a	406	76	0.09	0.21	0.59	0.1	0.24	0.79
5a	763	95	0.1	0.22	0.55	0.73	0.24	0.58
6a	392	79	0.09	0.2	0.51	0.11	0.24	0.57
7a	83	25	0.21	0.6	1.60	0.28	0.70	2.0
8a	50	28	0.23	0.66	1.90	0.27	0.71	2.1
9a	92	31	0.18	0.61	1.7	0.26	0.68	2.0
10a	132	40	0.23	0.66	1.90	0.34	0.76	2.3
11a	124	44	0.24	0.69	2.00	0.33	0.78	2.3
12a	17	11	0.33	0.96	2.6	0.43	1.0	2.7
13a	32	16	0.57	1.3	3.0	0.6	1.4	3.1
14a	54	24	0.49	1.2	3.0	0.52	1.2	3.0
15a	37	15	0.74	1.6	3.3	0.73	1.6	3.4
16a	92	55	0.61	1.4	3.1	0.6	1.4	3.2

Table 12

	3 months 40°C/75%RH			**6 months 40°C/75%RH**		
Suspension	x10 (µm)	x50 (µm)	x90 (µm)	x10 (µm)	x50 (µm)	x90 (µm)
1a	0.1	0.22	0.53	0.09	0.21	0.57
2a	0.11	0.26	0.62	0.10	0.24	0.63
3a	0.07	0.16	0.4	0.07	0.16	0.4
4a	0.08	0.22	0.83	0.09	0.23	0.8
5a	0.08	0.2	0.54	0.09	0.21	0.53
6a	0.1	0.23	0.58	0.09	0.24	0.71
7a	0.16	0.63	1.7	0.19	0.67	1.9
8a	0.15	0.67	1.8	0.21	0.67	1.9
9a	0.22	0.67	2.0	0.20	0.66	1.9
10a	0.19	0.69	2.0	0.21	0.73	2.0
11a	0.18	0.73	2.1	0.21	0.77	2.1
12a	0.41	1.0	2.7	0.35	0.99	2.6
13a	0.6	1.4	3.1	0.6	1.4	3.1
14a	0.52	1.2	3.0	0.54	1.3	3.0
15a	0.71	1.6	3.3	0.69	1.6	3.3
16a	0.6	1.4	3.2	0.6	1.4	3.2

Table 13 - No major changes observed in particle size after 6 months at 40°C/75%RH.

Example 6: 12-month stability of suspension 6a

A suspension with the P338 and PEG3350 composition and target size of suspension 6a was manufactured for a non-clinical safety study and monitored on stability for 12 months. The data is shown in Table 14. No changes in content, impurities or particle size were observed. A drop in pH was observed, but the pH is still within the acceptable pH range for injection.

Storage Condition/ Orientation	Storage Time (Months)	Cabotegravir Content by HPLC (mg/mL)	Drug Related Impurities (% area)	pH	Particle Size (µm)		
					X_{10}	X_{50}	X_{90}
Initial	Initial	398.8	0.05	5.6, 5.5	0.05	0.12	0.28
30°C/65%RH /Inverted	2	400.0	0.05	4.8, 4.8	0.05	0.14	0.36
	3	401.2	0.05	4.8, 4.6	0.05	0.13	0.29
	6	398.0	0.05	4.6, 4.7	0.06	0.14	0.31
	9	401.6	0.05	4.5, 4.7	0.06	0.13	0.31
	12	396.0	0.05	4.5, 4.7	0.05	0.12	0.29

Table 14

Example 7: Pharmacokinetics

The pharmacokinetics of cabotegravir suspensions were evaluated in male Sprague Dawley rats. Three suspensions were tested: (i) 200 mg/mL cabotegravir with PS20 and PEG3350; (ii) 400 mg/mL cabotegravir with P338; (iii) and 400 mg/mL cabotegravir with P338 and PEG3350. The suspensions tested are shown in Table 15.

Suspension	Cabotegravir (mg/mL) by HPLC	Excipients	Size (x10) in µm	Size (x50) in µm	Size (x90) in µm
i	195	18 mg/mL PS20, 18 mg/mL PEG3350, 31 mg/mL mannitol	0.07	0.17	0.51
ii	393	28 mg/mL P338, 14 mg/mL mannitol	0.12	0.28	0.74
iii	399	50 mg/mL P338, 50 mg/mL PEG3350, 30 mg/mL mannitol	0.05	0.12	0.28

Table 15

Rats were administered the cabotegravir suspensions by intramuscular injection in the right gastrocnemius muscle or subcutaneous injection at 200 or 400 mL/kg (rats weighed just prior to dosing) to achieve a target dose of 10 mg/kg/dose. A total of three rats were used per suspension. Blood samples were collected into 500 uL K_2EDTA tubes via lateral tail vein or tail tip amputation. 75 uL of whole blood was then transferred to a new matrix tube, combined with 75 uL of sterile water, vortexed and stored on dry ice. Samples were stored at -80°C for drug concentration analysis. Blood concentrations of cabotegravir were determined using an analytical method based on protein precipitation, followed by UHPLC/MS/MS analysis. Using a 25 µL aliquot of sample, the lower limit of quantification (LLQ) for cabotegravir was 50 ng/mL. The computer systems that were used on this study to acquire and quantify data included Analyst Version 1.6.1 and SMS2000 Version 3.1.

Figure 2 shows cabotegravir concentration in blood of individual rats after intramuscular administration of suspension i, ii or iii. Overall, the pharmacokinetic profiles for all three suspensions were found to be simiar. In particular, the slopes for the terminal phase, representing absorption rates for long acting formulations under the assumption of 'flip-flop kinetics', overlap for all formulations tested. This suggests that the long-acting profile for cabotegravir is maintained for the 400 mg/mL suspensions compared to the 200 mg/mL suspension.

Figure 3 shows cabotegravir concentrations in blood after a 10 mg/kg subcutaneous administration of 400 mg/mL cabotegravir with 50 mg/mL P338, 50 mg/mL PEG3350 and 30 mg/mL mannitol. 3 rats were used. Each line represents the blood concentration of a separate rat. Subcutaneous administration resulted in detectable blood cabotegravir concentrations out to 12 weeks.

Example 8: Comparison with a suspension comprising 400 mg/mL Cabotegravir with Polysorbate 20 (PS20) and Polyethylene Glycol 3350 (PEG3350)

A long acting suspension comprising 200 mg/mL cabotegravir, 20 mg/mL PS20 and 20 mg/mL PEG3350 was investigated to test stability when the cabotegravir concentration was increased to 400 mg/mL.

The suspension was prepared in a 250mL batch using a Netzsch miniCer and 0.3mm YTZ grinding beads. A range of excipient concentrations were explored.

The formulation vehicle was prepared by dissolving Polysorbate 20 (Croda), Polyethylene Glycol 3350 (Clariant), and mannitol (Roquette Freres) in water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was then added to Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired median particle diameter of less than 0.25µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The suspension was then filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The filled suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

30 mg/mL PS20, 30 mg/mL PEG3350 and 19 mg/mL mannitol with 400 mg/mL cabotegravir was prepared. The gamma irradiated suspension in vials was set down in the upright position and stored at 40°C/75%RH. After 1 month and 3 months of storage, suspensions were tested for stability. Table 16 shows particle size after formulation and after 1 month of storage at 40°C/75%RH for the 400 mg/mL cabotegravir formulation with 30 mg/mL PS20, 30 mg/mL PEG3350, 19 mg/mL mannitol. At 1 month, the particle size had increased compared to the initial time point (Table 13 and Figure 3). At 3 months, the suspension had become an unrecoverable gel which could not be removed from the vial with a syringe.

Time	x10	x50	x90
Initial	0.07	0.17	0.61
1 month	0.14	0.41	3.2

Table 16

Further suspensions comprising cabotegravir, PS20 and PEG3350 were prepared with the concentrations shown in Table 17. Experiments 1, 2 and 5 were prepared using the method described above for 20 mg/mL PS20 and PEG3350. In experiment 3, the suspension was first milled with PS20 (no PEG3350), and then PEG3350 was added, here 400 mg/mL cabotegravir was milled with 30 mg/mL PS20. After milling, a concentrated solution (400 mg/mL) of PEG3350 was added to dilute the 400 mg/mL suspension to 360 mg/mL cabotegravir, 27 mg/mL PS20, 27 mg/mL mannitol. Compositions were all prepared on a 250mL batch scale using the Netzsch miniCer with 0.3mm YTZ grinding beads.

Experiment Number	PS20 (mg/mL)	PEG3350 (mg/mL)
1	40.0	40.0
2	30.0	40.0
3	27*	40.0
4	20	20.0
5	20	0

Table 17

*400 mg/mL was diluted down by 10%, resulting in 360 mg/mL cabotegravir and 27 mg/mL PS20

In Experiments 1, 2, 4 and 5 during wet bead milling on the miniCer, the suspension thickened into a paste and was not recoverable. In Experiment 3, within 5 minutes of adding the 400 mg/mL PEG3350 solution, the suspension thickened and could no longer be stirred. The combination of PS20 and PEG3350 with 400 mg/mL cabotegravir did not produce a physically stable suspension.

Example 9: 500 mg/mL Cabotegravir with Poloxamer 338 or 407

Injectable suspensions comprising about 500 mg/mL cabotegravir were prepared with Poloxamer 407 or Poloxamer 338. Mannitol was also added as a tonicity agent. The formulation vehicle was prepared by dissolving: 8.8g Poloxamer 338 and 7.0g mannitol in 159.3 g WFI (Suspension 4); 9.7g P338 (BASF) and 11.1g mannitol (Roquette Freres) in 159.3g WFI (Suspension 5); and 9.7g P407 (BASF) and 11.1g mannitol (Roquette Freres) in 159.3g WFI (Suspension 6) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 125g Cabotegravir (free acid) to prepare a 500 mg/ml coarse suspension (Suspension 4) or 138.8g Cabotegravir (free acid) to prepare a 555 mg/mL coarse suspension (Suspensions 5 & 6). The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired mean particle diameter of around 0.2µm was reached. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. In the case of Suspensions 5 & 6, the milled suspension was diluted with concentrated PEG3350 solutions to produce final suspension compositions of 500 mg/mL Cabotegravir, 35 mg/mL P338 or P407, 40 mg/mL mannitol, and 0-40 mg/mL PEG3350. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Table 18 shows the suspensions which were made. Each suspension was stored at 40°C/75%RH in an upright position. Initial particle size and particle size after 1 month was measured as an indicator of suspension stability. Table 19 shows the particle size in each suspension after 1 month. There was no change between initial particle size and particle size after 1 month. The lack of change in particle size is an indicator of stability of the suspensions.

The viscosity of each of the suspensions made in Table 18 was measured initially after they were made. The particle size of the suspensions was also measured initially after they were made as well as after 1 month of storage at 50°C. Results are shown in Table 19. Across all suspensions, there was minimal change in particle size after storage under accelerated conditions. The viscosity of Suspension 4 is within the range of viscosities observed in the Cabotegravir 400 mg/mL compositional DoE and is modestly higher than the viscosity of Suspension 3a (discussed above), which has a similar P338 composition and similar size target x50 of 0.2µm. The shear

viscosity of the suspensions was measured using a Malvern Kinexus Pro rheometer equipped with a roughened cone and plate. Data was gathered at 20 °C with data collection at 10 points per decade across a shear rate range from 0.1 s-1 to 10 s-1.

Suspension 4	497 mg/mL cabotegravir (measured by HPLC)	35 mg/mL P338	40 mg/mL mannitol	0 mg/mL PEG
Suspension 5	500 mg/mL cabotegravir (theoretical)	35 mg/mL P338	40 mg/mL mannitol	0-40 mg/mL PEG3350
Suspension 6	500 mg/mL cabotegravir (theoretical)	35 mg/mL P407	40 mg/mL mannitol	0-40 mg/mL PEG3350

Table 18

Suspension	Visc @ 0.1 s^{-1} (cP)	Visc @ 10 s^{-1} (cP)	**Initial**			**1 month @ 50°C/ambient RH**		
			X10 (um)	X50 (um)	X90 (um)	X10 (um)	X50 (um)	X90 (um)
Suspension 4	197.016	61.419	0.07	0.22	0.72	0.09	0.24	0.69
Suspension 5	NT	NT	0.07	0.17	0.42	-		
Suspension 6	NT	NT	0.09	0.21	0.51	-		

Table 19

Example 10: Wettability study to define limits of Cabotegravir suspension strength

Wettability of Cabotegravir in 38 mg/mL P338, 35 mg/mL PEG3350, and 20 mg/mL mannitol was assessed to estimate the approximate concentration limit for Cabotegravir suspension in this vehicle. This was performed by adding increasing amounts of Cab to 5g of vehicle until a gross change in coarse suspension properties was observed. The results are summarized in Table 20 and show that the upper boundary of Cabotegravir solid suspension concentration in this vehicle is 600 mg/mL or less.

mg/mL Cabotegravir	Cababotegravir (g)	Vehicle* (g)	Gross viscosity
396	2.63	5	Similar to water
500	3.57	5	Similar to water
565†	4.33	5	Similar to water
580†	4.50	5	Boundary of thickening
600†	4.81	5	Thicker, but flowable
635†	5.28	5	Slightly paste-like

Table 20

*38 mg/mL P338, 35 mg/mL PEG3350, 20 mg/mL mannitol
†These values were calculated using densities approximated from lower concentrations

It will be understood that the present invention has been described above purely by way of example, and modification of detail can be made within the scope of the invention. Each feature disclosed in the description, and where appropriate the claims and drawings may be provided independently or in any appropriate combination.

CLAIMS

1. A pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

2. The pharmaceutical composition according to Claim 1, wherein the polyethylene glycol is polyethylene glycol 3350.

3. The pharmaceutical composition according to Claim 1 or Claim 2, wherein the poloxamer is poloxamer 407, poloxamer 237 or poloxamer 338.

4. The pharmaceutical composition according to Claim 3, wherein the poloxamer is poloxamer 407 or poloxamer 338.

5. The pharmaceutical composition according to any preceding claim wherein the polyethylene glycol is polyethylene glycol 3350 and the poloxamer is poloxamer 407.

6. The pharmaceutical composition according to any of Claims 1 to 4, wherein the polyethylene glycol is polyethylene glycol 3350 and the poloxamer is poloxamer 338.

7. The pharmaceutical composition according to any preceding claim, wherein the cabotegravir is present in the form of particles with a median particle diameter of about 0.1 to 10 µm.

8. The pharmaceutical composition according to Claim 7, wherein the cabotegravir is present in the form of particles with a median particle diameter of above 0.15 to 0.25 µm.

9. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition further comprises mannitol.

10. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a cabotegravir concentration of 350 to 600 mg/mL.

11. The pharmaceutical composition according to Claim 10, wherein the pharmaceutical composition comprises a cabotegravir concentration of 350 to 500 mg/mL.

12. The pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition comprises a cabotegravir concentration of 380 to 420 mg/mL.

13. The pharmaceutical composition according to Claim 12, wherein the pharmaceutical composition comprises a cabotegravir concentration of about 400 mg/mL.

14. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a poloxamer concentration of 4 to 50 mg/mL.

15. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a polyethylene glycol concentration of 5 to 50 mg/mL.

16. The pharmaceutical composition according to any preceding claim, wherein the composition is a parenteral pharmaceutical composition.

17. The pharmaceutical composition according to any preceding claim wherein the composition is suitable for use as an injectable composition.

18. A method for the treatment or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising administering to said human a therapeutically effective amount of a pharmaceutical composition as defined in any one of Claims 1 to 17.

19. The method according to Claim 18, wherein the method comprises a step of administering the pharmaceutical composition subcutaneously or intramuscularly.

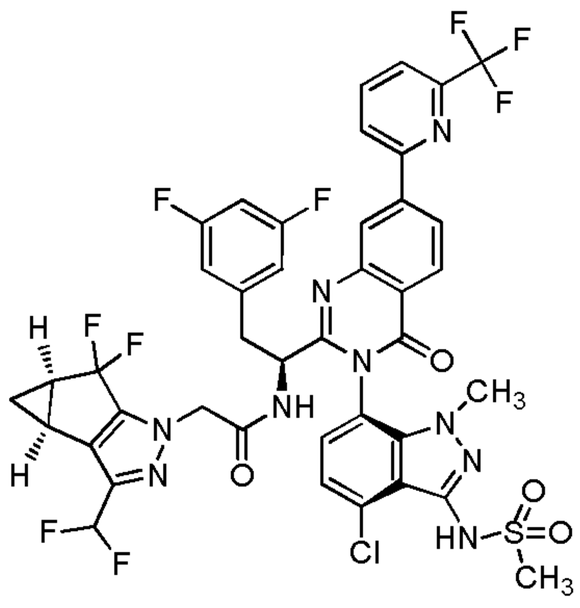
20. The method according to Claim 18 or 19, wherein about 1 mL to about 3 mL of the pharmaceutical composition is administered to the human.

21. The method according to any of Claims 18 to 20, wherein the method comprises administering the pharmaceutical composition to the human once every month, once every 2 months or once every 3 months.

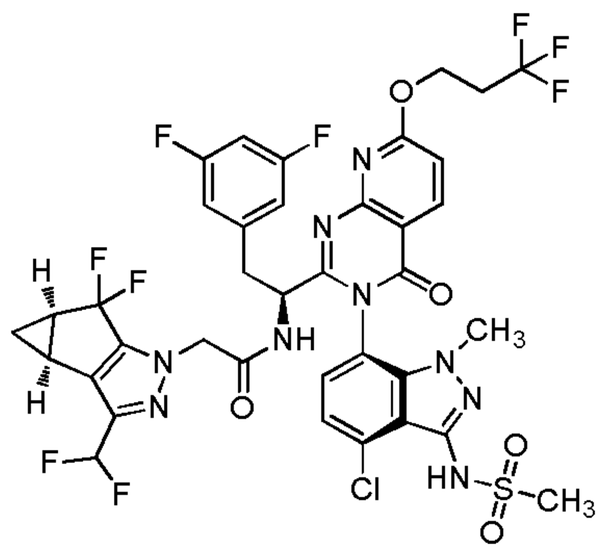
22. The method according to any of Claims 18 to 20, wherein the method comprises administering 1 to 1.5 mL of the pharmaceutical composition subcutaneously to a human once every month.

23. The method according to any of Claims 18 to 20, wherein the method comprises administering 2.5 to 3mL of the pharmaceutical composition intramuscularly to the human once every 3 months.

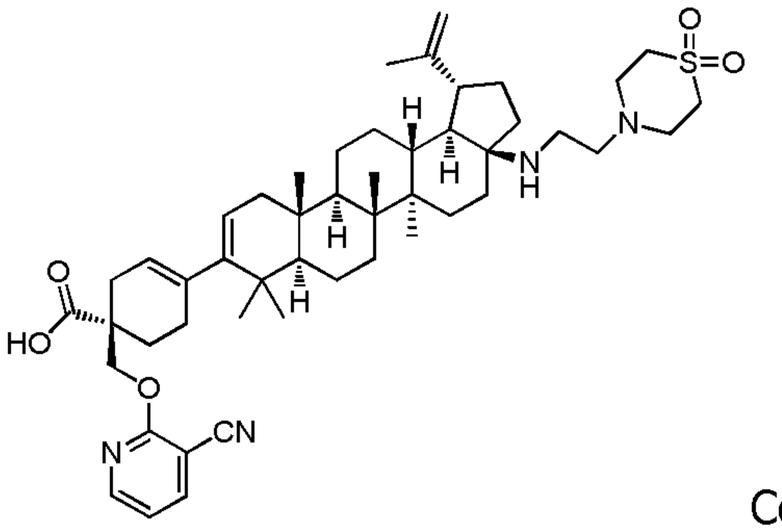
24. The method according to any of Claims 18 to 23, wherein the method comprises administering the pharmaceutical composition in combination with N6-LS,



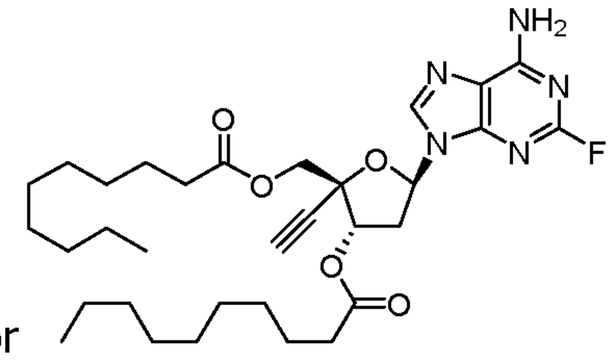
Compound 1,



Compound 2,



Compound 3 or



Compound 4.

25. A pharmaceutical composition defined in any of Claims 1 to 17 for use in the treatment or prevention of HIV.

26. The pharmaceutical composition for use according to Claim 25, wherein the pharmaceutical composition is administered to a human intramuscularly or subcutaneously.

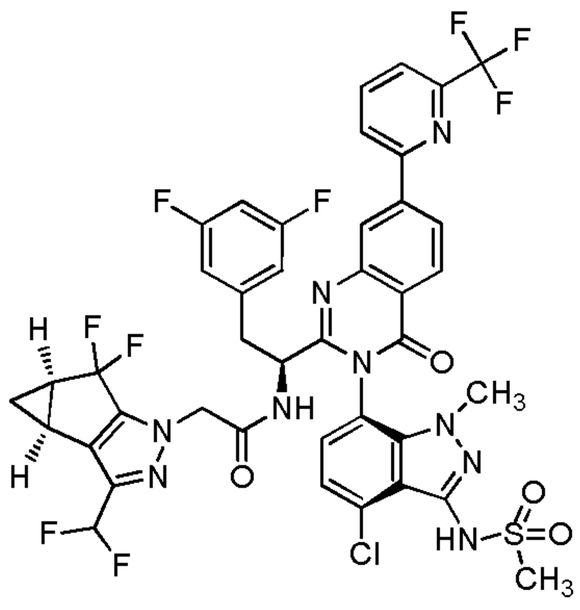
27. The pharmaceutical composition for use according to either Claim 25 or Claim 26, wherein about 1 mL to about 3 mL of the pharmaceutical composition is administered to a human.

28. The pharmaceutical composition for use according to any of Claims 25 to 27, wherein the pharmaceutical composition is administered once every month, once every 2 months or once every 3 months.

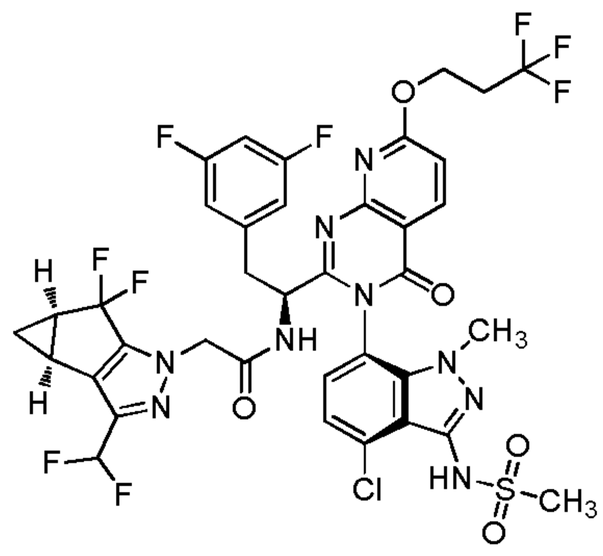
29. The pharmaceutical composition for use according to any of Claims 25 to 28, wherein 1 to 1.5 mL of the pharmaceutical composition is administered subcutaneously once every month.

30. The pharmaceutical composition for use according to any of Claims 25 to 29, wherein 2.5 to 3mL of the pharmaceutical composition is administered intramuscularly once every 3 months.

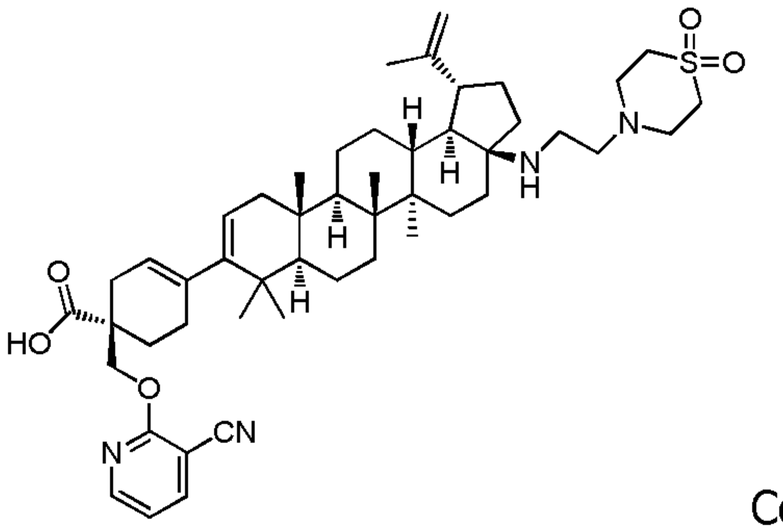
31. The pharmaceutical composition for use according to any of Claims 25 to 30, wherein the pharmaceutical composition is administered in combination with N6-LS,



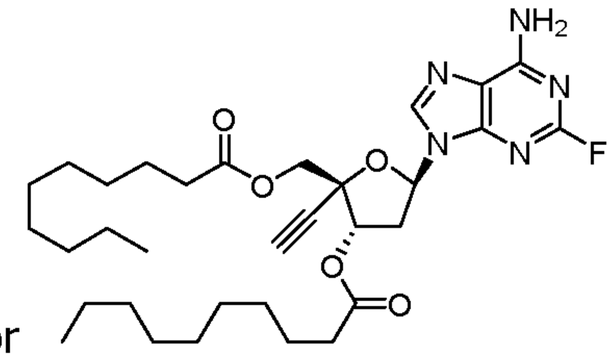
Compound 1,



Compound 2,



Compound 3 or



Compound 4.

32. A method of making a pharmaceutical composition according to any of Claims 1 to 17, wherein the method comprises contacting cabotegravir or a pharmaceutically acceptable salt thereof with polyethylene glycol and poloxamer.

33. A kit comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

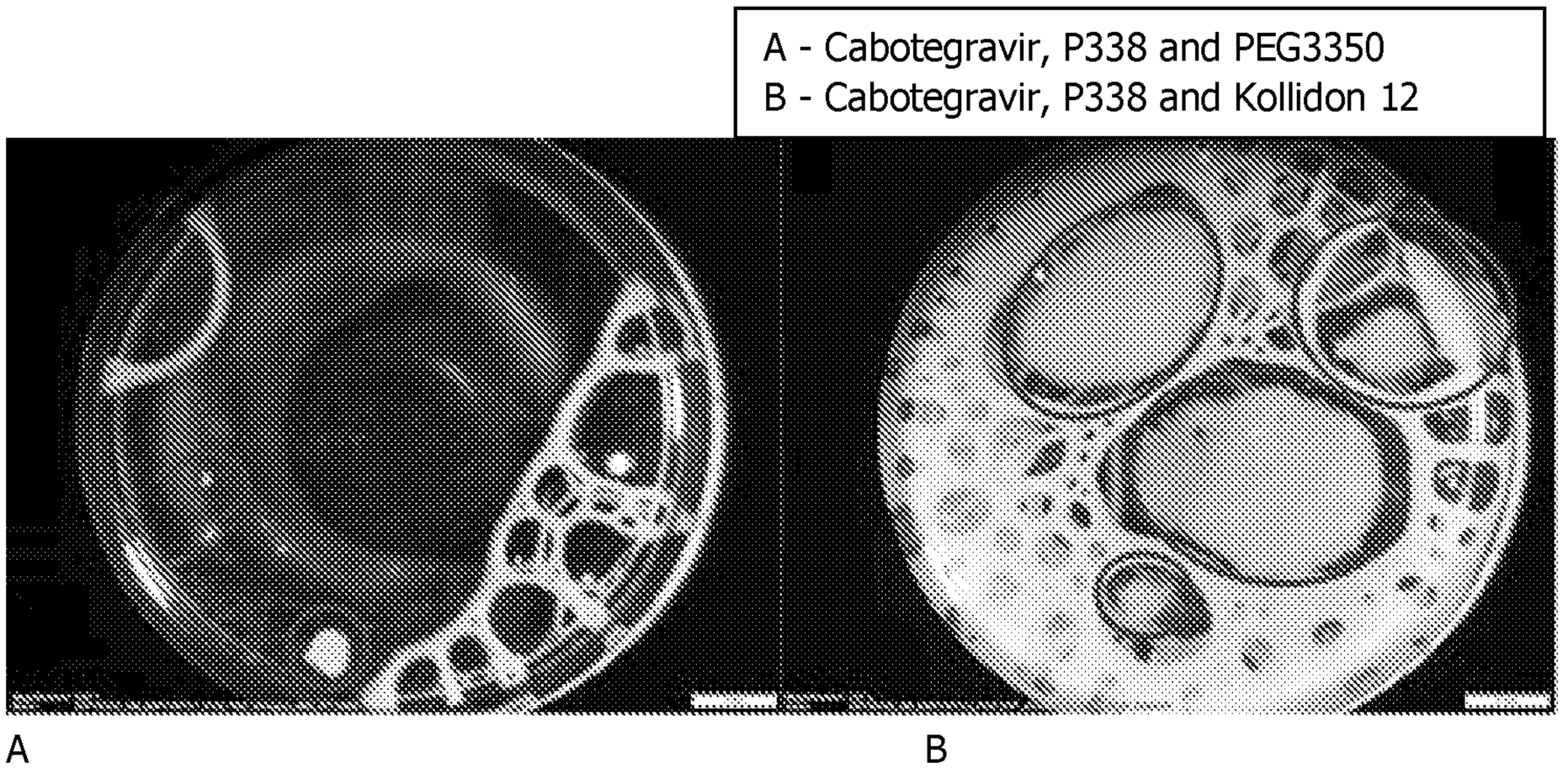

A - Cabotegravir, P338 and PEG3350
B - Cabotegravir, P338 and Kollidon 12
A
B

Figure 1

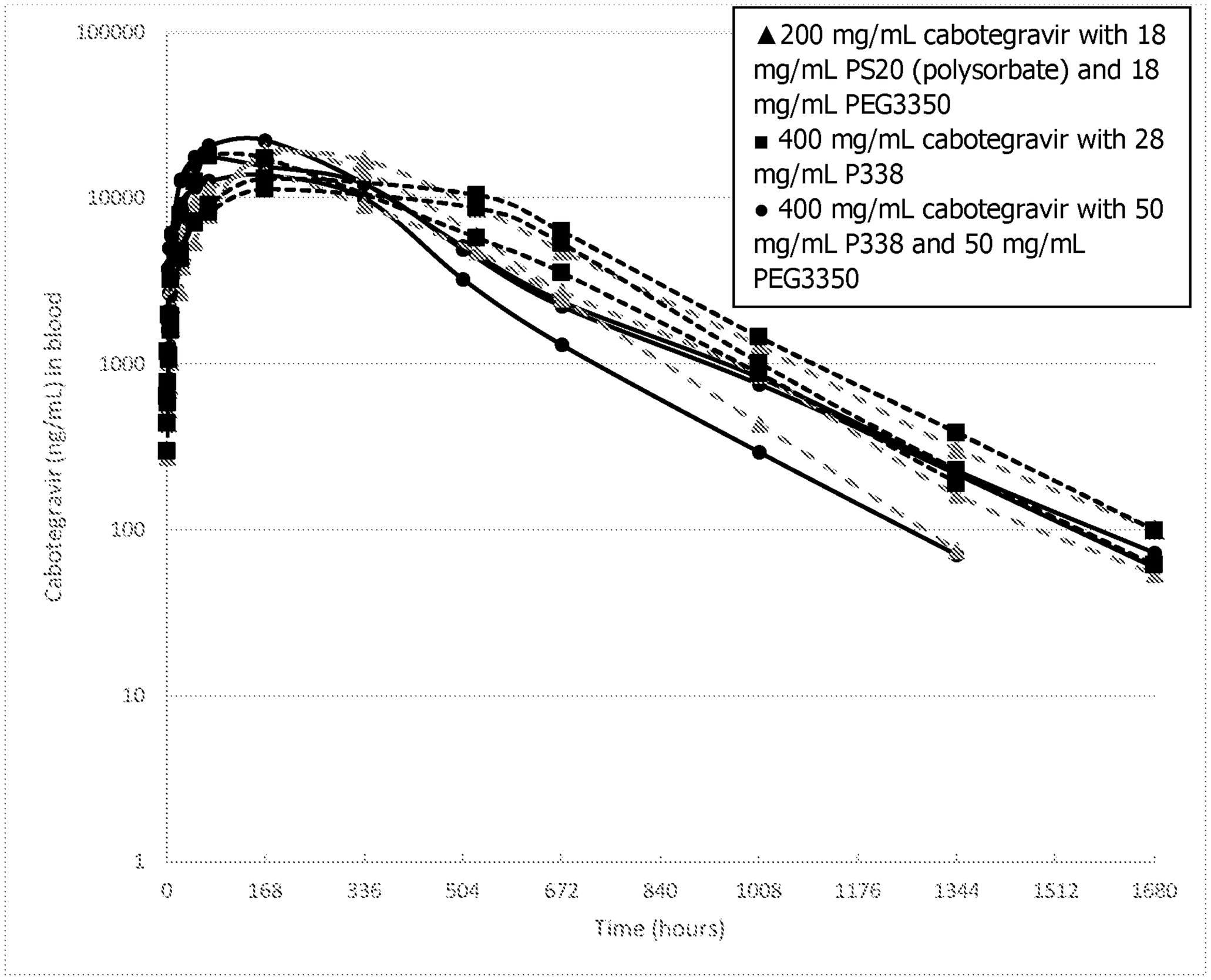

▲200 mg/mL cabotegravir with 18 mg/mL PS20 (polysorbate) and 18 mg/mL PEG3350
■ 400 mg/mL cabotegravir with 28 mg/mL P338
● 400 mg/mL cabotegravir with 50 mg/mL P338 and 50 mg/mL PEG3350
Cabotegravir (ng/mL) in blood
100000
10000
1000
100
10
1
0
168
336
504
672
840
1008
1176
1344
1512
1680
Time (hours)

Figure 2

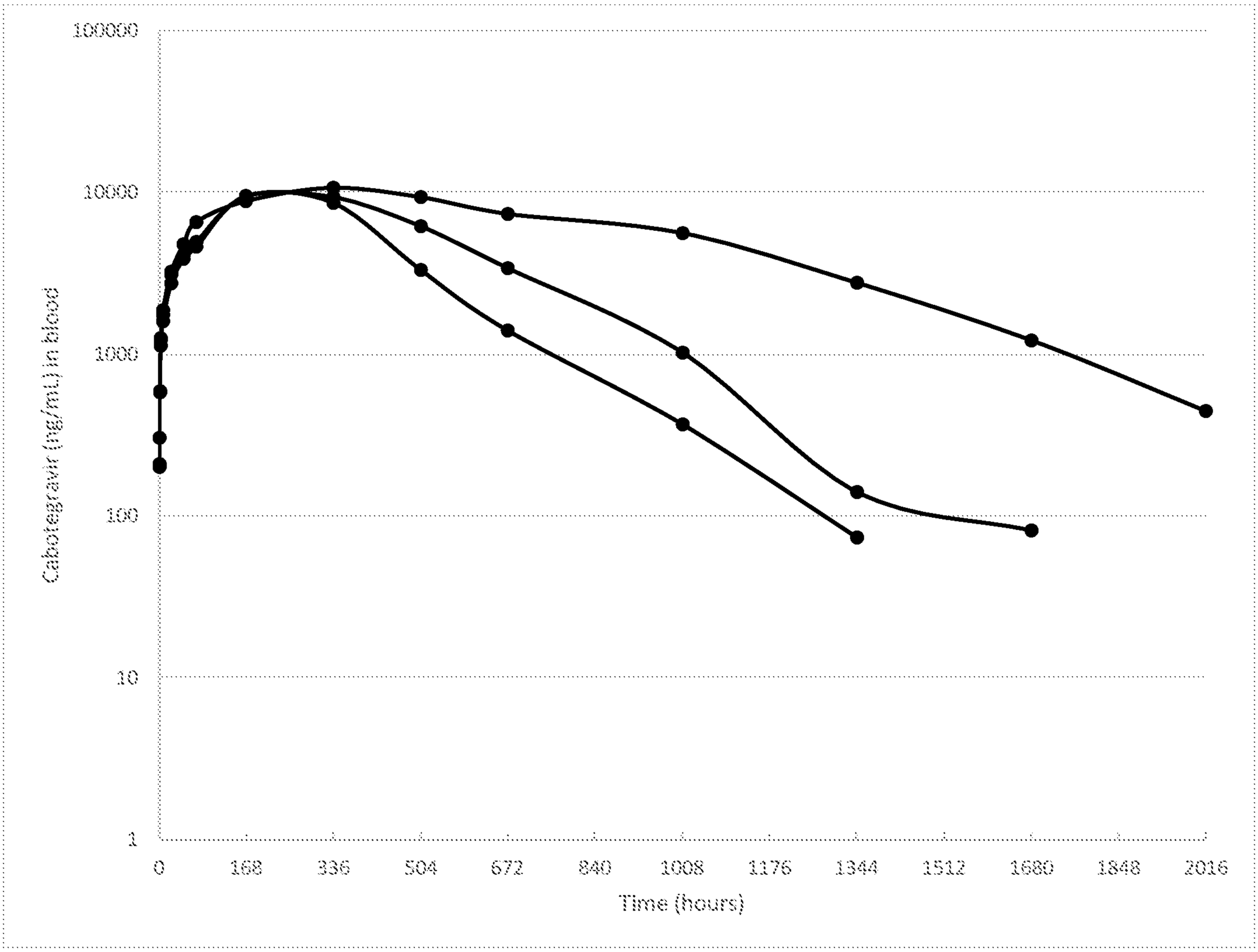
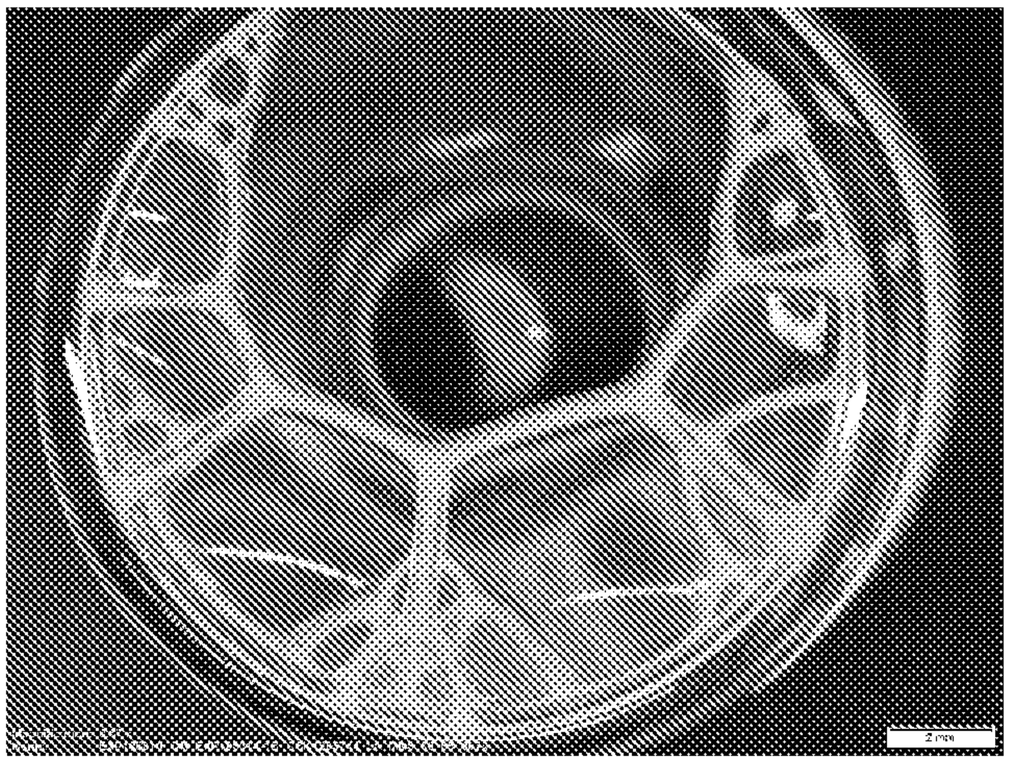

100000
10000
1000
100
10
1
Cabotegravir (ng/mL) in blood
0
168
336
504
672
840
1008
1176
1344
1512
1680
1848
2016
Time (hours)

Figure 3



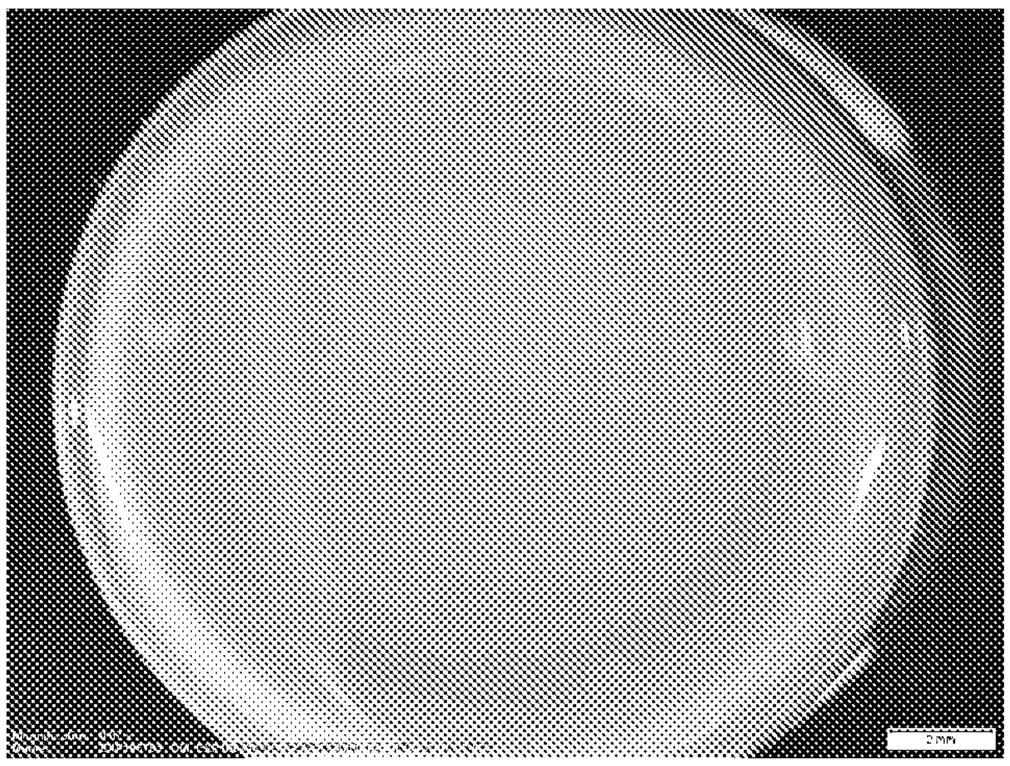


Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/20 A61K47/26 A61K47/34 A61K31/4985
A61K31/5365 A61P31/18 A61K39/00 C07K16/10
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2020/112931 A1 (UNIV NEBRASKA [US]) 4 June 2020 (2020-06-04) page 26, line 23; claims 1,5, 12-14,23-31,35 pages 9,14, 20 - page 22; example 2 page 25 - page 27 -----	1-33
X,P	WO 2020/018459 A1 (GILEAD SCIENCES INC [US]) 23 January 2020 (2020-01-23) page 30 - page 36; claims 1,17,43-45,81,93-94 page 129 - page 139 -----	1-33
Y	WO 2017/223280 A2 (VIIV HEALTHCARE CO [US]; UNIV NEBRASKA [US]) 28 December 2017 (2017-12-28) pages 17,20 - page 22; claims 13,21 page 27 -----	1-33

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 2021	10/05/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/046786 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]) 31 March 2016 (2016-03-31)	1-9, 16-19, 25,26, 32,33
Y	paragraph [0046] - paragraphs [0048], [0060]; claims 1-5,9,12,13,16,17 paragraph [0094] - paragraph [0095]; examples	1-33

X	WO 2015/127437 A1 (UNIV NEBRASKA [US]) 27 August 2015 (2015-08-27)	1,3,4,9, 16-20, 25,26, 32,33
Y	pages 11,12,17 - page 19; claims 1,8,21; figures; examples	1-33

X	WO 2012/037320 A2 (GLAXOSMITHKLINE LLC [US]; MUNDHRA DEEPAK B [US]; PAN RENNAN [US]) 22 March 2012 (2012-03-22)	1-9, 15-20, 25-27,33
Y	pages 3,4; claim 1; figures 1,2; examples	1-33

A	ZHOU TIAN ET AL: "Creation of a nanoformulated cabotegravir prodrug with improved antiretroviral profiles", BIOMATERIALS, ELSEVIER, AMSTERDAM, NL, vol. 151, 15 October 2017 (2017-10-15), pages 53-65, XP085235415, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2017.10.023 page 57, left-hand column page 61, right-hand column	1,18,25

X	Tian Zhou: "Next Generation of Translational Long-Acting Cabotegravir", Theses & Dissertations, 1 May 2018 (2018-05-01), XP055708824, University of Nebraska Medical Center Omaha, Nebraska Retrieved from the Internet: URL:https://digitalcommons.unmc.edu/cgi/viewcontent.cgi?article=1261&context=etd [retrieved on 2020-06-25]	1-5, 15-18, 25,26
Y	page 29 - page 31; figures 2.1, 2.2, 2.6 page 44 - page 51; figures 2.11, 2.12; table 2.3	1-33

X,P	WO 2020/222108 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 5 November 2020 (2020-11-05) claims	1,24,31

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Cabotegravir Crystalline Form", RESEARCH DISCLOSURE, KENNETH MASON PUBLICATIONS, HAMPSHIRE, UK, GB, vol. 633, no. 64, 1 January 2017 (2017-01-01), page 109, XP007145401, ISSN: 0374-4353 [retrieved on 2016-12-19] the whole document	1,25,33

A	WO 2019/198024 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 17 October 2019 (2019-10-17) claims 1,9,12,18,19,22,24; examples 107, 168, 170, 173, 181, 185	1,24,31

E	WO 2020/254985 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 24 December 2020 (2020-12-24) page 43, line 23 - line 30; claims 1,2,11,12 page 6	1,24,31

X,P	WO 2020/157692 A1 (VIIV HEALTHCARE UK LTD [GB]) 6 August 2020 (2020-08-06) page 41; claims 6,10,11; example 1	1,24,31

A	WO 2018/203235 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 8 November 2018 (2018-11-08) page 10, line 24 - line 25; claims 1,5,7,8,12,14	1,24,31

X	WO 2019/207460 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 31 October 2019 (2019-10-31) page 7	1,24,31

Y	MENDES E ET AL: "Synthesis, stability and in vitro dermal evaluation of aminocarbonyloxymethyl esters as prodrugs of carboxylic acid agents", BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 10, no. 3, 1 March 2002 (2002-03-01), pages 809-816, XP002296488, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(01)00336-4 page 809 - page 810; table 1	1,24,31

X	WO 2017/134596 A1 (VIIV HEALTHCARE UK LTD [GB]) 10 August 2017 (2017-08-10) cited in the application page 43	1,24,31

A	WO 2015/157483 A1 (SQUIBB BRISTOL MYERS CO [US]) 15 October 2015 (2015-10-15) page 46; claims 1,13,16,17	1,24,31

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/050961 A1 (SCRIPPS RESEARCH INST [US]) 18 March 2021 (2021-03-18) page 4; claims 2,6,12-14,21,23-25; table 1	1,24,31
Y	WO 2019/171285 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]; VIIV HEALTHCARE CO [US]) 12 September 2019 (2019-09-12) page 19, line 9 - line 10; claims 7,9,13,14; table 1 page 31 - page 35 page 21, line 21	1,24,31
Y	MASAYUKI KAGEYAMA ET AL: "Enantioselective Total Synthesis of the Potent Anti-HIV Nucleoside EFdA", ORGANIC LETTERS ., vol. 13, no. 19, 7 October 2011 (2011-10-07), pages 5264-5266, XP055582155, US ISSN: 1523-7060, DOI: 10.1021/ol202116k page 5264; figure 1; compound 1	1,24,31
Y	US 2018/002366 A1 (GIRIJAVALLABHAN VINAY M [US] ET AL) 4 January 2018 (2018-01-04) paragraphs [0147], [0148], [0163] - paragraph [0165]; claims 69,71	1,24,31
A	Harper Rachel: "Broadly neutralising antibody to be developed for HIV-1 treatment", European Pharmaceutical Review, 25 November 2019 (2019-11-25), pages 1-2, XP055795889, Retrieved from the Internet: URL:https://www.europeanpharmaceuticalreview.com/news/106488/investigational-broadly-neutralising-antibody-hiv-treatment/ [retrieved on 2021-04-15] the whole document	1,24,31
Y	GROBBEN MARLOES ET AL: "The potential of engineered antibodies for HIV-1 therapy and cure", CURRENT OPINION IN VIROLOGY, vol. 38, 1 October 2019 (2019-10-01), pages 70-80, XP055795898, United Kingdom ISSN: 1879-6257, DOI: 10.1016/j.coviro.2019.07.007 table 1	1,24,31

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) for Viral Suppression in Adults Living With HIV-1", ClinicalTrials.gov v Identifier: NCT03739996, 14 November 2018 (2018-11-14), pages 1-14, XP055795915, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT03739996 [retrieved on 2021-04-15] the whole document	1,24,31
Y	US 2017/232020 A1 (MALHOTRA GEENA [IN] ET AL) 17 August 2017 (2017-08-17) paragraphs [0062], [0066]; claims 1,4,19	1,24,31
Y	WO 2018/002902 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY LTD [GB]) 4 January 2018 (2018-01-04) page 17 - page 19; table 2 page 33, line 28 - page 34, line 4 pages 35,39 - page 43	1,24,31
Y	JUCKER BEAT M ET AL: "Multimodal imaging approach to examine biodistribution kinetics of Cabotegravir (GSK1265744) long acting parenteral formulation in rat", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 268, 16 October 2017 (2017-10-16), pages 102-112, XP085300178, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2017.10.017 page 103, right-hand column	1-31
Y	Rowe R. C. ET AL: "Poloxamer" In: "Handbook of Pharmaceutical Excipients", 1 January 2009 (2009-01-01), Pharmaceutical Press, UK, XP055629883, ISBN: 978-0-85369-792-3 pages 506-509, 651-6, page 506 - page 509	1-33

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Raymond C. Rowe Et Al: "Polyethylene Glycol" In: "Handbook of Pharmaceutical Excipients", 1 January 2006 (2006-01-01), Pharmaceutical Press [u.a.], London [u.a.] 031835, XP055399278, ISBN: 978-1-58212-058-4 pages 545-550, page 545 - page 550 -----	1-33
Y	US 2004/265388 A1 (ZHANG ZHONG [US] ET AL) 30 December 2004 (2004-12-30) paragraph [0130] - paragraph [0131]; claims 1,3,4 -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/061582

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-23, 25-30, 32, 33(completely); 24, 31(partially)

Pharmaceutical composition comprising cabotegravir as the sole active ingredient for the treatment and prevention of HIV-1

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2. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a Compound 1 or 2 for the treatment and prevention of HIV-1

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3. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a penta-fused Compound 3 for the treatment and prevention of HIV-1

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4. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a purine Compound 4 for the treatment and prevention of HIV-1.

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5. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and the broadly neutralising antibody (bNAb) N6LS for the treatment and prevention of HIV-1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2020/061582

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ANNEXURE-4

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

(19) World Intellectual Property Organization
International Bureau

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WIPO | PCT

(10) International Publication Number
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C07D 401/14 (2006.01) *A61K 31/4439* (2006.01)
A61P 31/18 (2006.01)

(21) International Application Number:
PCT/US2017/047416

(22) International Filing Date:
17 August 2017 (17.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/377,312 19 August 2016 (19.08.2016) US
62/457,555 10 February 2017 (10.02.2017) US

(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

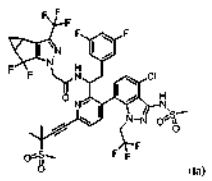
(72) Inventors: **GRAUPE, Michael**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **HENRY, Steven J.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **LINK, John O.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **ROWE, Charles William**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **SAITO, Roland D.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **SCHROEDER, Scott D.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **STEFANIDIS, Dimitrios**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **TSE, Winston C.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **ZHANG, Jennifer R.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

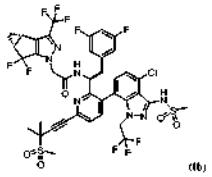
(74) Agent: **LO, Karen** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

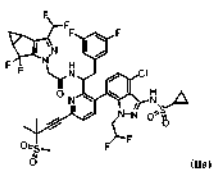
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

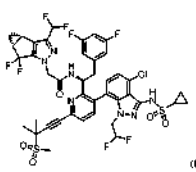
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: THERAPEUTIC COMPOUNDS USEFUL FOR THE PROPHYLACTIC OR THERAPEUTIC TREATMENT OF AN HIV VIRUS INFECTION









(57) Abstract: The present disclosure relates to a compound of formula (Ia), (Ib), (IIa), and (IIb): (Ia) (Ib) (IIa) (IIb) which are useful in the treatment of a Retroviridae viral infection including an infection caused by the HIV virus.

WO 2018/035359 A1

[Continued on next page]

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

THERAPEUTIC COMPOUNDS USEFUL FOR THE PROPHYLACTIC OR THERAPEUTIC TREATMENT OF AN HIV VIRUS INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit to U.S. Provisional Application Serial No. 62/377,312, filed on August 19, 2016 and to U.S. Provisional Application Serial No. 62/457,555, filed February 10, 2017, the disclosures of which are incorporated by reference in their entireties

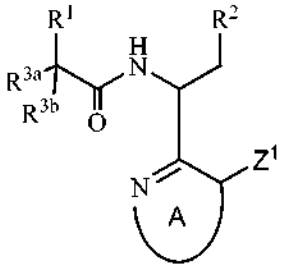
FIELD

[0002] The present disclosure relates to novel compounds for use in the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus. The present disclosure also relates to intermediates for its preparation and to pharmaceutical compositions containing said novel compound.

BACKGROUND

[0003] Positive-single stranded RNA viruses comprising the *Retroviridae* family include those of the subfamily *Orthoretrovirinae* and genera *Alpharetrovirus*, *Betaretrovirus*, *Gammaretrovirus*, *Deltaretrovirus*, *Epsilonretrovirus*, *Lentivirus*, and *Spumavirus* which cause many human and animal diseases. Among the *Lentivirus*, HIV-1 infection in humans leads to depletion of T helper cells and immune dysfunction, producing immunodeficiency and vulnerability to opportunistic infections. Treating HIV-1 infections with highly active antiretroviral therapies (HAART) has proven to be effective at reducing viral load and significantly delaying disease progression (Hammer, S.M., et al.; *JAMA* 2008, 300: 555-570). However, these treatments could lead to the emergence of HIV strains that are resistant to current therapies (Taiwo, B., *International Journal of Infectious Diseases* 2009, 13:552-559; Smith, R. J., et al., *Science* 2010, 327:697-701). Therefore, there is a pressing need to discover new antiretroviral agents that are active against emerging drug-resistant HIV variants.

[0004] U.S. Patent Publication No. 2014/0296266A1, published October 2, 2014, discloses compounds useful for treating a *Retroviridae* viral infection including an infection caused by the HIV virus. U.S. Patent Publication 2014/0296266A1 relates to, among other things, compounds of Formula I:



I

wherein:

A is a 6-membered monocyclic-heteroaryl with one or two nitrogen atoms, wherein the 6-membered monocyclic-heteroaryl is substituted with one Z^1 group at the position shown, one Z^2 group, and optionally substituted with one or more (e.g., 1 or 2) Z^3 groups;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl or 3-12 membered heterocycle of R^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^4 groups;

R^2 is phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle, wherein any phenyl, 5-membered monocyclic-heteroaryl, 6-membered monocyclic-heteroaryl or $(C_3$-$C_7)$carbocycle of R^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^5 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl, or R^{3a} is selected from H, $(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$haloalkyl and R^{3b} is selected from -OH and -CN;

Z^1 is selected from 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl and 3-14 membered heterocycle of Z^1 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b};

each Z^{1a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, $-OR^{n1}$, $-OC(O)R^{p1}$, $-OC(O)NR^{q1}R^{r1}$, $-SR^{n1}$, $-S(O)R^{p1}$, $-S(O)_2OH$, $-S(O)_2R^{p1}$, $-S(O)_2NR^{q1}R^{r1}$, $-NR^{q1}R^{r1}$, $-NR^{n1}COR^{p1}$, $-NR^{n1}CO_2R^{p1}$, $-NR^{n1}CONR^{q1}R^{r1}$, $-NR^{n1}S(O)_2R^{p1}$, $-NR^{n1}S(O)_2OR^{p1}$, $-NR^{n1}S(O)_2NR^{q1}R^{r1}$, NO_2, $-C(O)R^{n1}$, $-C(O)OR^{n1}$, $-C(O)NR^{q1}R^{r1}$ and $-S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl, wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^{1b} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from $(C_3$-$C_7)$carbocycle, phenyl, 5-6 membered monocyclic-heteroaryl, 3-7 membered heterocycle, halogen, -CN, $-OR^{n2}$, $-OC(O)R^{p2}$, $-OC(O)NR^{q2}R^{r2}$, $-SR^{n2}$, $-S(O)R^{p2}$, $-S(O)_2OH$, $-S(O)_2R^{p2}$, $-S(O)_2NR^{q2}R^{r2}$, $-NR^{q2}R^{r2}$, $-NR^{n2}COR^{p2}$, $-NR^{n2}CO_2R^{p2}$, $-NR^{n2}CONR^{q2}R^{r2}$, $-NR^{n2}S(O)_2R^{p2}$, $-NR^{n2}S(O)_2OR^{p2}$, $-NR^{n2}S(O_2NR^{q2}R^{r2}$, NO_2, $-C(O)R^{n2}$, $-C(O)OR^{n2}$, $-C(O)NR^{q2}R^{r2}$, halophenyl, 5-6 membered haloheteroaryl, 3-7 membered haloheterocycle and $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl and $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{n1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

each R^{p1} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{p1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups;

R^{q1} and R^{r1} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl and phenyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of R^{q1} or R^{r1} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} groups, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups;

each R^{n2} is independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

each R^{p2} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl;

R^{q2} and R^{r2} are each independently selected from H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, 5-6 membered monocyclic-heteroaryl, phenyl, halophenyl, 5-6 membered monocyclic-haloheteroaryl, 3-7 membered haloheterocycle, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$heteroalkyl, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

Z^2 is selected from $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$ and $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl and 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^2 is optionally substituted with one or more (e.g., 1, 2, 3, 4, or 5) Z^{2c} groups;

each Z^{2a} is independently selected from $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$, wherein any $(C_3$-$C_7)$carbocycle, 6-12 membered aryl, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{2a} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each Z^{2b} is independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^{2c} is independently selected from halogen, $-CN$, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, NO_2, $-C(O)R^{n4}$, $-C(O)OR^{n4}$ and $-C(O)NR^{q4}R^{r4}$;

each R^{n3} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl and $(C_2$-$C_4)$alkynyl of R^{n3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups;

R^{q3} and R^{r3} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl, wherein any $(C_3$-$C_7)$carbocycle, 3-12 membered heterocycle, 5-12 membered heteroaryl and 6-12 membered aryl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups, and wherein any $(C_1$-$C_4)$alkyl and $(C_2$-$C_4)$alkenyl of R^{q3} or R^{r3} is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2a} groups, or R^{q3} and R^{r3} together with the nitrogen to which they are attached form a heterocycle or heteroaryl, wherein the heterocycle or heteroaryl is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{2b} or Z^{2c} groups;

each R^{n4} is independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each R^{p4} is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

R^{q4} and R^{r4} are each independently selected from H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$haloalkyl and $(C_1$-$C_4)$heteroalkyl;

each Z^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, -OH, -CN, $(C_1$-$C_4)$heteroalkyl and $(C_1$-$C_4)$haloalkyl;

each Z^4 is independently selected from $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-OC(O)R^{p5}$, $-OC(O)NR^{q5}R^{r5}$, $-SR^{n5}$, $-S(O)R^{p5}$, $-S(O)_2OH$, $-S(O)_2R^{p5}$, $-S(O)_2NR^{q5}R^{r5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-NR^{n5}CONR^{q5}R^{r5}$, $-NR^{n5}S(O)_2R^{p5}$, $-NR^{n5}S(O)_2OR^{p5}$, $-NR^{n5}S(O)_2NR^{q5}R^{r5}$, NO_2, $-C(O)R^{n5}$, $-C(O)OR^{n5}$ and $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle, of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} or Z^{4b} groups, and wherein any $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl and $(C_2$-$C_8)$alkynyl of Z^4 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) Z^{4a} groups;

each Z^{4a} is independently selected from halogen, -CN, $-OR^{n6}$, $-OC(O)R^{p6}$, $-OC(O)NR^{q6}R^{r6}$, $-SR^{n6}$, $-S(O)R^{p6}$, $-S(O)_2OH$, $-S(O)_2R^{p6}$, $-S(O)_2NR^{q6}R^{r6}$, $-NR^{q6}R^{r6}$,

$-NR^{n6}COR^{p6}$, $-NR^{n6}CO_2R^{p6}$, $-NR^{n6}CONR^{q6}R^{r6}$, $-NR^{n6}S(O)_2R^{p6}$, $-NR^{n6}S(O)_2OR^{p6}$, $-NR^{n6}S(O)_2NR^{q6}R^{r6}$, NO_2, $-C(O)R^{n6}$, $-C(O)OR^{n6}$ and $-C(O)NR^{q6}R^{r6}$;

each Z^{4b} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl $(C_2\text{-}C_4)$alkynyl and $(C_1\text{-}C_4)$haloalkyl;

each R^{n5} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p5} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q5} and R^{r5} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{n6} is independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

each R^{p6} is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

R^{q6} and R^{r6} are each independently selected from H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$heteroalkyl, $(C_2\text{-}C_4)$alkenyl and $(C_2\text{-}C_4)$alkynyl;

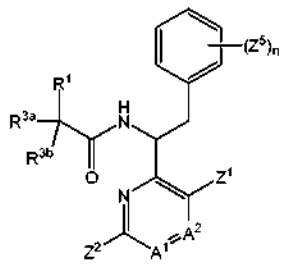
each Z^5 is independently selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN and $-OR^{n7}$,

wherein any $(C_1\text{-}C_6)$alkyl of Z^5 is optionally substituted with one or more (e.g., 1, 2, 3, 4 or 5) halogen; and

each R^{n7} is independently selected from H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$haloalkyl and $(C_3\text{-}C_7)$carbocycle;

or a pharmaceutically acceptable salt thereof.

[0005] U.S. Patent Publication No. 2014/0303164A1, published October 9, 2014, discloses compounds useful for treating a *Retroviridae* viral infection including an infection caused by the HIV virus. U.S. Patent Publication 2014/0303164A1 relates to, among other things, compounds of Formula IIId:



IIId

wherein

A^1 is CH, C-Z^3, or nitrogen;

A^2 is CH or nitrogen;

R^1 is 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle, wherein any 6-12 membered aryl, 5-12 membered heteroaryl, or 3-12 membered heterocycle of R^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^4 groups, wherein the Z^4 groups are the same or different;

each R^{3a} and R^{3b} is independently H or $(C_1$-$C_3)$alkyl;

Z^1 is 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle, wherein any 6-12 membered aryl, 5-14 membered heteroaryl, or 3-14 membered heterocycle of Z^1 is optionally substituted with 1, 2, 3, 4 or 5 Z^{1a} or Z^{1b}, wherein the Z^{1a} and Z^{1b} groups are the same or different;

each Z^{1a} is independently $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl, 3-12 membered heterocycle, halogen, -CN, -OR^{n1}, -$OC(O)R^{p1}$, -$OC(O)NR^{q1}R^{r1}$, -SR^{n1}, -$S(O)R^{p1}$, -$S(O)_2OH$, -$S(O)_2R^{p1}$, -$S(O)_2NR^{q1}R^{r1}$, -$NR^{q1}R^{r1}$, -$NR^{n1}COR^{p1}$, -$NR^{n1}CO_2R^{p1}$, -$NR^{n1}CONR^{q1}R^{r1}$, -$NR^{n1}S(O)_2R^{p1}$, -$NR^{n1}S(O)_2OR^{p1}$, -$NR^{n1}S(O)_2NR^{q1}R^{r1}$, -$C(O)R^{n1}$, -$C(O)OR^{n1}$, -$C(O)NR^{q1}R^{r1}$ and -$S(O)_2NR^{n1}COR^{p1}$, wherein any $(C_3$-$C_7)$carbocycle, 5-12 membered heteroaryl and 3-12 membered heterocycle of Z^{1a} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each Z^{1b} is independently $(C_1$-$C_8)$alkyl optionally substituted with 1, 2, 3, 4 or 5 halogen, which are the same or different;

each Z^{1c} is independently halogen, -CN, -OH, -NH_2, -$C(O)NR^{q2}R^{r2}$, or $(C_1$-$C_8)$heteroalkyl;

each Z^{1d} is independently $(C_1$-$C_8)$alkyl or $(C_1$-$C_8)$haloalkyl;

each R^{n1} is independently H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any $(C_1$-$C_8)$alkyl of R^{n1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{p1} is independently $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any $(C_3$-$C_7)$carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same

or different, and wherein any (C_1-C_8)alkyl of R^{p1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different;

each R^{q1} and R^{r1} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl, wherein any (C_3-C_7)carbocycle, 3-7 membered heterocycle, or 5-6 membered monocyclic-heteroaryl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different, and wherein any (C_1-C_8)alkyl of R^{q1} or R^{r1} is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} groups, wherein the Z^{1c} groups are the same or different, or R^{q1} and R^{r1} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle, wherein the 5, 6 or 7-membered heterocycle is optionally substituted with 1, 2, 3, 4 or 5 Z^{1c} or Z^{1d} groups, wherein the Z^{1c} and Z^{1d} groups are the same or different;

each R^{q2} and R^{r2} is independently H, (C_1-C_8)alkyl, (C_3-C_7)carbocycle, or R^{q2} and R^{r2} together with the nitrogen to which they are attached form a 5, 6, or 7-membered heterocycle;

Z^2 is (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, 3-12 membered C-linked-heterocycle, $-C(O)R^{n3}$, or $-C(O)NR^{q3}R^{r3}$, wherein any 6-12 membered aryl, 5-12 membered C-linked-heteroaryl, or 3-12 membered C-linked-heterocycle of Z^2 is optionally substituted with 1, 2, 3, 4 or 5 Z^{2b} or Z^{2c} groups, wherein the Z^{2b} and Z^{2c} groups are the same or different, and wherein any (C_2-C_8)alkenyl or (C_2-C_8)alkynyl of Z^2 is optionally substituted with 1, 2, 3, 4, or 5 Z^{2c} groups, wherein the Z^{2c} groups are the same or different;

each R^{n3} is independently H or (C_1-C_4)alkyl;

each R^{q3} and R^{r3} is independently H or (C_1-C_4)alkyl;

each Z^{2b} is independently oxo, (C_1-C_4)alkyl, (C_1-C_4)heteroalkyl or (C_1-C_4)haloalkyl;

each Z^{2c} is independently oxo, halogen, -CN, $-OR^{n4}$, $-OC(O)R^{p4}$, $-OC(O)NR^{q4}R^{r4}$, $-SR^{n4}$, $-S(O)R^{p4}$, $-S(O)_2OH$, $-S(O)_2R^{p4}$, $-S(O)_2NR^{q4}R^{r4}$, $-NR^{q4}R^{r4}$, $-NR^{n4}COR^{p4}$, $-NR^{n4}CO_2R^{p4}$, $-NR^{n4}CONR^{q4}R^{r4}$, $-NR^{n4}S(O)_2R^{p4}$, $-NR^{n4}S(O)_2OR^{p4}$, $-NR^{n4}S(O)_2NR^{q4}R^{r4}$, $-NO_2$, $-C(O)R^{n4}$, $-C(O)OR^{n4}$, or $-C(O)NR^{q4}R^{r4}$;

each R^{n4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{p4} is independently (C_1-C_8)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each R^{q4} and R^{r4} is independently H, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, or (C_1-C_4)heteroalkyl;

each Z^3 is independently a (C_1-C_4)heteroalkyl;

each Z^4 is independently oxo, $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$carbocycle, halogen, -CN, $-OR^{n5}$, $-NR^{q5}R^{r5}$, $-NR^{n5}COR^{p5}$, $-NR^{n5}CO_2R^{p5}$, $-C(O)R^{n5}$, $-C(O)OR^{n5}$, or $-C(O)NR^{q5}R^{r5}$, wherein any $(C_3$-$C_7)$carbocycle or $(C_1$-$C_8)$alkyl of Z^4 is optionally substituted with 1, 2, 3, 4 or 5 Z^{4a} groups, wherein the Z^{4a} groups are the same or different;

each Z^{4a} is independently halogen, -CN, or $-OR^{n6}$;

each R^{n5}, R^{p5}, R^{q5}, R^{r5}, and R^{n6} is independently H or $(C_1$-$C_4)$alkyl;

each Z^5 is independently halogen, which may be same or different; and

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

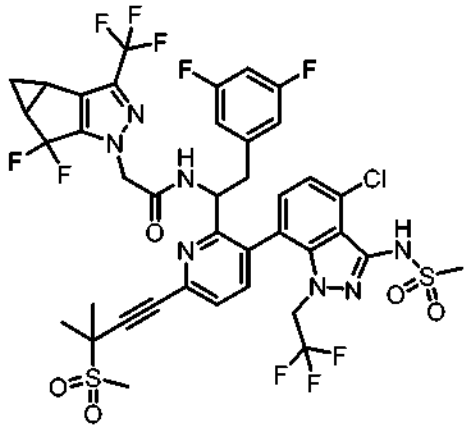
[0006] The above disclosures notwithstanding, there is a need for compounds that are potent and stable and exhibit improved pharmacokinetic and/or pharmacodynamic profiles for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0007] Also of interest in the area of HIV therapies and treatments is extending the pharmacokinetic property of regimens provided to patients. While current regimens for treating HIV have progressed enough that patients no longer have to take multiple pills multiple times a day, patients today still are required to take a pill every day for the foreseeable span of their life. Thus, it would be beneficial to have HIV therapies that require patients take medication less than once a day (e.g. once every couple of days, once a week, once every other week, once a month, and so forth).

[0008] Provided herein are novel compounds exhibiting improved potency, improved metabolic stability, and improved pharmacokinetic and/or pharmacodynamic profiles.

SUMMARY

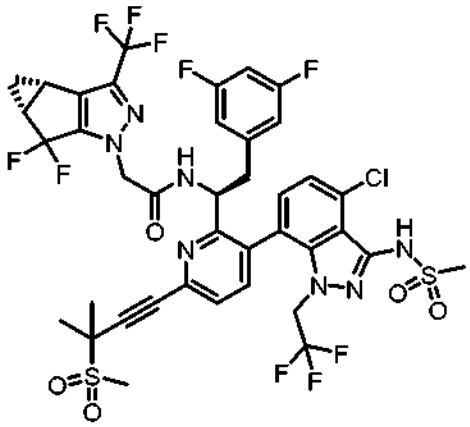
[0009] In some embodiments, the current disclosure relates to a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

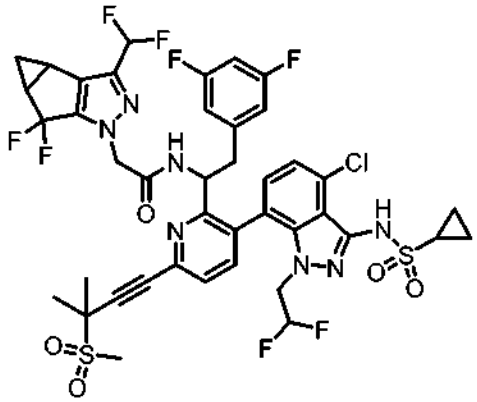
[0010] In some embodiments, the current disclosure relates to a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof.

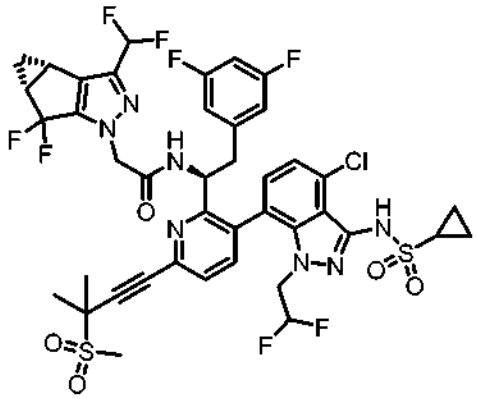
[0011] In some embodiments, the current disclosure relates to a compound of formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the current disclosure relates to a compound of formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof.

[0013] In one embodiment, the current disclosure relates to the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the treatment of a disease in a subject in need thereof.

[0014] In one embodiment, the current disclosure relates to the use of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in the treatment of a disease in a subject in need thereof.

[0015] In certain embodiments, the current disclosure relates to a pharmaceutical composition comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is an injectable form. In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[0016] In some embodiments, the current disclosure relates to a pharmaceutical composition comprising a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is a parenteral (e.g., injectable) form. In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[0017] In certain embodiments, the current disclosure relates to an article of manufacture comprising a unit dosage of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

[0018] In some embodiments, the current disclosure relates to an article of manufacture comprising a unit dosage of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[0019] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

[0020] In some embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[0021] In certain embodiments, the current disclosure relates to a method for preventing an HIV infection in a subject, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[0022] In certain embodiments, the current disclosure relates to a method for preventing an HIV infection in a subject, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[0023] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0024] In certain embodiments, the current disclosure relates to a method for treating or preventing an HIV infection in a subject in need thereof, comprising administering to the subject a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

[0025] In certain embodiments, the current disclosure relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in medical therapy.

[0026] In certain embodiments, the current disclosure relates to a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in medical therapy.

[0027] In certain embodiments, the current disclosure relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in treating or preventing an HIV infection in a subject.

[0028] In certain embodiments, the current disclosure relates to a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in treating or preventing an HIV infection in a subject.

[0029] In certain embodiments, the current disclosure relates to the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing an HIV infection in a subject.

[0030] In certain embodiments, the current disclosure relates to the use of a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating or preventing an HIV infection in a subject.

[0031] In another embodiment, the current disclosure relates to intermediates useful for the synthesis of the compound of formula (Ia) or (Ib).

[0032] In another embodiment, the current disclosure relates to intermediates useful for the synthesis of the compound of formula (Ia), (Ib), (IIa), and/or (IIb).

[0033] In some embodiments, the pharmaceutically acceptable salt of the compound of formula (Ia), (Ib), (IIa), and/or (IIb) is the sodium salt.

[0034] Additional embodiments of the current disclosure are disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] FIG. 1 shows ^{1}H NMR of (400 MHz, Methanol-d_4) of *N*-((*S*)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-7-yl)-6-(3-methyl-3-

(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamide.

[0036] FIG. 2 shows ^{1}H NMR of (400 MHz, Methanol-d_4) N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

[0037] FIG. 3 shows the plasma concentration (nM) of Compound 38 after a single subcutaneous (SC) dose in rats.

[0038] FIG. 4 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0039] FIG. 5 shows a plot of plasma concentration over time of 100mg/mL of Formula Ib in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0040] FIG. 6 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, sodium salt in 2% poloxamer 188 in saline when subcutaneously dosed in dogs at 6mg/kg.

[0041] FIG. 7 shows a plot of plasma concentration over time of 100mg/mL of Formula Ib, free acid form in NMP when subcutaneously dosed in dogs at 6 mg/kg.

[0042] FIG. 8 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, free acid form in NMP when subcutaneously dosed in dogs at 6mg/kg.

[0043] FIG. 9 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, sodium salt in NMP when subcutaneously dosed in subjects at 6mg/kg.

[0044] FIG. 10 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 10% ethanol, 12% water, and 78% PEG 200 when dosed subcutaneously in subjects at 6mg/kg.

[0045] FIG. 11 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib, *in situ* salt, in 10% ethanol, 12% water, and 77% PEG 200 when dosed subcutaneously in subjects at 6mg/kg.

[0046] FIG. 12 shows a plot of plasma concentration over time of 200mg/mL of Formula Ib in 10% ethanol, 13% water, and 77% glycofurol, with 1.2 mol-eq. NaOH to form *in situ* Na salt when dosed in subjects at 6mg/kg.

[0047] FIG. 13 shows a plot of plasma concentration over time of a fixed 7.5mg oral dose of Formula Ib in 10% ethanol, 20% Vitamin E TPGS, 70% MIGLYOL 812 in dogs.

DETAILED DESCRIPTION

[0048] The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0049] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0050] When trade names are used herein, it is intended to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

[0051] As used herein and in the appended claims, the singular forms "a" and "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, *e.g.*, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays, and so forth.

[0052] As used herein, the term "C_{max}" refers to the maximum observed plasma/serum concentration of drug.

[0053] "Pharmaceutically acceptable" refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0054] "Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0055] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid,

malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, *e.g.*, an alkali metal ion (*e.g.* a sodium or potassium), an alkaline earth ion (*e.g.* calcium or magnesium), or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, *N*-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0056] "Subject" and "subjects" refers to humans, domestic animals (*e.g.*, dogs and cats), farm animals (*e.g.*, cattle, horses, sheep, goats and pigs), laboratory animals (*e.g.*, mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys), and the like.

[0057] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment, "treatment" or "treating" includes one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and/or c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0058] As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop the disease or condition. For example, a method that "delays" development of AIDS is a method that

reduces the probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method. Such comparisons may be based on clinical studies, using a statistically significant number of subjects. For example, the development of AIDS can be detected using known methods, such as confirming a subject's HIV^+ status and assessing the subject's T-cell count or other indication of AIDS development, such as extreme fatigue, weight loss, persistent diarrhea, high fever, swollen lymph nodes in the neck, armpits or groin, or presence of an opportunistic condition that is known to be associated with AIDS (*e.g.*, a condition that is generally not present in subjects with functioning immune systems but does occur in AIDS patients). Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence and onset.

[0059] As used herein, "prevention" or "preventing" refers to a regimen that protects against the onset of the disease or disorder such that the clinical symptoms of the disease do not develop. Thus, "prevention" relates to administration of a therapy (e.g., administration of a therapeutic substance) to a subject before signs of the disease are detectable in the subject (e.g., administration of a therapeutic substance to a subject in the absence of detectable infectious agent (e.g., virus) in the subject). The subject may be an individual at risk of developing the disease or disorder, such as an individual who has one or more risk factors known to be associated with development or onset of the disease or disorder. Thus, the term "preventing HIV infection" refers to administering to a subject who does not have a detectable HIV infection an anti-HIV therapeutic substance. It is understood that the subject for anti-HIV preventative therapy may be an individual at risk of contracting the HIV virus. Further, it is understood that prevention may not result in complete protection against onset of the disease or disorder. In some instances, prevention includes reducing the risk of developing the disease or disorder. The reduction of the risk may not result in complete elimination of the risk of developing the disease or disorder.

[0060] As used herein, an "at risk" individual is an individual who is at risk of developing a condition to be treated. An individual "at risk" may or may not have detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment of methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk

factors has a higher probability of developing the disease or condition than an individual without these risk factor(s). For example, individuals at risk for AIDS are those having HIV.

[0061] As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease or to an amount that is effective to protect against the contracting or onset of a disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment outcome. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[0062] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. A mixture of enantiomers at a ratio other than 1:1 is a "scalemic" mixture.

[0063] "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0064] The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and/or hindered rotation about a bond axis and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present disclosure is meant to include all such possible isomers, including racemic mixtures, scalemic mixtures, diastereomeric mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0065] Except as expressly defined otherwise, the present disclosure includes all tautomers of compounds detailed herein, even if only one tautomer is expressly represented (*e.g.*, both tautomeric forms are intended and described by the presentation of one tautomeric form where a pair of two tautomers may exist). For example, if reference is made to a compound containing an amide (*e.g.*, by structure or chemical name), it is understood that the corresponding imidic acid tautomer is included by this disclosure and described the same as if the amide were expressly recited either alone or together with the imidic acid. Where more than two tautomers may exist, the present disclosure includes all such tautomers even if only a single tautomeric form is depicted by chemical name and/or structure.

[0066] The present disclosure also provides for prodrugs of the compound of Formula (Ia) or (Ib). A "prodrug" is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

[0067] Additionally, in some embodiments, the present disclosure also provides for prodrugs of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb).

[0068] It is understood by one skilled in the art that this disclosure also includes any compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^{2}H or D).

[0069] Disclosed are also compounds in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds when administered to a mammal. *See, e.g.*, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0070] Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate

receptor occupancy. Isotopically-labeled compounds of Formula (Ia) or (Ib), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0071] Additionally, in some embodiments, isotopically-labeled compounds of Formula (Ia), (Ib), (IIa), and/or (IIb), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0072] Compounds described herein may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that all such optical, enantiomeric, diastereoisomeric and geometric isomers are encompassed. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

[0073] Also provided are also pharmaceutically acceptable hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein.

[0074] In a preferred embodiment, the current disclosure relates to the use of the compound of formula (Ia) or (Ib) in treating a *Retroviridae* viral infection including an infection caused by the HIV virus comprising administering a therapeutically effective amount to a subject in need thereof.

[0075] In a preferred embodiment, the current disclosure relates to the use of the compound of formula (Ia), (Ib), (IIa), and/or (IIb) in treating a *Retroviridae* viral infection including an infection caused by the HIV virus comprising administering a therapeutically effective amount to a subject in need thereof.

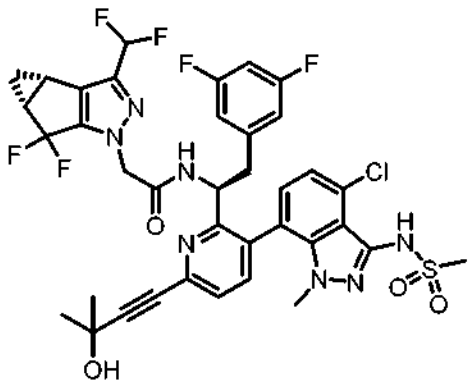
[0076] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof having a low EC_{50}. The EC_{50} value refers to the concentration of a compound in an assay that achieves 50% of the maximum efficacy. A compound with a lower EC_{50} achieves similar efficacy with lower compound concentration relative to a compound with a higher EC_{50}. Thus, a lower EC_{50} is generally preferred for drug development.

[0077] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has good physical and/or chemical stability. An increase in overall stability of a compound can provide an increase in circulation time in the body. With less degradation, a stable compound can be administered in lower doses and still maintain efficacy. Also, with less degradation, there is less concern about by-products from degradation of a compound.

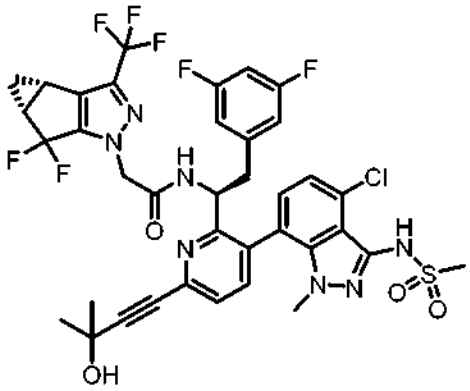
[0078] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has improved pharmacokinetic and/or pharmacodynamic profiles and long half-life. It is advantageous for a drug to have a moderate or low clearance and a long half-life, as this can lead to a good bioavailability and high exposure in systemic exposure. Reducing the clearance and increasing half-life time of a compound could reduce the daily dose required for efficacy and therefore give a better efficacy and safety profile. Thus, improved pharmacokinetic and/or pharmacodynamic profiles and long half-life can provide for better patient compliance.

[0079] It is a desirable goal to discover a compound or a pharmaceutically acceptable salt thereof that has good pharmacokinetic profile from a slow release injectable formulation. It is advantageous for a drug to have a low EC_{50} and long acting pharmacokinetics, as this can lead to low frequency of administration. Reducing the frequency of administration can provide for better patient compliance. Reducing the frequency of administration can be desirable for patients with difficult or limited access to health care.

[0080] Advantageously, discovered is a compound of formula (Ia) and (Ib) herein that provides advantages compared to structurally close compounds (herein designated as compounds A and B) disclosed in U.S. Patent Publication Nos. 2014/0296266A1 and 2014/0303164A1:

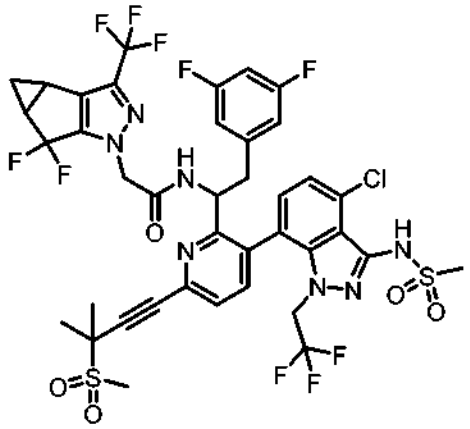


Compound A



Compound B

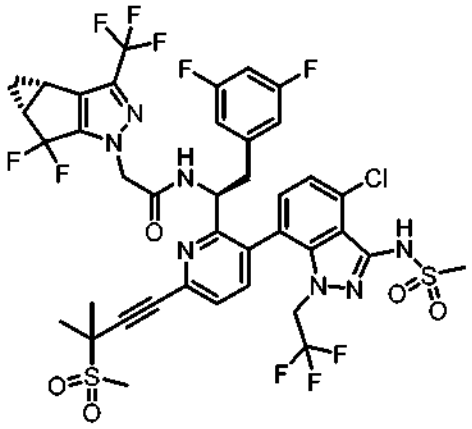
[0081] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (Ia)



(Ia)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (Ia) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0082] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (Ib)

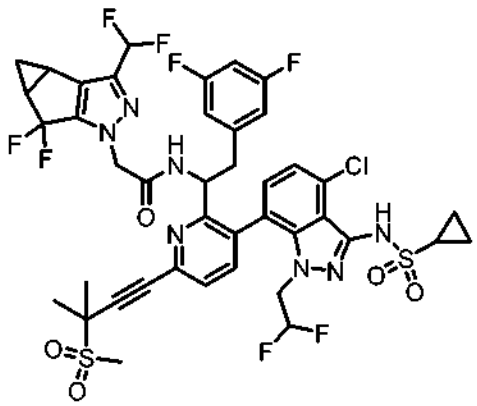


(Ib)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (Ib) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0083] Also disclosed herein is a compound of formula (IIa) and (IIb), which provides advantages compared to Compounds A and B (shown above).

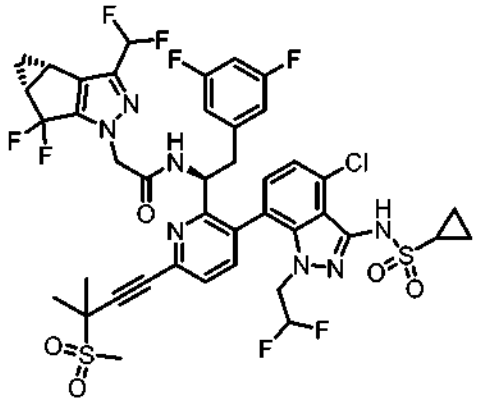
[0084] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (IIa)



(IIa)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (IIa) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0085] Therefore, the present disclosure includes but is not limited to the provision of a compound of formula (IIb)



(IIb)

or pharmaceutically acceptable salt thereof, and methods of using the compound of formula (IIb) for the treatment of a *Retroviridae* viral infection including an infection caused by the HIV virus.

[0086] In some embodiments, the compounds disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or pharmaceutically acceptable salt thereof) are used for preventing an HIV infection in a subject. In some embodiments, the compounds disclosed herein are used for preventing an HIV infection in a subject at risk for infection. In some embodiments, the compounds disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

[0087] It is believed that the compounds disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) are active against major HIV-1 mutants selected by clinical Protease Inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase inhibitors (INSTIs).

Combination Therapy

[0088] In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound

disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

[0089] In some embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

[0090] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0091] In some embodiments, pharmaceutical compositions comprising a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0092] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0093] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0094] In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof.

[0095] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

[0096] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt

thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HIV Combination Therapy

[0097] In certain embodiments, a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, and the one or more additional therapeutic agents are both present in the body of the subject. When administered sequentially, the combination may be administered in two or more administrations.

[0098] In some embodiments, a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, and the one or more additional therapeutic agents are both present in the body of the subject. When administered sequentially, the combination may be administered in two or more administrations.

[0099] Co-administration includes administration of unit dosages of the compounds disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or pharmaceutically acceptable

salts thereof, before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)) is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)).

[00100] In some embodiments, co-administration includes administration of unit dosages of the compounds disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or pharmaceutically acceptable salts thereof, before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (e.g., a compound of formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first,

followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)).

[00101] For the avoidance of doubt, co-administration of a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents, may refer to co-administration with one or more of the thereapeutic agents described herein, e.g. for example those agents listed in paragraphs [00111] to [00162].

[00102] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a subject. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

[00103] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a subject. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

[00104] The compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof), in combination with one or more additional

therapeutic agents can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00105] The compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), in combination with one or more additional therapeutic agents can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00106] In certain embodiments, a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00107] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00108] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a solution formulation, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00109] In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is formulated as a suspension, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[00110] In certain embodiments, such tablets are suitable for once daily dosing.

HIV Combination Therapy

[00111] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent selected from the group consisting of combination drugs for treating HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing

factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV vaccines, and combinations thereof.

[00112] In some embodiments, the additional therapeutic agent is selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry (fusion) inhibitors, HIV maturation inhibitors, latency reversing agents, capsid inhibitors, immune-based therapies, PI3K inhibitors, HIV antibodies, and bispecific antibodies, and "antibody-like" therapeutic proteins, and combinations thereof.

HIV Combination Drugs

[00113] Examples of combination drugs include ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF+FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat; efavirenz, lamivudine, and tenofovir disoproxil fumarate; lamivudine and tenofovir disoproxil fumarate; tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); KALETRA® (ALUVIA®; lopinavir and ritonavir); TRIUMEQ® (dolutegravir, abacavir, and lamivudine); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); atazanavir and cobicistat; atazanavir sulfate and cobicistat; atazanavir

sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; cabotegravir and rilpivirine; cabotegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dolutegravir + lamivudine; lamivudine + abacavir + zidovudine; lamivudine + abacavir; lamivudine + tenofovir disoproxil fumarate; lamivudine + zidovudine + nevirapine; lopinavir + ritonavir; lopinavir + ritonavir + abacavir + lamivudine; lopinavir + ritonavir + zidovudine + lamivudine; tenofovir + lamivudine; and tenofovir disoproxil fumarate + emtricitabine + rilpivirine hydrochloride; lopinavir , ritonavir, zidovudine and lamivudine; Vacc-4x and romidepsin; and APH-0812.

Other HIV Drugs

[00114] Examples of other drugs for treating HIV include acemannan, alisporivir, BanLec, deferiprone, Gamimune, metenkefalin, naltrexone, Prolastin, REP 9, RPI-MN, VSSP, H1viral, SB-728-T, 1,5-dicaffeoylquinic acid, rHIV7-shl-TAR-CCR5RZ, AAV-eCD4-Ig gene therapy, MazF gene therapy, BlockAide, ABX-464, AG-1105, APH-0812, BIT-225, CYT-107, HGTV-43, HPH-116, HS-10234, IMO-3100, IND-02, MK-1376, MK-8507, MK-8591, NOV-205, PA-1050040 (PA-040), PGN-007, SCY-635, SB-9200, SCB-719, TR-452, TEV-90110, TEV-90112, TEV-90111, TEV-90113, RN-18, Immuglo, and VIR-576.

HIV Protease Inhibitors

[00115] Examples of HIV protease inhibitors include amprenavir, atazanavir, brecanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, tipranavir, DG-17, TMB-657 (PPL-100), T-169, BL-008, and TMC-310911.

HIV Reverse Transcriptase Inhibitors

[00116] Examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, rilpivirine, AIC-292, KM-023, and VM-1500. Further

examples of non-nucleoside reverse transcriptase inhibitors are disclosed in U.S. Patent Publication No. US2016/0250215.

[00117] Examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, and KP-1461.

[00118] In some embodiments, examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, KP-1461, and 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

HIV Integrase Inhibitors

[00119] Examples of HIV integrase inhibitors include elvitegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, dolutegravir, JTK-351, bictegravir, AVX-15567, diketo quinolin-4-1 derivatives, integrase-LEDGF inhibitor, ledgins, M-522, M-532, NSC-310217, NSC-371056, NSC-48240, NSC-642710, NSC-699171, NSC-699172, NSC-699173, NSC-699174, stilbenedisulfonic acid, T-169 and cabotegravir.

[00120] Examples of HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) include CX-05045, CX-05168, and CX-14442.

HIV Entry Inhibitors

[00121] Examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, gp120 inhibitors, and CXCR4 inhibitors.

[00122] Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

[00123] Examples of gp41 inhibitors include albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

[00124] Examples of CD4 attachment inhibitors include ibalizumab and CADA analogs

[00125] Examples of gp120 inhibitors include Radha-108 (receptol) 3B3-PE38, BanLec, bentonite-based nanomedicine, fostemsavir tromethamine, IQP-0831, and BMS-663068

[00126] Examples of CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

HIV Maturation Inhibitors

[00127] Examples of HIV maturation inhibitors include BMS-955176 and GSK-2838232.

Latency Reversing Agents

[00128] Examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors such as velcade, protein kinase C (PKC) activators, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA (suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), IL-15, JQ1, disulfram, amphotericin B, and ubiquitin inhibitors such as largazole analogs, and GSK-343.

[00129] Examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

[00130] Examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

Capsid Inhibitors

[00131] Examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide, HIV p24 capsid protein inhibitors, AVI-621, AVI-101, AVI-201, AVI-301, and AVI-CAN1-15 series;

Immune-based Therapies

[00132] Examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin; rintatolimod, polymer polyethyleneimine (PEI); gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, RPI-MN, GS-9620, and IR-103.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

[00133] Examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib, puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, taselisib, AMG-319, AZD-8186, BAY-1082439, CLR-1401, CLR-457, CUDC-907, DS-7423, EN-3342, GSK-2126458, GSK-2269577, GSK-2636771, INCB-040093, LY-3023414, MLN-1117, PQR-309, RG-7666, RP-6530, RV-1729, SAR-245409, SAR-260301, SF-1126, TGR-1202, UCB-5857, VS-5584, XL-765, and ZSTK-474.

HIV Antibodies, Bispecific Antibodies, and "Antibody-like" Therapeutic Proteins

[00134] Examples of HIV antibodies, bispecific antibodies, and "antibody-like" therapeutic proteins include DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, bnABs (broadly neutralizing HIV-1 antibodies), BMS-936559, TMB-360, and

those targeting HIV gp120 or gp41, antibody-Recruiting Molecules targeting HIV, anti-CD63 monoclonal antibodies , anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs (PGT-121), ibalizumab, Immuglo, MB-66

[00135] Examples of those targeting HIV in such a manner include bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117, PGT145, PGT121, MDX010 (ipilimumab), VRC01, A32, 7B2, 10E8, VRC-07-523, VRC-HIVMAB080-00-AB, MGD-014 and VRC07.

Pharmacokinetic Enhancers

[00136] Examples of pharmacokinetic enhancers include cobicistat and ritonavir.

Additional Therapeutic Agents

[00137] Examples of additional therapeutic agents include the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), WO 2013/159064 (Gilead Sciences), WO 2014/100323 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US 2014/0221378 (Japan Tobacco), US 2014/0221380 (Japan Tobacco), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/006792 (Pharma Resources), US 20140221356 (Gilead Sciences), US 20100143301 (Gilead Sciences) and WO 2013/091096 (Boehringer Ingelheim).

HIV Vaccines

[00138] Examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine,

HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-UGR7C, EN41-FPA2, PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16, VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine.

HIV Combination Therapy

[00139] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA®

(KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; and abacavir sulfate.

[00140] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA® (KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine;

nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; abacavir sulfate; 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA); and Bictegravir, or a pharmaceutically acceptable salt thereof.

[00141] It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

[00142] In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with one or two HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[00143] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with one or two HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In a specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV

nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[00144] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

[00145] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

[00146] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a HIV integrase inhibitor.

[00147] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

[00148] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

[00149] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[00150] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[00151] In a particular embodiment, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, the compound of formula (Ia) or

(Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered simultaneously. Optionally, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a subject. In other embodiments, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

[00152] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered simultaneously. Optionally, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a subject. In other embodiments, the compound of formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

[00153] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with bictegravir or a pharmaceutically acceptable salt thereof.

[00154] A compound as disclosed herein (e.g., any compound of formula (Ia) or (Ib)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of formula (Ia) or (Ib) (e.g., from 1 mg to 1000 mg of compound).

[00155] In some embodiments, a compound as disclosed herein (e.g., any compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb) (e.g., from 1 mg to 1000 mg of compound).

[00156] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia) or (Ib)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00157] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 5-10, 5-15, 5-20, 5-25, 25-30, 20-30, 15-30, or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed

herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00158] In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia) or (Ib)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00159] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 200-250, 200-300, 200-350, 250-350, 250-400, 350-400, 300-400, or 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a

pharmaceutically acceptable salt thereof, is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00160] In some embodiments, a compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is combined with 20-80 mg of bictegravir or a pharmaceutically acceptable salt thereof. A compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 1 mg to 1000 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[00161] In one embodiment, kits comprising a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[00162] In some embodiments, kits comprising a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

Pharmaceutical Compositions

[00163] Pharmaceutical compositions disclosed herein comprise a compound disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients and optionally other therapeutic agents. Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration.

[00164] In some embodiments, pharmaceutical compositions disclosed herein comprise a compound disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients and optionally other therapeutic agents. Pharmaceutical compositions

containing the active ingredient may be in any form suitable for the intended method of administration.

[00165] Pharmaceutical compositions comprising the compound disclosed herein (e.g. a compound of Formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be prepared with conventional carriers (*e.g.*, inactive ingredient or excipient material) which may be selected in accord with ordinary practice. Tablets may contain excipients including glidants, fillers, binders and the like. Aqueous compositions may be prepared in sterile form, and when intended for delivery by other than oral administration generally may be isotonic. All compositions may optionally contain excipients such as those set forth in the Rowe et al, Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[00166] In some embodiments, pharmaceutical compositions comprising the compound disclosed herein (e.g. a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be prepared with conventional carriers (*e.g.*, inactive ingredient or excipient material) which may be selected in accord with ordinary practice. Tablets may contain excipients including glidants, fillers, binders and the like. Aqueous compositions may be prepared in sterile form, and when intended for delivery by other than oral administration generally may be isotonic. All compositions may optionally contain excipients such as those set forth in the Rowe et al, Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. For example, excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[00167] While it is possible for the active ingredient to be administered alone, it may be preferable to present the active ingredient as pharmaceutical compositions. The compositions, both for veterinary and for human use, comprise at least the compound of formula (Ia) or (Ib), together with one or more acceptable carriers and optionally other therapeutic ingredients. In one embodiment, the pharmaceutical composition comprises a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional

therapeutic agents as defined hereinbefore. In one embodiment, the pharmaceutical composition comprises a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic ingredient. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient thereof.

[00168] In some embodiments, even though it is possible for the active ingredient to be administered alone, it may be preferable to present the active ingredient as pharmaceutical compositions. The compositions, both for veterinary and for human use, comprise at least the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), together with one or more acceptable carriers and optionally other therapeutic ingredients. In some embodiments, the pharmaceutical composition comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as defined hereinbefore. In some embodiments, the pharmaceutical composition comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic ingredient. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient thereof.

[00169] The compositions include those suitable for various administration routes. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound of formula (Ia) or (Ib) or a pharmaceutical salt thereof) with one or more inactive ingredients (*e.g.*, a carrier, pharmaceutical excipient, etc.). The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[00170] In some embodiments, the compositions include those suitable for various administration routes. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound

of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof) with one or more inactive ingredients (*e.g.*, a carrier, pharmaceutical excipient, etc.). The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[00171] Compositions described herein that are suitable for oral administration may be presented as discrete units (a unit dosage form) including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

[00172] When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[00173] In some embodiments, disclosed herein are oral dosage forms (e.g., tablets), which may be prepared from hot melt extrusion or spray-drying dispersion (SDD) technologies.

[00174] In some embodiments, disclosed herein are hard capsules filled with powder, beads, or granules containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients may be, for example, inert diluents, such as calcium or sodium

carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc.

[00175] In some embodiments, disclosed herein are hard or soft capsules filled with liquid or semi-solid mixtures containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients may be, for example, solubilizing oils such as maize oil, sesame oil, or corn oil; medium chain triglycerides and related esters, such as, derivitized palm kernel oil or coconut oil; self-emulsifying lipid systems (SEDDS or SMEDDS), such as caprylic triglyceride or propylene glycol monocaprylate; viscosity modifiers, such as, cetyl alcohol, steryl alcohol, glycerol stearate; and solubilizing agents and surfactants, such as polyethylene glycol, propylene glycol, glycerin, ethanol, polyethoxylated castor oil, poloxamers, or polysorbates.

[00176] The pharmaceutical compositions of the present disclosure may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[00177] In some embodiments, the sterile injectable preparation disclosed herein may also be a sterile injectable solution or suspension prepared from a reconstituted lyophilized powder in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland

fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[00178] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. In certain embodiments the suspension is a microsuspension. In certain embodiments the suspension is a nanosuspension.

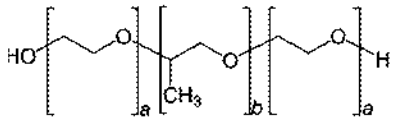
[00179] In some embodiments, formulations suitable for parenteral administration (e.g., intramuscular (IM) and subcutaneous (SC) administration) will include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of parenteral formulation and may be found e.g., in Handbook of Pharmaceutical Excipients (eds. Rowe, Sheskey & Quinn), 6th edition 2009.

[00180] Examples of solubilizing excipients in a parenteral formulation (e.g., an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) and poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed herein is a parenteral administration (e.g., an SC or IM formulation) that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and a poloxamer, in particular poloxamer 338. In some embodiments, the amount of poloxamer (e.g., poloxamer 388) in a parenteral administration disclosed herein is less than about 5%, such as less than about 3%, about 2%, about 1%, or about 0.5%.

[00181] Examples of solubilizing excipients in a parenteral formulation (e.g., an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) , poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed herein is a parenteral administration (e.g., an SC or IM formulation) that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and a poloxamer.

[00182] In certain embodiments, excipients include N-methyl-2- pyrrolidone (NMP), dimethyl sulfoxide, polyethylene glycol and/or tetraglycol/glycofurol.

[00183] In general, poloxamers are synthetic non-ionic triblock of linear copolymers having a central hydrophobic chain of polyoxypropylene adjacent to two hydrophilic polypropylene oxide, in certain instances in a 4:2:4 weight ratio. Accordingly, in certain embodiments, the compositions disclosed herein include a compound of Formula (Ia), (Ib),

(IIa), and/or (IIb), or a pharmaceutical salt thereof, and a block copolymer comprised of one polyoxypropylene segment and two hydrophilic polypropylene oxide segments. In certain embodiments, the ratio of the polyoxypropylene segment to the two hydrophilic polypropylene oxide segments is 4:2:4 (hydrophilic polypropylene oxide: polyoxypropylene: hydrophilic polypropylene oxide). Poloxamers are generally understood to have th following structure:  , where a and b are integers (e.g. a is 2-130 and b is 15-67). Poloxamer 188, for example, is understood to range in molecular weight from about 7680 to about 9510 Daltons (where a is about 80 and b is about 27). International Journal of PharmTech Research, Vol.1, No.2, pp 299-303, April-June 2009. In some instances, poloxamer 188 has an average molecular weight of about 8400 Daltons. Similarly, poloxamer 338 has a molecular weight in the range of from about 12700 to about 17400 Da (where a is about 141 and b is about 44).

[00184] Examples of excipients in a parenteral formulation (e.g. an SC or an IM formulation) may also include polyethylene glycol. In general, polyethylene glycol (PEG) is a polyether having a general formula $H-(O-CH_2-CH_2)_n-OH$. In certain embodiments the PEG may be "capped" by an alkyl group. In those embodiments, the capped PEG is of the formula alkyl-$(O-CH_2-CH_2)_n$-O-alkyl (e.g. $CH_3-(O-CH_2-CH_2)_n-OCH_3$. The pharmaceutical compositions of the present disclosure may include PEG having an average molecular weight of approximately 100 to approximately 1000. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 100 to approximately 800. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 200 to approximately 600. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 400. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 300. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is approximately 200. In some embodiments of the pharmaceutical composition, different molecular weight PEG may be combined to obtain a desired property or properties (e.g. viscosity). Specific examples of PEG include but are not limited to PEG 100, PEG 200, PEG 300, PEG 400, PEG 500, PEG 600, and so forth. PEG 100, for example, refers to a polyethylene glycol with an average molecular weight of about 100.

[00185] In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and saline. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and a poloxamer (such as poloxamer 338, 188, or 207).

[00186] In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, and saline. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and a suspending agent. In some embodiments, the parenteral formulation (e.g., an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, saline, and poloxamer (such as poloxamer 338, 188, or 207).

[00187] In some embodiments, a suspension comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, in a poloxamer and saline is provided. In some embodiments, the concentration of poloxamer in saline is from about 0.1 to about 20%. In some embodiments, the concentration of poloxamer in saline is from about 0.1 to about 10%. In some in embodiments, the concentration of poloxamer in saline is about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2,%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or about 10%. In certain embodiments, the concentration of poloxamer in saline is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula (Ib) or a pharmaceutically acceptable salt therof. In certain embodiments, the compound is a compound of Formula (Ib). In certain embodiments, the compound is a sodium salt of the compound of Formula (Ib).

[00188] In some embodiments, a suspension comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof, in a poloxamer and mannitol is provided. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1 to about

20%. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1 to about 10%. In some in embodiments, the concentration of poloxamer in mannitol is about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2,%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or about 10%. In certain embodiments, the concentration of poloxamer in mannitol is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula (Ib) or a pharmaceutically acceptable salt therof. In certain embodiments, the compound is a compound of Formula (Ib). In certain embodiments, the compound is a sodium salt of the compound of Formula (Ib).

[00189] In certain embodiments, the composition is disclosed as a solid dosage form, including a solid injectable dosage form, such as a solid depot form.

[00190] In certain embodiments, the active ingredient (e.g. a compound of Formula Ib) is present as a free acid. In certain embodiments, the active ingredient (e.g. a compound of Formula Ib) is present as a sodium salt.

[00191] In certain embodiments the pharmaceutical composition disclosed herein is a parenteral formulation. In certain embodiments, the formulation is administered subcutaneously to a subject in need thereof. In certain embodiments, the formulation is administered intramuscularly to a subject in need thereof.

[00192] In certain embodiments, the parenteral formulation comprises N-methyl-2-pyrrolidone. In certain embodiments, the parenteral formulation consists essentially of N-methyl-2-pyrrolidone. In certain embodiments, the parenteral formulation comprises dimethyl sulfoxide.

[00193] In certain embodiments, the parenteral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutical salt thereof and water. In certain embodiments, the parenteral formulation comprises a compound of Formula (Ib) or a pharmaceutical salt thereof and water. In certain embodiments, the parenteral formulation further comprises an alcohol. In certain embodiments, the alcohol is ethanol. In certain embodiments, the parenteral formulation further comprises polyethylene glycol. In certain embodiments, the polyethylene glycol has an average molecular weight of about 200 g/mol. (polyethylene glycol 200). In certain embodiments, the parenteral formulation further comprises an inorganic base. In certain embodiments, the inorganic base is sodium hydroxide. In certain embodiments, the the inorganic base a sodium ethoxide. In certain embodiments the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments, the

formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises about 1.2 molar equivalents inorganic base (e.g. NaOH or NaOEt).

[00194] In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, and polyethylene glycol 200.

[00195] In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, polyethylene glycol 200 (polyethylene glycole with an average molecular weight of 200 g/mol.), and NaOH. In certain embodiments, the parenteral formulation consists essentially of a compound of Formula (Ib) or a pharmaceutical salt thereof, water, ethanol, polyethylene glycol 200, and NaOEt. In certain embodiments,the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of NaOH or NaOEt. In certain embodiments the formulation comprises about 1.2 molar equivalents of NaOH or NaOEt.

[00196] In certain embodiments, the parenteral formulation is a solution formulation comprises a mixture of ethanol, water, and polyethylene glycol. In certain embodiments, the parenteral formulation is a solution formulation comprising a mixture of ethanol, water, and PEG 200. In certain embodiments, the solution formulation comprises about 5%-20% ethanol, about 5% to 20% water, and about 60% to 90% PEG 200. In certain embodiments, the solution formulation comprises about 10%-15% ethanol, about 10% to 15% water, and about 70% to 80% PEG 200. In certain embodiments, the solution formulation comprises about 10% ethanol, about 12% water, and about 78% PEG 200. In certain embodiments, the solution formulation further comprises an inorganic base. In certain embodiments, the solution formulation further comprises sodium hydroxide or sodium ethoxide. In certain embodiments, the solution formulation further comprises sodium hydroxide. In certain embodiments the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the

inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of the inorganic base (e.g. NaOH or NaOEt). In certain embodiments the formulation comprises about 1.2 molar equivalents inorganic base (e.g. NaOH or NaOEt).

[00197] In some embodiments, solution formulations containing 200 mg/mL of Formula Ib with about 0.1 to about 1.5 equivalents of NaOH in about 10% ethanol, about 12% water, and about 77% PEG are provided.

[00198] In certain embodiments, an oral formulation of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), comprising at least one excipient is provided. Excipients can include ethanol, medium chain triglycerides (e.g. MIGLYOL 810, MIGLYOL 821, MIGLYOL 840, and so forth), Vitamin E TPGS, glycerin, and/or pharmaceutically acceptable oils (e.g. sesame oil, castor oil, safflower oil, vegetable oil, soybean oil, and so forth). Oral formulations disclosed herein can include any combination of one or more suitable excipients. Excipients taken together can be present in >65% by weight of the total oral formulation, >70% by weight of the total oral formulation, >80% by weight of the total oral formulation, >90% by weight of the total oral formulation, or >95% by weight of the total oral formulation.

[00199] In some embodiments, an oral formulation of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), is provided. In certain embodiments the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), about 5% to about 20% ethanol, about 10% to about 30% Vitamin E TPGS, and about 50% to about 85% MIGLYOL 812. In some embodiments, the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), about 8% to about 15% ethanol, about 15% to about 25% Vitamin E TPGS, and about 60% to about 77% MIGLYOL 812. In certain embodiments the oral formulation comprises a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), in about 10% ethanol, about 20% Vitamin E TPGS, and about 70% MIGLYOL 812. In certain embodments, the oral formulation is prepared in hard gelatin capsules.

[00200] The amount of active ingredient that may be combined with the inactive ingredients to produce a dosage form may vary depending upon the intended treatment subject and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of carrier material

(*e.g.*, inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight: weight).

[00201] It should be understood that in addition to the ingredients particularly mentioned above the compositions of these embodiments may include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration may include flavoring agents.

[00202] In certain embodiments, a composition comprising an active ingredient disclosed herein (*e.g.*, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof) in one variation does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that compositions comprising a compound of formula (Ia) or (Ib) in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of formula (Ia) or (Ib) or any other active ingredient administered separately, sequentially or simultaneously with a compound of formula (Ia) or (Ib). It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of formula (Ia) or (Ib) or any other active ingredient administered separately, sequentially or simultaneously with a compound of any one of formula (Ia) or (Ib).

[00203] In some embodiments, a composition comprising an active ingredient disclosed herein (*e.g.*, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof) in one variation does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that compositions comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) or any other active ingredient administered separately, sequentially or simultaneously with a compound of Formula (Ia), (Ib), (IIa), and/or (IIb). It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in certain embodiments do not comprise an agent that would affect (*e.g.*, slow, hinder or retard) the metabolism of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb) or any other active ingredient administered separately, sequentially or simultaneously with a compound of any one of Formula (Ia), (Ib), (IIa), and/or (IIb).

Methods of Use

[00204] In certain embodiments, a method for treating or preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.
In some embodiments, a method for treating or preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.
In certain embodiments, a method for inhibiting the replication of the HIV virus, treating AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

[00205] In some embodiments, a method for inhibiting the replication of the HIV virus, treating AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.
In certain embodiments, a method for preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[00206] In some embodiments, a method for preventing an HIV infection in a subject (*e.g.*, a human), comprising administering a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed. In certain embodiments, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus.

[00207] In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.
In some embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, to the subject is disclosed.

[00208] In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof is disclosed. In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase

PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof is disclosed.

[00209] In some embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof is disclosed. In certain embodiments, a method for treating an HIV infection in a subject (*e.g.*, a human), comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1

modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof is disclosed.
In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in medical therapy of an HIV infection (*e.g.* HIV-1 or the replication of the HIV virus (*e.g.* HIV-1) or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human)) is disclosed.

[00210] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in medical therapy of an HIV infection (*e.g.* HIV-1 or the replication of the HIV virus (*e.g.* HIV-1) or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human)) is disclosed.
In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human) is disclosed. One embodiment relates to a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection or AIDS or for use in the therapeutic treatment or delaying the onset of AIDS.

[00211] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human) is disclosed. One embodiment relates to a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection or AIDS or for use in the therapeutic treatment or delaying the onset of AIDS.
In certain embodiments, the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for an HIV infection in a subject (*e.g.*, a human) is disclosed. In certain embodiments, a compound of any of formula (Ia) or

(Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is disclosed.

[00212] In some embodiments, the use of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for an HIV infection in a subject (*e.g.*, a human) is disclosed. In certain embodiments, a compound of any of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is disclosed.

[00213] In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) in need of the treatment. In certain embodiments, in the methods of use, the administration is to a subject (*e.g.*, a human) who is at risk of developing AIDS.

Disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in therapy. In one embodiment, the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, is for use in a method of treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human).

[00214] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in therapy. In some embodiments, the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, is for use in a method of treating an HIV infection or the replication of the HIV virus or AIDS or delaying the onset of AIDS in a subject (*e.g.*, a human).

Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing HIV infection in a subject in need thereof. In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in a method of treating HIV infection in a subject in need thereof is provided. In certain embodiments, the subject in need thereof is a human who has been infected with HIV. In certain embodiments, the subject in need thereof is a human who has been infected with HIV but who has not developed AIDS. In certain embodiments, the subject in need thereof is a subject at risk for developing AIDS. In certain embodiments, the subject in need thereof is a human who has been infected with HIV and who has developed AIDS.

[00215] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in a method of treating or

preventing HIV infection in a subject in need thereof. In certain embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in a method of treating HIV infection in a subject in need thereof is provided. In certain embodiments, the subject in need thereof is a human who has been infected with HIV. In certain embodiments, the subject in need thereof is a human who has been infected with HIV but who has not developed AIDS. In certain embodiments, the subject in need thereof is a subject at risk for developing AIDS. In certain embodiments, the subject in need thereof is a human who has been infected with HIV and who has developed AIDS.

[00216] In one embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g. one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as described herein for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In one embodiment, said additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof. In one

embodiment, said additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

[00217] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g. one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as described herein for use in a method of treating or preventing HIV infection in a subject in need thereof is provided. In one embodiment, said additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof. In one embodiment, said additional therapeutic agents are selected

from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

In one embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof. In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof.

[00218] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof. In a particular embodiment, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine, is provided for use in a method of treating or preventing HIV infection in a subject in need thereof.

[00219] In a particular embodiment, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing

a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, for example for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula (Ia) or (Ib), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00220] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood, for example for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00221] In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of formula (Ia) or (Ib), or a

pharmaceutically acceptable salt thereof, in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who is at risk of sexual transmission of HIV.

[00222] In some embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1 and/or HIV-2) comprise administration to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who is at risk of sexual transmission of HIV.

[00223] In certain embodiments, the reduction in risk of acquiring HIV is at least about 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In certain embodiments, the reduction in risk of acquiring HIV is at least about 75%. In certain embodiments, the reduction in risk of acquiring HIV is about 80%, 85%, or 90%.

[00224] In another embodiment, the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

[00225] In some embodiments, the use of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

[00226] Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment or delaying the onset of AIDS.

[00227] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment or delaying the onset of AIDS.

[00228] Also disclosed herein is a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

[00229] In some embodiments, disclosed herein is a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of an HIV infection.

[00230] In certain embodiments, a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof can be used as a research tool (e.g. to study the inhibition of HIV reverse transcriptase in a subject or *in vitro*).

[00231] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof can be used as a research tool (e.g., to study the inhibition of HIV reverse transcriptase in a subject or *in vitro*).

Routes of Administration

[00232] The compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, (also referred to herein as the active ingredient) can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00233] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, (also referred to herein as the active ingredient) can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example, the condition of the recipient. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

[00234] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered with a syringe suitable for

administration of the compound. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

[00235] In some embodiments, the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered with an auto-injector comprising a syringe. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of the Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof.

Dosing Regimen

[00236] The compound, such as a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule. In one variation, the compound is administered on a monthly schedule. In one variation, the compound is administered every two months. In one variation, the compound is administered every three months. In one variation, the compound is administered every four months. In one variation, the compound is administered every five months. In one variation, the compound is administered every 6 months.

[00237] In some embodiments, the compound, such as a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In some embodiments, the compound is administered on a daily or intermittent schedule. In some embodiments, the compound is administered on a monthly schedule. In some embodiments, the compound is administered every two months. In some embodiments, the compound is administered every three months. In some embodiments, the compound is administered every four months. I In some

embodiments, the compound is administered every five months. In some embodiments, the compound is administered every 6 months.

[00238] In some embodiments, the compound, such as a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be administered to a subject at least about one month, at least about 4 months, or at least about 6 months. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously administered to a subject at least about one month. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously or intramuscularly administered to a subject at least about 4 months, or at least about 6 months. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously administered to a subject at least about one month. In some embodiments, the compound (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof), may be subcutaneously or intramuscularly administered to a subject at least about every 3 months.

[00239] The dosage or dosing frequency of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[00240] In some embodiments, the dosage or dosing frequency of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[00241] The compound may be administered to a subject (*e.g.*, a human) in an effective amount. In certain embodiments, the compound is administered once daily.

In some embodiments, the compound may be administered to a subject (*e.g.*, a human) in an therapeutically effective amount. In some embodiments, the compound is administered once daily. In some embodiments, the compound is administered monthly. In some embodiments, the compound is administered every three months. In some embodiments, the compound is administered every four months. In some embodiments, the compound is administered every six months.

[00242] A compound as disclosed herein (e.g., a compound of formula (Ia) or (Ib)), or a pharmaceutically acceptable salt thereof, may be administered in a dosage amount that is effective. For example, the dosage amount can be from 1 mg to 1000 mg of compound. In

certain embodiments, the dosage amount is about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 100, 105, 110, 120, 130, 140, or 150 mg of compound. In certain embodiments the dosage amount is about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg.

[00243] In some embodiments, a compound as disclosed herein (e.g., a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, may be administered in a dosage amount that is effective. For example, the dosage amount can be from 1 mg to 1000 mg of compound. In certain embodiments, the dosage amount is about 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, 100, 105, 110, 120, 130, 140, or 150 mg of compound. In certain embodiments the dosage amount is about 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg.

[00244] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered in a once daily dose. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg.

[00245] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered monthly. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg.

[00246] In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered every 6 months. In some embodiments, a compound of Formula (Ia), (Ib), (IIa), and/or (IIb)), or a pharmaceutically acceptable salt thereof, is administered every 6 months at a dose of about 600 mg.

Kits and Articles of Manufacture

[00247] The present disclosure relates to a kit comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit may comprise one or more additional therapeutic agents as described hereinbefore. The kit may further comprise instructions for use, *e.g.*, for use in inhibiting an HIV reverse transcriptase, such as for use in treating an HIV infection or AIDS or as a research tool. The instructions for use are generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable.

[00248] In some embodiments, the present disclosure relates to a kit comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit may comprise one or more additional therapeutic agents as described hereinbefore. The kit may further comprise instructions for use, *e.g.*, for use in inhibiting an HIV reverse transcriptase, such as for use in treating an HIV infection or AIDS or as a research tool. The instructions for use are generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable.

[00249] The present disclosure also relates to a pharmaceutical kit comprising one or more containers comprising a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice reflects approval by the agency for the manufacture, use or sale for human administration. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[00250] In some embodiments, the present disclosure also relates to a pharmaceutical kit comprising one or more containers comprising a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice reflects approval by the agency for the manufacture, use or sale for human administration. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

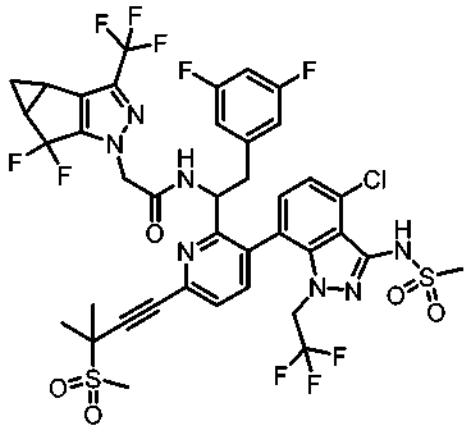
[00251] Also disclosed are articles of manufacture comprising a unit dosage of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in suitable

packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

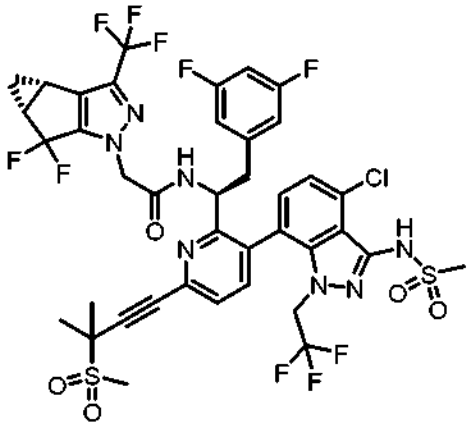
In some embodiments, disclosed herein are articles of manufacture comprising a unit dosage of a compound of Formula (Ia), (Ib), (IIa), and/or (IIb), or a pharmaceutically acceptable salt thereof, in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

Nomenclature

[00252] The name of the compound of formula (Ia) and (Ib) of the current disclosure as generated using ChemBioDraw Ultra 11.

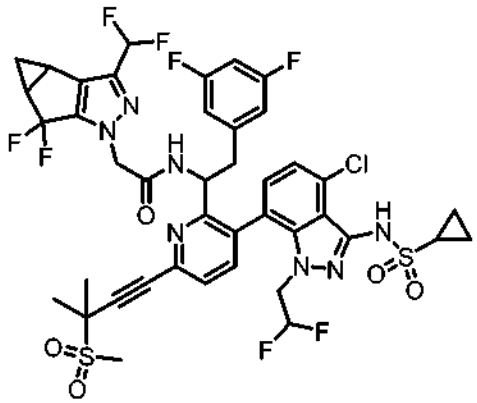


is N-(1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

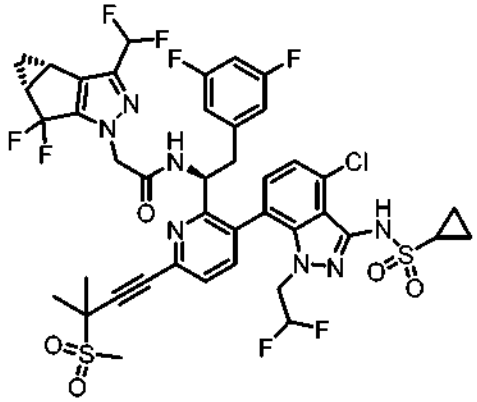


is N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

[00253] The name of the compound of formula (IIa) and (IIb) of the current disclosure as generated using ChemBioDraw Ultra 14.



is N-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.



is N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

Synthesis of the Compound of Formula (Ia), (Ib), (IIa), and (IIb)

[00254] The present disclosure is also directed to processes and intermediates useful for preparing the subject compound or pharmaceutically acceptable salts thereof.

[00255] Except as otherwise noted, the methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, *e.g.*, Loudon, Organic Chemistry, 5th edition, New York: Oxford University Press, 2009; Smith, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 7th edition, Wiley-Interscience, 2013.

[00256] In certain instances, the processes disclosed herein involve a step of forming a salt of a compound of the present disclosure.

[00257] In certain instances, the intermediates useful in preparing a compound of formula (Ia) or (Ib) of the present disclosure are provided. For example, those intermediates include any one of or a combination of Compounds 1 to 23 or a salt thereof. In certain embodiments, the intermediates are selected from Compound 8a, 12, 14, 19, 20, 21, 22, 23, and/or 23b, combinations thereof, or salts thereof.

[00258] In some embodiments, the intermediates useful in preparing a compound of formula (IIa) or (IIb) of the present disclosure are provided. For example, those intermediates include any one of or a combination of Compounds 1, 10, 20 and 25-37 or a salt thereof. In some embodiments, the intermediates are selected from Compound 20, 32, 34, 35, 36, and/or 37, combinations thereof, or salts thereof.

[00259] Compounds as described herein can be purified by any of the means known in the art, including chromatographic means, such as high performance liquid chromatography (HPLC), preparative thin layer chromatography, flash column chromatography, supercritical fluid chromatography (SFC), and ion exchange chromatography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, *e.g.*, Introduction to Modern Liquid Chromatography, 2nd ed., ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, E. Stahl (ed.), Springer-Verlag, New York, 1969.

[00260] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules

concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," 4th ed., Wiley, New York 2006. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[00261] Exemplary chemical entities useful in methods of the embodiments will now be described by reference to illustrative synthetic schemes for their general preparation herein and the specific examples that follow. One of skill in the art will recognize that the transformations shown in the schemes below may be performed in any order that is compatible with the functionality of the particular pendant groups. Each of the reactions depicted in the general schemes is preferably run at a temperature from about 0 °C to the reflux temperature of the organic solvent used.

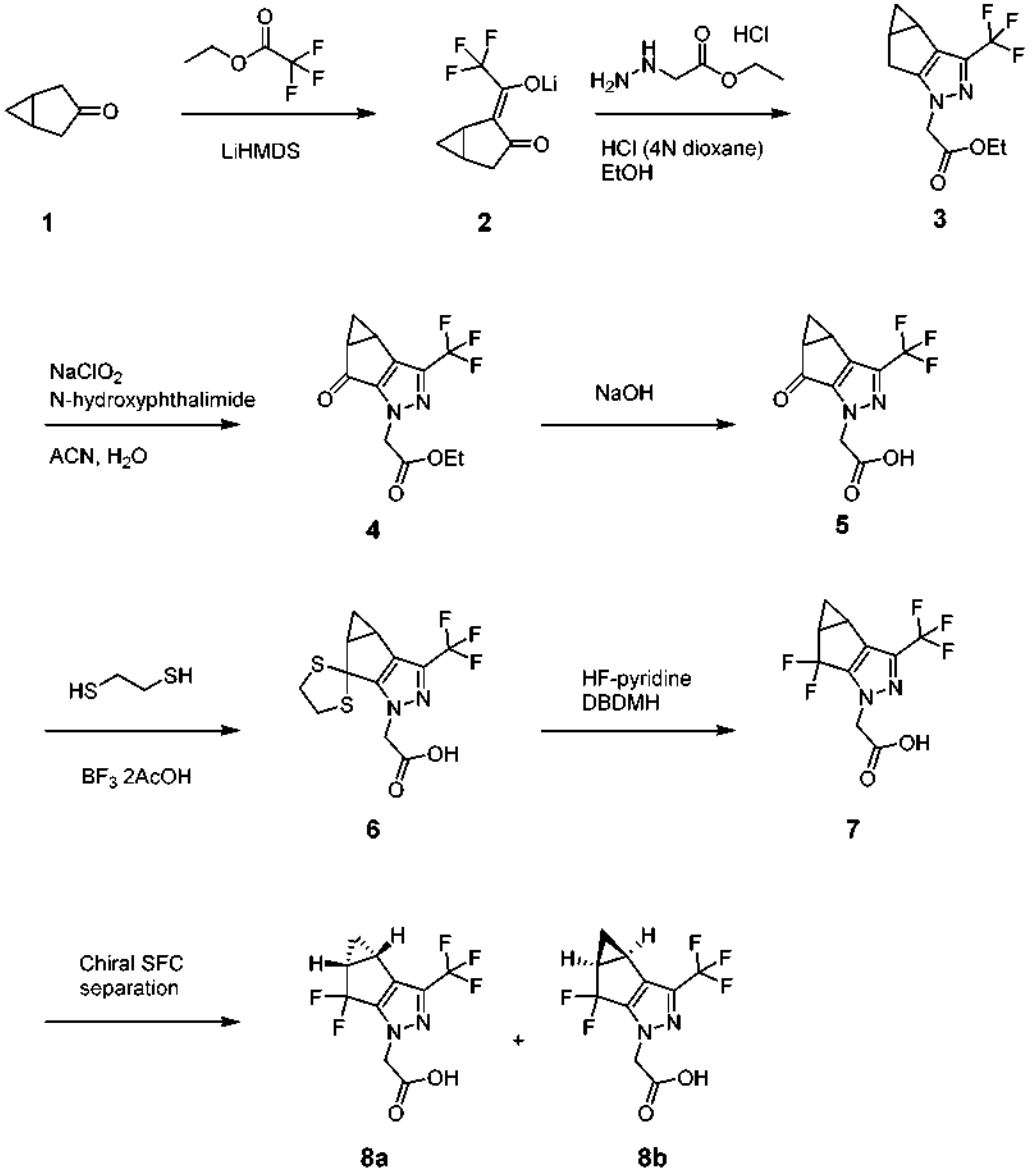
[00262] The compounds disclosed herein may display atropisomerism resulting from steric hindrance affecting the axial rotation rate around a single bond. The resultant conformational isomers may each be observed as distinct entities by characterization techniques such as NMR and HPLC. The compounds disclosed herein may exist as a mixture of atropisomers. However, the detection of atropisomers is dependent on factors such as temperature, solvent, conditions of purification, and timescale of spectroscopic technique. The interconversion rate at room temperature has a half-life of minutes to hours, hours to days, or days to years. The ratio of atropisomers at equilibrium may not be unity. Characterization data presented herein may not represent the equilibrium state depending on the conditions of isolation and characterization which may include but not limited to handling, solvents used, and temperature.

[00263] Representative syntheses of compounds of the present disclosure are described in schemes below, and the particular examples that follow. The following examples are merely illustrative, and not intended to limit this disclosure in any way.

Preparation of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8a) and 2-((3bR,4aS)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (8b):

Example 1

Preparation of Compounds 8a and 8b



Synthesis of lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (**2**):
A reactor was charged with bicyclo[3.1.0]hexan-3-one (95.6 g, 0.99 mol) and ethyl 2,2,2-trifluoroacetate (113.2 mL, 0.95 mol) and THF (50 mL). The reaction mixture was cooled to 0 °C. LiHMDS (Lithium bis(trimethylsilyl)amide) (1L of 1.0M solution in THF, 1 mol) was added via an addition funnel at a rate to maintain internal temperature at ≤ 1 °C. After the addition was complete, hexanes (235 mL) was added in a steady stream via an addition funnel and stirred for 15 min. The resultant solids were collected by filtration, washed with hexanes (3 x 400 mL), and dried to provide the title compound.

Synthesis of ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**3**):
A reactor was charged with lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (177.2 g, 0.89 mol) and EtOH (ethanol) (779 mL). The temperature was brought to and maintained at 0 °C. HCl in dioxane (4.0 N, 443 mL) was added via an addition funnel followed by the addition of solid ethyl hydrazinoacetate HCl salt (138.4 g, 0.90 mol). The reaction temperature was adjusted to 35 °C. After 1 h, the reaction volume was reduced by ~40% by distillation at reduced pressure. Water (1.3 L) was added with vigorous agitation and temperature adjusted to 15 °C. The resultant solids were collected by filtration, washed with water (3 x 500 mL), hexanes (3 x 400 mL), and dried to provide the title compound. MS (*m/z*) 275.1 $[M+H]^+$.

Synthesis of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**4**):
A reactor was charged with ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (291.2 g, 1.06 mol), acetonitrile (1.65 L) and water (825 mL) to which N-hydroxyphthalimide (17.4 g, 0.103 mol) and $NaClO_2$ (41.0 g, 0.45 mol, ~20% of total amount to be added) were added. The reaction mixture was heated to 50 °C and the remaining $NaClO_2$ (163.0 g, 1.80 mol) was added in five portions over 2 h. After consumption of starting material, the temperature was adjusted to 20 °C and aqueous sodium bisulfite (40% w/w, 350 mL) was added via an addition funnel. Ethyl acetate (1.75 L) was added and the layers were separated. The aqueous layer was back extracted with EtOAc (ethyl acetate) (500 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (500 mL) and 1:1 water/ brine (500 mL). The

organic layer was concentrated under reduced pressure and co-evaporated with IPAc (isopropyl acetate) (300 mL). The crude solid was crystallized from a mixture of IPAc /heptane. The resultant solids were collected by filtration, washed with heptane, and dried to provide the title compound. MS (*m/z*) 289.0 $[M+H]^+$.

Synthesis of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**5**):
To a solution of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (80.40 g, 278.95 mmol) in 2-MeTHF (2-methyltetrahydrofuran) (167 mL) was added 2M aqueous sodium hydroxide (167 mL). After 25 minutes of stirring at room temperature, the reaction mixture was diluted with 2-MeTHF and was slowly acidified by the dropwise addition of concentrated HCl. The organic layer was isolated and the aqueous layer was extracted with an additional portion of 2-MeTHF. The combined organic layers were washed with saturated aqueous sodium chloride, then dried over sodium sulfate, filtered, and concentrated. The resulting oil was taken in ethyl acetate. Hexanes was added with vigorous stirring until solid formation was observed. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 259.00 $[M-H]^-$.

Synthesis of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid (**6**):
To a solution of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (3.0 g, 11.5 mmol) in DCM (dichloromethane) (25 mL) was added 1,2-ethanedithiol (1.07 mL, 12.68 mmol) followed by boron trifluoride-acetic acid complex (4.0 mL, 28.8 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water (60 mL) and 2-MeTHF (60 mL). The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated. The crude was dissolved in ethyl acetate (2 mL) and the solution diluted with hexanes (12 mL) with vigorous stirring to provide a solid. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 337.12 $[M+H]^+$.

Synthesis of 2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (7):

To a suspension of 1,3-dibromo-5,5-dimethylhydantoin (12.75 g, 44.6 mmol) in DCM (35 mL) was added pyridine hydrofluoride (5.0 mL) at 0 °C. The suspension was stirred at 0 °C for 10 minutes. To the suspension was added a solution of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid (5.00 g, 14.9 mmol) dropwise. After addition was complete, the reaction mixture was stirred at 0 °C for an additional 15 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (300 mL) with vigorous stirring. The organic layer was removed and the aqueous layer was acidified to pH ~1 with concentrated HCl. The aqueous phase was extracted with three portions of MTBE (methyl *tert*-butyl ether). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting solid was taken in MTBE (16 mL) and filtered to remove any resulting solid. The solution was then extracted with 2N NaOH (16 mL). The aqueous layer was diluted with water (16 mL) with vigorous stirred and stirred at room temperature for 15 minutes. The resulting solid was removed by filtration. The aqueous layer was acidified by slow, dropwise addition of concentrated HCl to pH ~1 with vigorous stirring to provide a solid precipitate. The solid was isolated by filtration to provide the title compound. MS (*m/z*) 281.12 $[M+H]^+$.

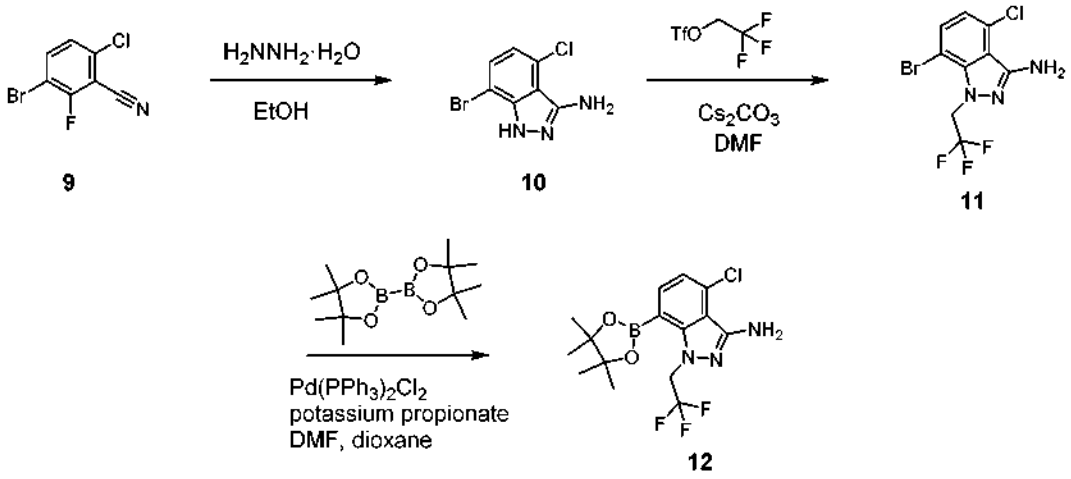
Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**8a**) and 2-((3bR,4aS)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**8b**):

2-(5,5-Difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid was separated to its constituent enantiomers, the title compounds, by chiral SFC under the following conditions: Instrument: Thar 350 preparative SFC; Column: ChiralPak IC-10 u, 300×50mmI.D; Mobile phase: 35% Isopropanol(0.1% $NH_3 \cdot H_2O$) and CO_2; Flow rate: 200 mL / min; Column temperature: 38 °C; UV detection: 220 nm; Sample preparation: Compound was dissolved in isopropanol to ~ 45 mg/mL; Injection: 6.5 mL per injection. Analytical SFC [mobile phase: A for CO_2 and B for Isopropanol (0.05% DEA); Gradient: B 20%; A; Flow rate: 2.35 mL/min; Column: Chiralpak IC-3, 150×4.6 mm, 3um; Wavelength: 254 nm] **8a:** t= 3.39 min, **8b:** t= 2.17 min.

Compound **8a** - ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.93 (s, 2H), 2.52 – 2.43 (m, 2H), 1.44 – 1.38 (m, 1H), 1.15 (m, 1H).

Example 2

Preparation of Compound 12



Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine (**10**):

To 3-bromo-6-chloro-2-fluorobenzonitrile (13.9 g, 59.3 mmol) in EtOH (ethanol) (60 mL) was added hydrazine monohydrate (5.77 mL). The reaction mixture was heated to 80 °C for 3 h. After cooling to ambient temperature, EtOH (20 mL) was added to allow for stirring. The solids were isolated by filtration, washed with cold EtOH, and dried to provide the title compound. MS (*m/z*) 247.9 $[M+H]^+$.

Synthesis of 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (**11**):

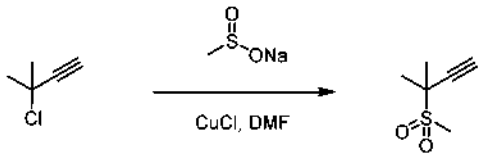
A reactor was charged with 7-bromo-4-chloro-1H-indazol-3-amine (397.2 g, 1.6 mol) and Cs_2CO_3 (1052 g, 3.2 mol) then diluted with DMF (dimethylformamide) (4000 mL). To this was slowly added 2,2,2-trifluoroethyl trifluoromethanesulfonate (463.2 g, 1.9 mol) via addition funnel. Upon completion of the addition, the reaction mixture was allowed to stir for 1 hour, at which time, H_2O (16 L) was added slowly. Upon completion of the addition, the mixture was allowed to stir for 12 hours at 15 °C. The slurry was filtered and the collected solids were suspended in DMF (800 mL). To this was added H_2O (4800 mL) and the resulting solids were collected by filtration and dried to provide the title compound. MS (*m/z*) 330.1 $[M+H]^+$.

Synthesis of 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (**12**):

A reaction vessel was charged with 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (15.00 g, 45.66 mmol), bis(pinacolato)diboron (17.39 g, 68.49 mmol), potassium propionate (15.36 g, 136.98 mmol), dioxane (90 mL) and DMF (dimethylformamide) (30 mL). Bis(triphenylphosphine)palladium(II) dichloride (0.64g, 0.91 mmol) was added and the reaction solution degassed by bubbling argon for 2 min. The reaction mixture was heated to 105 °C for 4 hrs. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite and silica gel washing with EtOAc. The filtrate was washed with 5% LiCl solution and brine. The organic layers were separated, dried, and concentrated under reduced pressure. The residue was treated with IPAc/heptane (1/10) at 60 °C then cooled to ambient temperature and stirred for 15 h. The solids were collected by filtration and dried to afford the title compound. MS (*m/z*) 376.7 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, 1H), 7.06 (d, 1H), 5.55 (s, 2H), 5.45 (q, 2H), 1.32 (s, 12H).

Example 3

Preparation of Compound 14



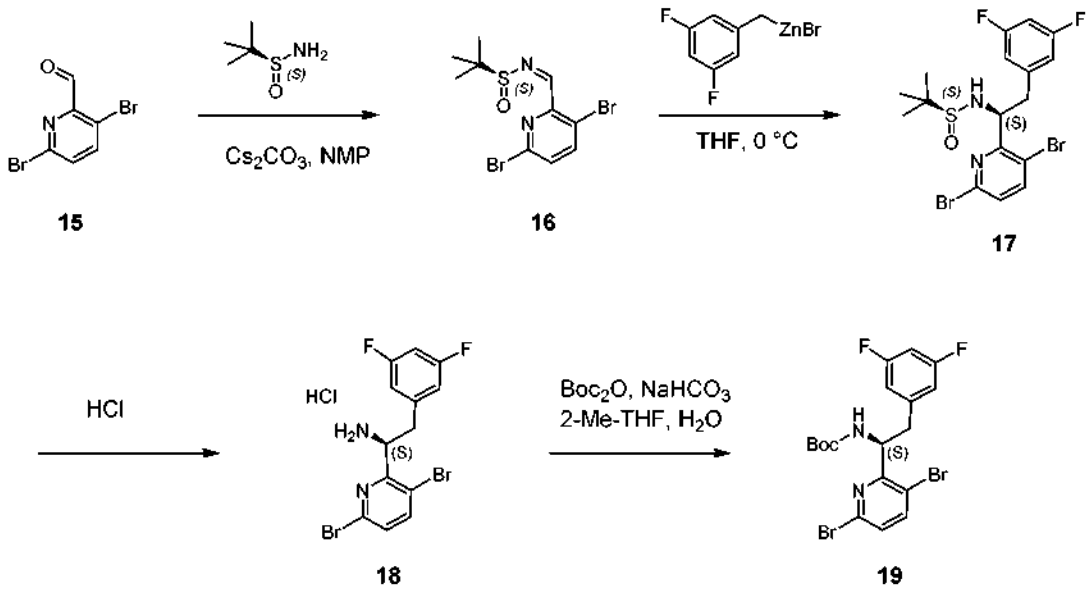
13 **14**

Synthesis of 3-methyl-3-(methylsulfonyl)but-1-yne (**14**):

To a stirred suspension of sodium methanesulfinate (18.47 g, 175.5 mmol) and copper(I) chloride (1.45 g, 14.6 mmol) in DMF (dimethylformamide) (50 mL) was added 3-chloro-3-methylbut-1-yne (15.00 g, 146.3 mmol, 16.4 mL) dropwise. The resulting reaction mixture was heated to 40 °C and stirred for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The solution was washed with water and brine. The organic layer was collected and dried over sodium sulfate, then filtered. The solution was concentrated under vacuum and purified by silica gel chromatography to provide the title compound. Mp: 114.8–115.5 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.04 (s, 3H), 2.58 (s, 1H), 1.67 (s, 6H).

Example 4

Preparation of Compound 19



15 16 17 18 19

Synthesis of (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**16**):

3,6-Dibromopicolinaldehyde (76.0g, 0.287 mol) and (S)-2-methylpropane-2-sulfinamide (36.51g, 0.301 mol) were combined in NMP (*N*-methyl-2-pyrrolidone) (200 mL). To the reaction mixture was added Cs_2CO_3 (41.94g, 0.316 mol) as a solid in one portion. The reaction mixture was stirred 2h then cooled to 5 °C. Water (1.3 L) was added to the reaction

mixture. The resulting suspension was stirred for 1h, solids isolated by filtration, washed with water (5x100mL) and dried to provide the title compound. MS (*m/z*) 368.9 $[M+H]^+$.

Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**17**):

A reaction vessel was charged with (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (65.5 g, 177.95 mmol) followed by DMF (dimethylformamide) (260 mL). The mixture was stirred for 5 min until homogeneous and the solution was cooled to 8 °C. To the reaction mixture was added (3,5-difluorobenzyl)zinc bromide (0.5 M in THF (tetrahydrofuran), 516.04 mL) dropwise over 90 mins. The mixture was stirred for an additional 2.5h. To the reaction mixture, 5% AcOH (acetic acid) in water (640 mL) was added over 10 mins followed by CPME (cyclopentyl methyl ether) (320 mL) in one portion. The mixture was stirred for 5 mins, warmed to room temperature, and the layers were separated. The organic layer was washed with 5% AcOH (320 mL) then treated with 0.5M NaOH (330 mL) and washed with brine. The organic layer was collected, dried with Na_2SO_4, and filtered. To the crude mixture was added MeOH (methanol) (33 mL). To the stirring mixture was added dropwise 3M HCl in CPME (128 mL) over 15 mins. After stirring for 1h, the precipitate was removed by filtration. The filtrate was diluted with hexane (300 mL) and the product was extracted with water (450 mL). The aqueous layer was basified with 8M NaOH and extracted with CPME (375 mL). The organic layer was washed with brine, dried over Na_2SO_4 and filtered to provide the title compound in solution which was used directly in the next reaction. MS (*m/z*) 497.0 $[M+H]^+$.

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine (**18**):

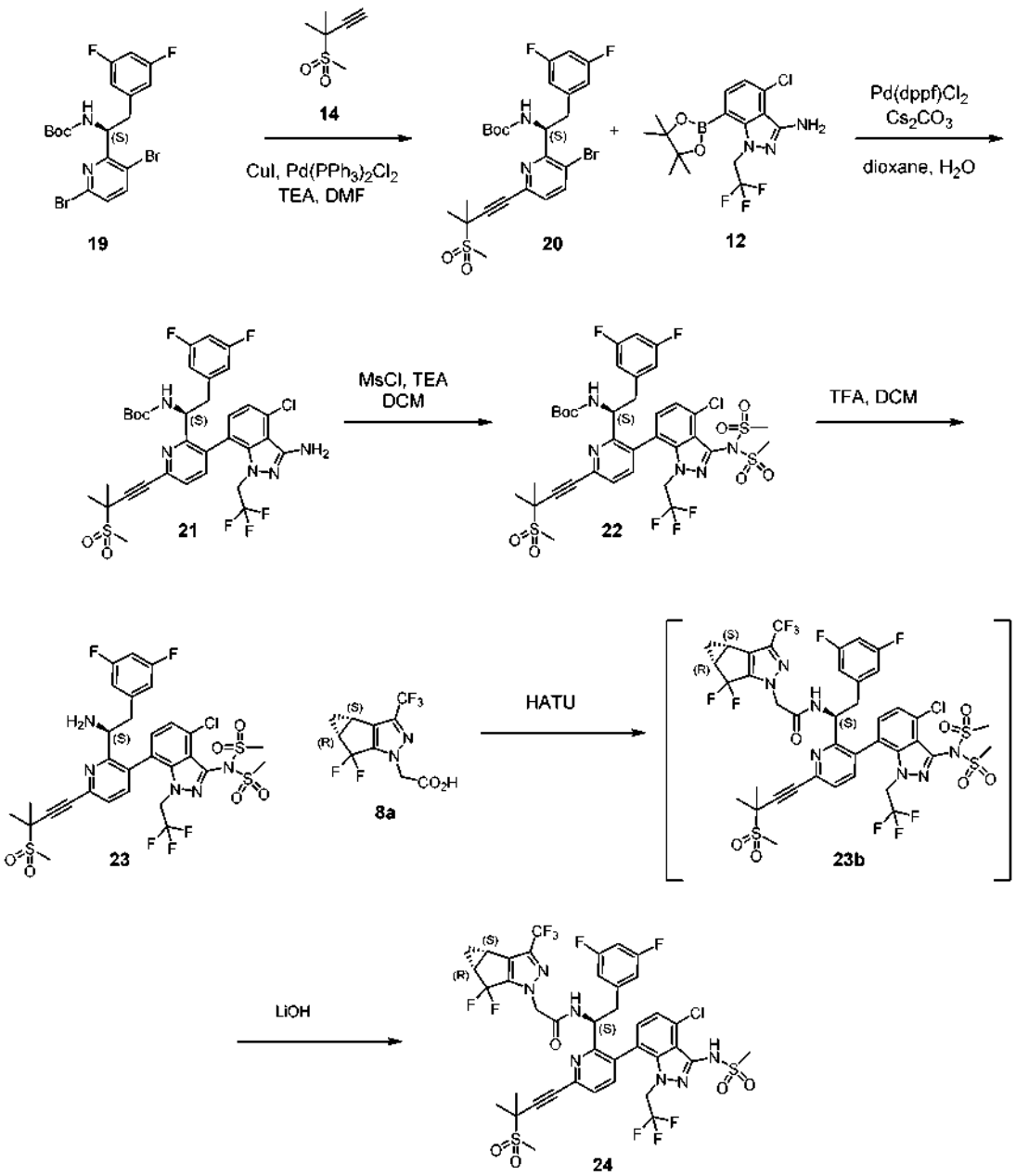
The resulting solution of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide was diluted with CPME to a volume of 700 mL to which acetonitrile (350 mL) was added. To the stirring mixture, concentrated HCl (37%, 16.4 mL) was added dropwise over 10 mins at room temperature. The thick slurry was vigorously stirred for 4h. The solids were filtered and washed with 2:1 CPME (cyclopropyl methyl ether):ACN to provide the title compound. MS (*m/z*) 393.3 $[M+H]^+$.

Synthesis of tert-butyl (S)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**19**):

A reaction vessel was charged with 2-MeTHF (190 mL), water (190 mL) and (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine (46.9 g, 0.11 mol) followed by portionwise addition of $NaHCO_3$ (30.34 g, 0.36 mol). The reaction mixture was cooled to 5 °C and di-tert-butyl dicarbonate (27.47 g, 0.13 mol) was added. The reaction mixture was stirred at 0 °C for 2h and ambient temperature for 2h. The reaction mixture was diluted with water and extracted with MTBE (methyl *tert*-butyl ether). The organic layers were washed with brine, dried and concentrated. Crude compound was purified by column chromatography on silica to provide the title compound. MS (*m/z*) 492.8 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, 1H), 7.42 (d, 1H), 6.90 – 6.72 (m, 3H), 5.33 (dd, 1H), 3.10 (dd, 1H), 2.92 (dd, 1H), 1.36 (s, 9H).

Example 5

Preparation of Formula (Ib) (Compound 24)



Synthesis of tert-butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (20)

A reactor was charged with tert-butyl (*S*)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (50.00 g, 101.8 mmol), 3-methyl-3-methylsulfonyl-but-1-yne (17.86 g, 122.2 mmol), DMF (dimethylformamide) (90 mL) and Et_3N (trimethylamine) (42.5

mL, 305.4 mmol). The reaction mixture was heated to 50 °C. Bis(triphenylphosphine)palladium(II) dichloride (2.14 g, 3.1 mmol) and copper(I) iodide (0.58 g, 3.1 mmol) were added. After 30 min, the reaction mixture was diluted with MeCN (acetonitrile) (200 mL) and then 7% aq. NH_4Cl (200 mL) was added dropwise. A slurry was formed and adjusted to ambient temperature. After 3h, the solids were collected by filtration. The cake was washed with MeCN/water (1:1, 75 mL) twice and MTBE (methyl *tert*-butyl ether) (75 mL). The solid was dried to provide the title compound. MS (*m/z*) 556 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.15 (m, 1H), 6.70 – 6.55 (m, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 5.57 – 5.45 (m, 1H), 3.21 – 3.05 (m, 4H), 2.99 – 2.88 (m, 1H), 1.80 (s, 6H), 1.40* (s, 7H), 1.30* (s, 2H). *denotes presence of atropisomers in 4.6:1 ratio.

Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**21**):

tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (1000.0 mg, 1.79 mmol), 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine (808.5 mg, 2.15 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (65.6 mg, 0.09 mmol), and cesium carbonate (876.7 mg, 2.69 mmol) were charged in a round bottom flask and placed under argon. Dioxane (10 mL) and water (2 mL) were added, and the suspension was degassed by bubbling argon for 60 seconds. After degassing, the reaction flask was fitted with a reflux condenser and heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and the aqueous layer was removed. The organic layer was concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography to provide the title compound. MS (*m/z*) 726.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.55 (m), 7.55 – 7.42 (m), 7.16 – 7.06 (m), 7.07 – 6.96 (m), 6.89 (d), 6.60 (tt), 6.44 (dd), 6.20 (d), 6.16 (d), 6.08 (s), 5.69 – 5.53 (m), 5.29 (s), 5.26 (d), 4.95 – 4.85 (m), 4.64 (q), 4.59 – 4.46 (m), 4.36 – 4.19 (m), 3.94 – 3.76 (m), 3.64 – 3.54 (m), 3.18 (s), 3.17 (s), 3.01 – 2.84 (m), 2.78 – 2.68 (m), 1.86 – 1.82 (m), 1.38 (s), 1.34 (s), 1.26 (s), 1.23 (s), 1.15 (s).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**22**):

tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (37.89 g, 52.18 mmol) was dissolved in methylene chloride (380 mL) with stirring at ambient temperature. To it was added triethylamine (21.82 mL, 156.54 mmol) followed by slow addition of methanesulfonyl chloride (8.08 mL, 104.36 mmol). When the reaction was complete, water (200 mL) was added and stirred for 0.5 hours. The organic layer was separated and the aqueous layer was extracted with methylene chloride once. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to a small volume. Hexanes was added. The liquid suspension was decanted. The remaining solid was dried under reduced pressure to afford the title compound. MS (*m/z*): 882.69 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.87 (d), 7.83 (d), 7.76 (s), 7.74 (s), 7.69 (s), 7.67 (s), 7.65 (s), 7.52 – 7.47 (m), 7.46 (s), 7.37 (d), 7.33 (d), 7.11 – 7.03 (m), 4.79 – 4.55 (m), 4.51 (t), 4.36 (dt), 4.20 – 4.05 (m), 3.64 (s), 3.62 (s), 3.60 (s), 3.59 (s), 3.23 (s), 3.04 (d), 3.01 (d), 2.95 – 2.83 (m), 1.81 (s), 1.34 (s), 1.29 (s), 0.98 (s).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (**23**):

To tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (39 g, 44 mmol) dissolved in methylene chloride (120 mL) was added trifluoroacetic acid (80 mL). The reaction mixture was stirred at ambient temperature for 50 minutes. The reaction mixture was diluted with methylene chloride and slowly poured into ice cold saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford the title compound. MS (*m/z*): 782.84 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d), 7.54 – 7.44 (m), 7.40 (d), 7.33 (d), 7.20 (d), 6.66 – 6.57 (m), 6.44 (d), 6.33 (d), 6.17 (d), 4.64 (s), 3.68 (s), 3.64 (s), 3.61 (s), 3.55 (s), 3.19 (s), 3.05 (dd), 2.85 – 2.72 (m), 1.86 (s), 1.62 (s).

Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**24**):

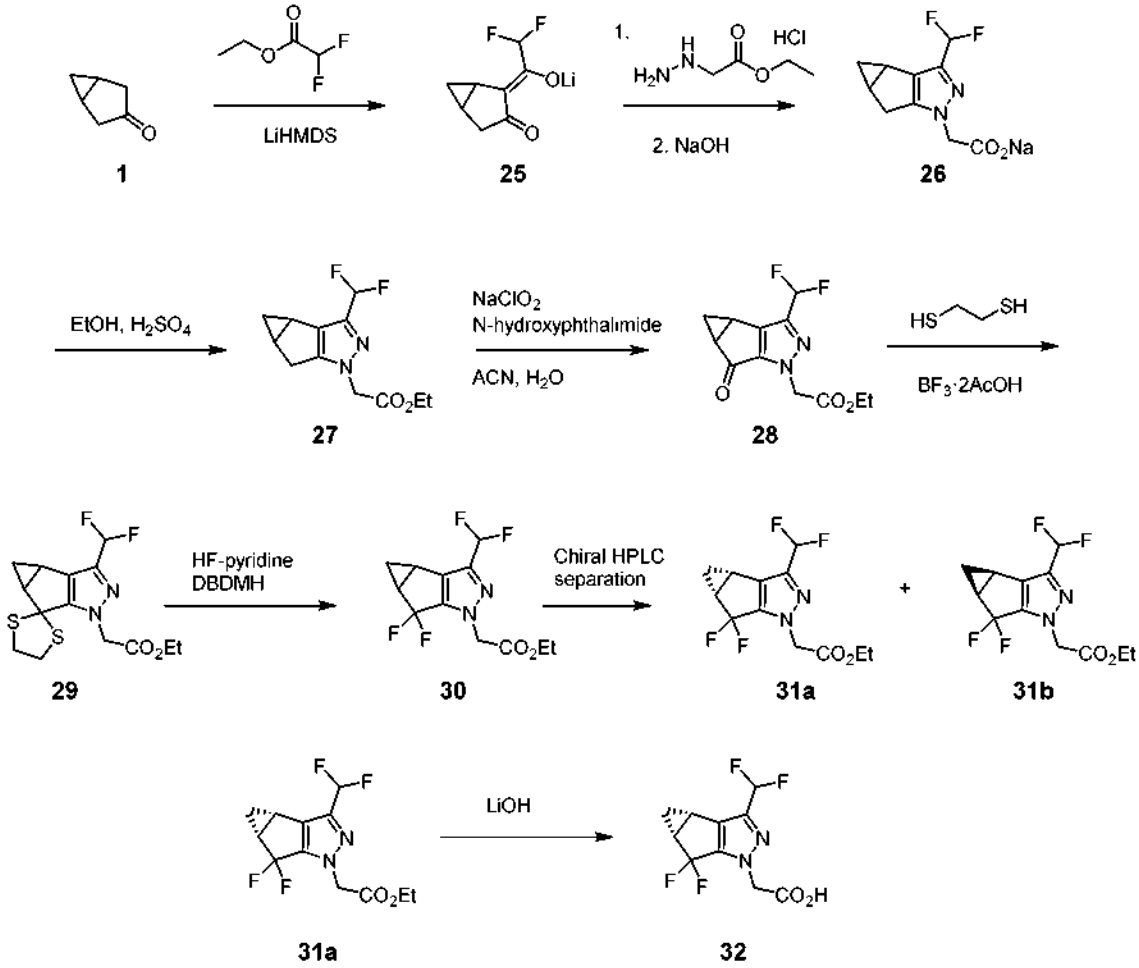
(S)-N-(7-(2-(1-Amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide (1757 mg, 2.25 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (666 mg, 2.36 mmol), and HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (854 mg, 2.25 mmol) were charged in a round bottom flask and dissolved in DMF (dimethylformamide) (10.0 mL). To the solution was added N,N-diisopropylethylamine (0.80 mL, 4.49 mmol) at a rapid dropwise rate. After addition was complete, the reaction mixture was stirred at room temperature for 15 minutes to provide the intermediate **23b** which was not isolated (MS (*m/z*) 1046.65 $[M+H]^+$). To the solution was added 2N aq. sodium hydroxide solution (5.0 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with two portions of 5% lithium chloride solution followed by brine. The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to yield the title compound as an amorphous solid. MS (*m/z*) 968.24 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 – 7.57 (m), 7.33 – 7.09 (m), 6.80 – 6.70 (m), 6.54 (d), 6.47 (d), 6.37 – 6.19 (m), 5.02-4.94(m), 4.90 – 4.70 (m), 4.70 – 4.51 (m), 3.94 (dq), 3.32-3.28 (m), 3.23 (d), 3.07 (dd, J = 13.1, 7.6 Hz), 2.93 (dd), 2.68 – 2.35 (m), 1.81 (s), 1.41 (q), 1.12 – 1.00 (m). ^{19}F NMR (377 MHz, Methanol-d_4) δ –63.65 , –71.78 (t), –72.35 (t), –82.75 (dd), –105.70 (ddd), –111.73 – –113.10 (m).

To more fully characterize **23b**, that compound was isolated. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d), 8.99 (d), 7.96 (d), 7.83 (d), 7.80 (d), 7.76 (d), 7.45 (d), 7.41 (d), 7.31 (d), 7.02 (tt), 6.92 (m), 6.91 (d), 6.48 (m), 4.92 (m) 4.88 (d), 4.79 (d), 4.73 (d), 4.71 (m), 4.69 (m), 4.62 (m), 4.60 (m), 4.38 (dq), 4.12 (dq), 3.68 (s), 3.66 (s), 3.63 (s), 3.58 (s), 3.26 (s), 3.12 (dd), 3.05 (dd), 2.97 (dd), 2.78 (dd), 2.59 (m), 2.53 (m), 1.75 (s), 1.39 (m), 0.98 (m).

Preparation of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (32)

Example 6

Preparation Compound 32



Synthesis of lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (**25**):

The title compound was prepared according to the method presented for the synthesis of compound **2** utilizing ethyl 2,2-difluoroacetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, J = 53.6 Hz, 1H), 2.78-2.73 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.24 (m, 1H), 1.70-1.69 (m, 1H), 1.22-1.14 (m, 1H), 0.31-0.27 (m, 1H).

Synthesis of sodium 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**26**):

Me-THF (1.32L) was added in to 4L reactor followed by lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate (247g, 1.32mol). HCl (4N in dioxane) (0.685L, 2.74mol) was slowly added to the mixture maintaining an internal temperature around 20 °C. Following addition of ethyl hydrazinoacetate hydrochloride (212.05g, 1.372 mol), the resulting mixture was stirred at 20 °C for 4 hours. The reaction mixture was heated to 50 °C for overnight. 10N aqueous NaOH (0.548 L, 5.48 mol) was slowly added to the reaction mixture and the internal temperature was maintained at 20 °C. After addition, 300ml MeTHF was added, and the resultant suspension was stirred at 20°C for 3 hours. The suspension was drained and filtered. The filter cake was washed with hexane (1 L) and dried in vacuum oven at 56°C to obtain the title compound which was used directly in the next step. MS (m/z) 229.1 $[M–Na+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**27**):

Ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate from the previous step was charged in 4 L reactor and followed by the addition of EtOH (3.5 L) and concentrated H_2SO_4 (152 ml. 2.74 mol). The resulting mixture was stirred under reflux for 2 hours. EtOH was reduced under vacuo to 150ml. H_2O (500ml) was added slowly. Solids were collected and washed with H_2O and $NaHCO_3$, and followed by hexane (500ml). Solid was dried under oven at 45 °C to obtain the title compound. MS (m/z) 257.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**28**):

The title compound was prepared according to the method presented for the synthesis of compound **4** utilizing ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate. MS (m/z) 271.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (**29**):

To ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (148.5 g, 0.55 mol) in DCM (2.0 L) was added ethane-1,2-dithiol (88.0 g, 0.94 mol) in one portion followed by BF_3•2AcOH (175.8 g, 0.94 mol). The reaction was stirred at room temperature for 12 h. The system was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (1000 ml). The organic layer was separated, washed with brine (500 ml) and dried over Na_2SO_4. Solvents were removed in vacuo and the residue was purified by silica gel column chromatography to provide the title compound. MS (m/z): 347.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**30**):

A solution of DBDMH (99 g, 0.35 mol) in DCM (120 mL) was cooled to –8 °C in a teflon bottle. HF/Py (120 mL) was added drop-wise over a period of 30 min. The reaction was stirred at –78 °C for 30 min. A solution of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (40 g, 0.12 mol) in DCM (80 mL) was added drop-wise over a period of 15 min at –78 °C. The resulting mixture was stirred for 30 min then slowly warm to –30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. $NaHCO_3$ (500 mL) and extracted with EA (500 mLx3). The combined organic layer was washed with 10% aq. $Na_2S_2O_3$ (500 mL), brine (500 mL) and dried over Na_2SO_4. Solvents were removed in vacuo to afford the crude product, which was further purified by column chromatography to provide the title compound. MS (m/z): 293.2 $[M+H]^+$.

Separation of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**31a**) and ethyl 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**31b**):

Ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate was separated to its constituent enantiomers, the title compounds, by chiral HPLC under the following conditions: Column: ChiralPak AD; Mobile phase: Hex/3C EtOH = 95/5; Room temperature; UV detection: 250

nm. Analytical HPLC [mobile phase: Hex/3C EtOH = 95/5; Flow rate: 0.75 mL/min; Column: Chiralpak AD-H, 150×4.6 mm, 5um; Wavelength: 220 nm] **31a:** t= 5.30 min, **31b:** t= 7.00 min.

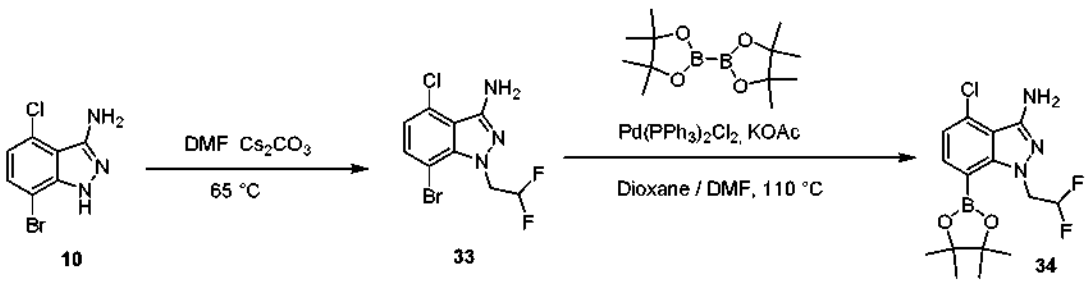
Compound **31a** - ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.63 (t, J = 54.8 Hz, 1H), 4.83 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.48-2.45 (m, 2H), 1.38-1.36 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.13-1.12 (m, 1H).

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**32**):

To a solution of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (26 g, 89.0 mmol) in THF (180 mL), MeOH (90 mL) and water (90 mL) was added LiOH (5.13 g, 213.5 mmol). The mixture was stirred for 4 h. The mixture was concentrated to remove most of THF and MeOH, the aqueous was acidified by 1N HCl to adjust pH to 2-3, then extracted with EA (600 mLx2). The organic phase was separated and combined, dried over Na_2SO_4, filtered and concentrated in vacuum to provide the title compound. MS (m/z) 265.0 $[M+H]^+$.

Example 7

Preparation of Compound 34



Synthesis of 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine (**33**):

To a 2000-mL 4-necked round-bottom flask was placed 7-bromo-4-chloro-1H-indazol-3-amine (130 g, 527.40 mmol, 1.00 equiv), N,N-dimethylformamide (1300 mL), Cs_2CO_3 (260 g, 797.99 mmol, 1.50 equiv) with stirring for 20 min, followed by the addition of 1,1-difluoro-2-iodoethane (122 g, 635.59 mmol, 1.20 equiv). The resulting mixture was stirred overnight at 65°C, then cooled to room temperature, quenched by the addition of 3 L of water/ice, extracted with 3x1.5 L of ethyl acetate. The combined organic layer was washed

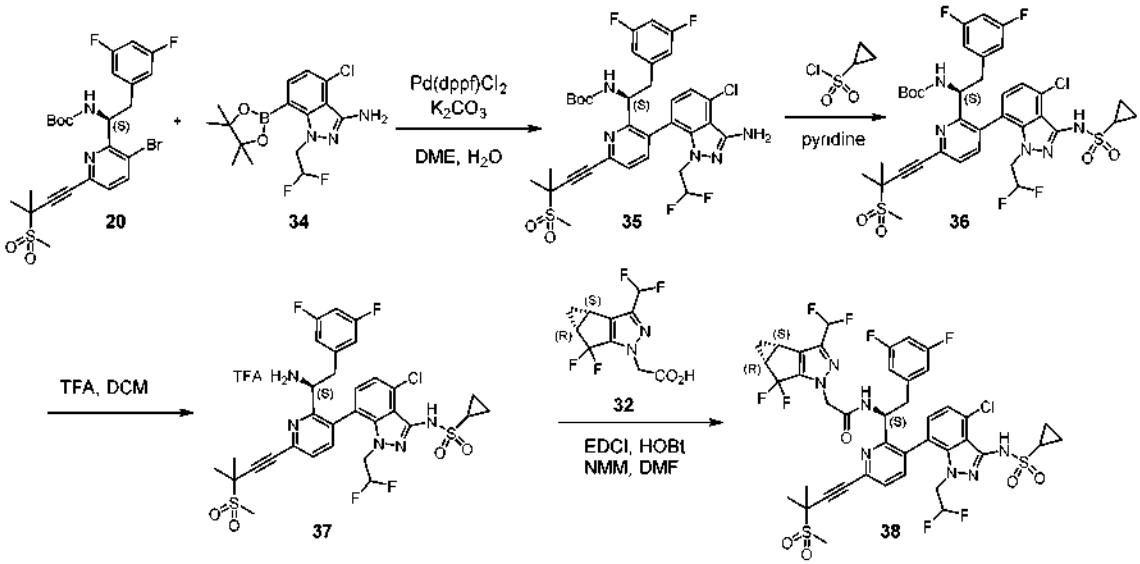
with 1x1.5 L of H_2O, 1x1.5 L of brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and recrystallized from ethanol to afford the title compound. MS (m/z) 312.1 $[M+H]^+$.

Synthesis of 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (**34**):

To a 3000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine (80 g, 257.63 mmol, 1.00 equiv), 1,4-dioxane (800 mL), N,N-dimethylformamide (800 mL), KOAc (76 g, 774.40 mmol, 3.00 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (197 g, 775.78 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8 g, 11.40 mmol, 0.04 equiv). The mixture was stirred for 4 h at 110°C, then cooled to room temperature, quenched by the addition of 5 L of water/ice, extracted with 2x2 L of ethyl acetate. The combined organic layer was washed with 1x1 L of H_2O, 1x1 L of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column eluted with ethyl acetate/petroleum ether (1:10) to afford the title compound. MS (*m/z*): 358 $[M+H]^+$. ^{1}H-NMR: (DMSO-d6, 300MHz, ppm): δ7.63-7.66 (1H, d), 7.00-7.03 (1H, d), 6.06-6.43 (1H, t), 5.46 (2H, s), 4.90-5.01 (2H, t), 1.34 (12H, s).

Example 8

Preparation of Formula (IIb) (Compound 38)



Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**35**):

tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (300 mg, 0.53 mmol), 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine (250 mg, 0.7 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14 mg, 0.016 mmol), and potassium carbonate (186 mg, 1.35 mmol) were charged in a microwave tube and placed under argon. Dimethoxyethane (2.5 mL) and water (0.3 mL) were added, and the reaction mixture was heated to 130 °C in a microwave reactor (Biotage® Initiator+) for 7 minutes. The reaction mixture was cooled to room temperature, and partitioned between EtOAc and 0.1 N HCl. The aqueous layer was removed and the organic layer was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to provide the title compound. MS (m/z) 708.20 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 7.91 – 7.50 (m), 7.28 – 6.89 (m), 6.88 – 6.65 (m), 6.56 (dd), 6.46 – 6.17 (m), 6.08 – 5.60 (m), 4.76 – 4.47 (m), 4.04 – 3.73 (m), 3.73 – 3.41 (m), 3.22 (s), 3.17 – 2.69 (m), 1.80 (s), 1.29 (d), 0.98 (d).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (**36**):

tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (700 mg, 0.99 mmol) and 4-dimethylaminopyridine (24 mg, 0.2 mmol) were dissolved in pyridine (2 mL) with stirring at ambient temperature. To it was added cyclopropane-1-sulfonyl chloride (222 μL, 2.2 mmol). The reaction mixture was stirred at 70 °C until the reaction was complete. Water was added and stirred for 1 hour, and the resulting precipitate was collected by vacuum filtration then dissolved in methylene chloride, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica chromatography to afford the title compound. MS (m/z): 812.44 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 7.93 – 7.58 (m), 7.50 – 7.15 (m), 7.00 (dd), 6.82 – 6.51 (m), 6.47 – 6.29 (m), 6.18 – 5.65 (m), 4.77 – 4.43 (m), 4.31 – 4.08 (m), 3.99 – 3.63 (m), 3.22 (s), 3.18 – 2.71 (m), 1.80 (s), 1.28 (s), 1.20 – 0.76 (m).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide (**37**):

To a solution of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate (705 mg, 0.87 mmol) in methylene chloride (5 mL) was added trifluoroacetic acid (3 mL). The reaction mixture was stirred for 1 hour then slowly poured into a saturated sodium bicarbonate solution. It was extracted with EtOAc. Organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the title compound. MS (m/z): 712.34 [M+H]+. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.93 - 7.58 (m), 7.50 - 7.15 (m), 7.00 (dd), 6.82 - 6.51 (m), 6.47 - 6.29 (m), 6.18 - 5.65 (m), 4.77 - 4.43 (m), 4.31 - 4.08 (m), 3.99 - 3.63 (m), 3.22 (d), 3.18 - 2.71 (m), 1.80 (d), 1.28 (s), 1.20 - 0.76 (m).

Synthesis of N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**38**):

(S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide (514 mg, 0.72 mmol), 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (191 mg, 0.72 mmol), 1-hydroxybenzotriazole (49 mg, 0.36 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (180 mg, 0.94 mmol) were charged in a round bottom flask and dissolved in DMF (10 mL). n-Methylmorpholine (0.20 mL, 1.8 mmol) was added. The reaction mixture was stirred at ambient temperature for 30 minutes. Water was added and stirred for 1 hour. The resulting precipitate was collected by vacuum filtration then dissolved in methylene chloride, dried over $MgSO_4$, filtered and concentrated. The residue was purified by RP-HPLC to yield the title compound as a TFA salt. MS (m/z) 958.88 $[M+H]^+$. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.90 – 7.56 (m), 7.30 – 7.07 (m), 6.91 – 6.54 (m), 6.54 – 6.39 (m), 6.37 – 6.21 (m), 6.16 – 5.70 (m), 4.85 – 4.57 (m), 4.34 – 4.12 (m), 3.87 – 3.41 (m), 3.23 (s), 3.17 – 3.02 (m), 3.00 – 2.77 (m), 2.57 – 2.37 (m), 1.81 (s), 1.50 – 0.84 (m).

Biological Examples

Example A

Test A: Antiviral assay in MT4 Cells

For the antiviral assay, 0.4 µL of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 µL of cell growth medium (RPMI 1640, 10% FBS, 1% Penicillin-Streptomycin, 1% L-Glutamine, 1% HEPES) in each well of 384-well plate (10 concentrations) in quadruplicate.

1 mL Aliquots of MT4 cells were pre-infected for 3 hours at 37°C with 25 µL of cell growth medium (mock-infected) or a fresh 1:250 dilution of an HIV-IIIb concentrated ABI stock (0.004 m.o.i.). Infected and uninfected cells were diluted in cell growth media and 35 µL (2000 cells) was added to each well of the assay plates.

Assay plates were then maintained in a humidified, 5% CO_2 incubator at 37°C. After 5 days of incubation, 25 µl of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7573, Promega Biosciences, Inc., Madison, WI) was added to each well of the assay plate. Cell lysis was carried out by incubating at room temperature for 10 minutes and then chemiluminescence was read using an Envision plate reader (PerkinElmer). EC_{50} values were calculated as the compound concentration that caused a 50% decrease in luminescence signal, a measure of HIV-1 replication.

Example B

Test B: Cytotoxicity assay

Compound cytotoxicity and the corresponding CC_{50} values was determined using the same protocol as described in the antiviral assay (Test A) except that uninfected cells were used.

The compound of the present disclosure demonstrates antiviral activity (Test A) as depicted in the table below in comparison to Compound A and Compound B.

Compound	EC_{50} (nM)	CC_{50} (nM)
Compound 24	0.185	30068
Compound 38	0.399	55218
Compound A	1.715	21839

Compound B	2.991	14491

Example C

Test C. Pharmacokinetic Analysis Following Intravenous Administration to Sprague-Dawley Rats and Beagle Dogs and Cynomologous Monkeys

Test article and formulation

Compound 24 and 38 IV administration was formulated in 5% ethanol, 20% PG, 45% PEG 300, 30% pH 2 (0.01N HCl) water at 0.5 mg/mL. Compound A and Compound B intravenous infusion doses were formulated in a sterile solution of 5% ethanol, 45% PEG 400 and 50% water (pH 2.0) at 0.5 mg/mL. All IV formulations were in solution.

Animals Used

Each rat IV dosing group consisted of 3 male SD rats. At dosing, the animals generally weighed between 0.317 and 0.355 kg. The animals were fasted overnight prior to dose administration and up to 4 hr after dosing. Each dog IV dosing group consisted of 3 male, naïve beagle dogs. At dosing, the animals weighed ~ 10-12 kg. The animals were fasted overnight prior to dose administration and up to 2 hr after dosing.

Each cynomolgus (cyno) monkey IV dosing group consisted of 3 male, naïve cyno monkeys At dosing, the animals weighed ~3.2-4 kg. The animals were fasted overnight prior to dose administration and up to 2 hr after dosing.

Dosing

For the IV infusion group, the test compound was administered by intravenous infusion over 30 minutes. The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 1 mg/kg at 2 mL/kg.

Sample collection

Serial venous blood samples (approximately 0.4 mL each for rat and 1.0 mL for dog) were taken at specified time points after dosing from each animal. The blood samples were collected into Vacutainer™ tubes (Becton-Disckinson Corp, New Jersey, USA) containing EDTA as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. Centrifugation began within 1 hour of collection. All samples were placed into 96-well tubes and maintained on dry ice prior to storage at approximately -70°C.

Determination of the concentrations of the Compound of Formula (I) in plasma

An LC/MS/MS method was used to measure the concentration of test compounds in plasma.

Calculations

Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. A summary of pharmacokinetic parameters are shown in the tables below.

Compound	Rat CL (L/h/kg)	Rat V_{ss} (L/kg)	Rat $t_{1/2}$ (h)	Dog CL (L/h/kg)	Dog V_{ss} (L/kg)	Dog $t_{1/2}$ (h)	Cyno CL (L/h/kg)	Cyno Vss (L/kg)	Cyno $t_{1/2}$ (h)
Compound 24	0.05	1.8	28	0.07	1.6	22	0.24	2.7	12
Compound 38	0.08	1.8	19	0.33	1.77	7	0.21	2.1	9.5
Compound A	0.50	1.0	2	0.25	0.8	4	0.45	1.18	2.3
Compound B	0.43	1.4	3	0.28	1.3	6	0.42	1.59	3.4
CL: observed clearance; Vss: volume of distribution at steady state; $t_{1/2}$: terminal half-life									

Compound	Rat C_{max}	Rat AUC_{inf} (μM·h)	Dog C_{max}	Dog AUC_{inf} (μM·h)	Cyno C_{max}	Cyno AUC_{inf} (μM·h)
Compound 24	1.8	19	2.2	14.8	1.3	4.5
Compound 38	2.4	13	1.6	3.3	1.3	4.9
Compound A	1.4	2.7	2.1	5	1.8	2.6
Compound B	1.1	2.7	1.4	4.3	1.4	2.9
AUC_{inf}: Area Under the Curve from t = 0 to infinity; C_{max}: Maximum plasma concentration						

Example D

Test D. Metabolic Stability in Cultured Human Liver Hepatocytes

Radiolabelled test compounds, wherein tritium was introduced into the structure in place of one or more hydrogens, were prepared according to known methods in the art.

The radiolabelled compounds were incubated in pooled cryopreserved hepatocytes at a substrate concentration of 0.25 μM and radioactivity concentration of 10 uCi/mL. The final hepatocyte concentration was 1 million cells/mL. The hepatocyte/compound reaction mixture was dissolved in InVitroGRO™ KHB buffer (catalog # Z99074, BioreclamationIVT, Inc., Baltimore, MD) at pH 7.4. The incubations were performed in duplicate. A cell free control and a positive control were included in the incubations. The incubations were carried out with gentle shaking in a 37°C incubator under a humid atmosphere of 95% air/5% CO_2 (v/v). Aliquots (100 mL) were removed after 0, 1, 3, and 6 hours and added to 200 mL quenching solution that comprised 0.1% (v/v) TFA in 5% water/95% acetonitrile (v/v). The samples were placed on a shaker for 10 min, followed by centrifugation at 3000 g for 30 min. The samples of the supernatant were analyzed on a Dionex HPLC/PerkinElmer Flow Scintillation Analyzer as described below.

Liquid Chromatography–Radiochromatography

Quantification was done by comparison of radiolabeled metabolites and parent peaks measured on a Radiomatic 625TR Flow Scintillation Analyzer coupled to a Dionex/Chromeleon chromatography system. The column was a Phenomenex Synergi fusion RP (150 x 4.6 mm, 4 mm) maintained at 32 degrees Celsius. Mobile Phase A consisted of 0.1% (v/v) TFA in 99% water/1% acetonitrile (v/v). Mobile Phase B consisted of 0.1% (v/v) TFA in 5% water/95% acetonitrile (v/v). The flow rate was 1 mL/min using a sample injection volume of 100 mL. Gradient was as following: Mobile phase B was linearly increased from to 75% over 47 min, maintained at 75% for 3 min, changed back to 2%, maintained at 2% for 10 min.

Metabolic stability was determined by measuring the change in relative abundance of metabolites and parent over time and calculating from it the rate of disappearance of the parent compound. The stability data was utilized to calculate predicted human hepatic clearance values according to methods known in the art. The predicted human hepatic clearance values are shown in the table below.

	Predicted Human Hepatic Clearance (L/hr/kg)
Compound 24	0.01

Compound 38	0.02
Compound A	0.09
Compound B	0.04

The following can be deduced from the above comparative data:

Compound 24 is more potent in an HIV antiviral assay relative to compounds A and B (about 9 and about 16 times more potent, respectively). Compound 24 has a longer *in vivo* terminal half-life in rat relative to compounds A and B (about 14 and about 9 times longer, respectively). Compound 24 has a lower *in vivo* clearance in rat relative to compounds A and B (about 10 and about 8.6 times lower, respectively). Compound 24 has a longer *in vivo* terminal half-life in dog relative to compounds A and B (about 5 and about 4 times longer, respectively). Compound 24 has a lower *in vivo* clearance in dog relative to compounds A and B (about 3 and about 4 times lower, respectively). Compound 24 is more stable in human hepatocytes with a lower predicted hepatic clearance relative to compounds A and B (about 9 and about 4 times more stable, respectively).

The above data demonstrate that compound 24, has improved antiviral potency and an improved pharmacokinetic profile (which is demonstrated by longer half-life in rat and dog and lower predicted human clearance) when compared to compounds A and B.

Additionally, compound 38 is more potent in an HIV antiviral assay relative to compounds A and B (about 4 and about 8 times more potent, respectively). Compound 38 has a longer *in vivo* terminal half-life in rat relative to compounds A and B (about 9.5 and about 6.3 times longer, respectively). Compound 38 has a lower *in vivo* clearance in rat relative to compounds A and B (about 6.3 and about 5.4 times lower, respectively). Compound 38 has a similar *in vivo* clearance and terminal half-life in dog compared to compounds A and B. Compound 38 is more stable in human hepatocytes with a lower predicted hepatic clearance relative to compounds A and B (about 4.5 and about 2 times more stable, respectively).

The above data demonstrate that compound 38, has improved antiviral potency and an improved pharmacokinetic profile (which is demonstrated by longer half-life in rat and dog and lower predicted human clearance) when compared to compounds A and B.

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present disclosure.

The Examples disclosed herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. It is to be understood that individual steps described herein may be combined. It is also to be understood that separate batches of a compound may be combined and then carried forth in the next synthetic step.

Formulation Example

Compound 38 (about 30 mg/kg) was formulated as an aqueous suspension in 2% poloxamer 338 in saline (about 150 mg/mL). This formulation was then administered as a single subcutaneous (SC) injection to rats and the pharmacokinetic (PK) profile was determined. As can be seen in FIG. 3, Compound 38 maintains plasma concentrations well above paEC95 for > 10 weeks from a single SC injection. This data demonstrates that Compound 38 displays extended release pharmacokinetics.

A suspension of a compound of Formula Ib in 2% poloxamer 188 in saline (200mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 4 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 4, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A suspension of a compound of Formula Ib in 2% poloxamer 188 in saline (100mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 5 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 5, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A suspension of the sodium salt of a compound of Formula Ib in 2% poloxamer 188 in saline (200mg/mL) was prepared. The suspension was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 6 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As FIG. 6 shows, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of a compound of Formula Ib in NMP (100mg/mL) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 7 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 7, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of a compound of Formula Ib in NMP (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 8 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 8, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution of the sodium salt of a compound of Formula Ib in NMP (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 9 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 9, the compound of Formula Ib has measurable plasma concentrations at day 70 demonstrating extended release pharmacokinetics.

A solution formulation of a compound of Formula Ib in 10% ethanol, 12% water, and 78% PEG 200 (200mg/ml) was prepared. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 10 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the

data shows in FIG. 10, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

A solution formulation containing 200mg/mL of Formula Ib with 1.2 molar equivalent NaOH to form *in situ* sodium salt in 10% ethanol, 12% water, and 77% PEG are provided. Subjects were orally dosed with this formulation at 6mg/kg. A solution of the the compound of Formula Ib in 10% ethanol, 12% water, and 7% PEG 200 (200mg/ml) with 1.2 molar equivalent NaOH was prepared to form *in situ* sodium salt. The solution was administered to dogs subcutaneously at a dose of 6mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 11 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 11, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

A solution formulation of the compound of Formula Ib in 10% ethanol, 13% water, and 77% glycofurol (200 mg/mL) with 1.2 molar equivalent NaOH was prepared to form in situ sodium salt. The solution was administered to dogs subcutaneously at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 12 shows a plot of the plasma concentration of the compound of Formula Ib as a function of time. As the data shows in FIG. 12, the compound of Formula Ib has measurable plasma concentrations at day 28 demonstrating extended release pharmacokinetics.

Oral Formulation Example

[00264] An oral formulation containing a compound of Formula Ib in 10% ethanol, 20% Vitamin E TPGS, and 70% MIGLYOL 812 was prepared in hard gelatin capsules was preapared. Dogs were orally given a fixed 7.5mg dose of the compound of Formula Ib and the pharmacokinetic (PK) profile was determined. FIG. 13 shows the change in plasma concentration over time for the compound of Formula Ib.

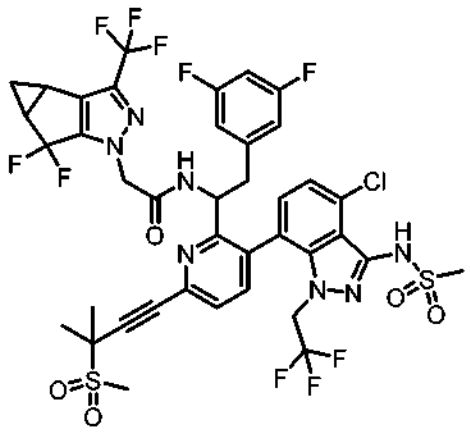
All references, including publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The present disclosure provides reference to various embodiments and techniques. However, it should be

understood that many variations and modifications may be made while remaining within the spirit and scope of the present disclosure.

CLAIMS

What is claimed is:

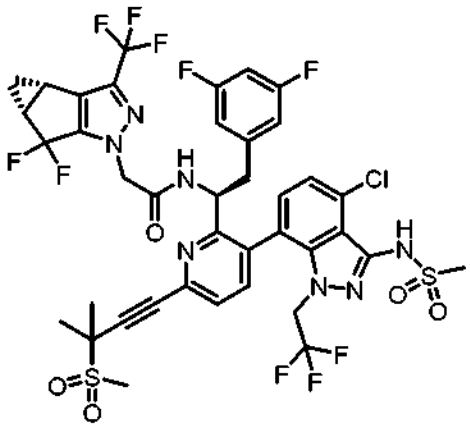
1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, which is a compound of Formula (Ib)



(Ib)

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

4. The pharmaceutical composition of claim 3, further comprising one, two, three, or four additional therapeutic agents.

5. The pharmaceutical composition of claim 4, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

6. The pharmaceutical composition of claim 4, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

7. The pharmaceutical composition of claims 4 to 6, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

8. The pharmaceutical composition of claims 4 to 7, wherein the additional therapeutic agents are selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

9. A method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of a compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

10. The method of claim 9, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with one, two, three, or four additional therapeutic agents.

11. The method of claim 10, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev

protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

12. The method of claim 10 or 11, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

13. The method of claims 10 to 12, wherein the additional therapeutic agents are selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

14. The method of claims 10 to 13, wherein the additional therapeutic agents are selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

15. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in therapy.

16. A compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of said compound to a subject in need thereof.

17. The compound for use according to claim 16, wherein said method comprises administering one, two, three or four additional therapeutic agents.

18. The compound for use as claimed in claim 17, wherein the additional therapeutic agents are administered simultaneously with the compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof.

19. The compound for use as claimed in claim 18, wherein the compound of formula (Ia) or (Ib) is combined with the additional therapeutic agents in a unitary dosage form for simultaneous administration.

20. The compound for use as claimed in claim 17, wherein the compound of formula (Ia) or (Ib) is administered and the additional therapeutic agents are administered sequentially.

21. The compound for use according to claim 17, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent

kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

22. The compound for use according to claim 17, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

23. The compound for use according to claim 17, wherein said compound is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

24. The compound for use according to claim 17, wherein said compound is combined with tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

25. The compound for use according to claim 17, wherein said compound is combined with tenofovir disoproxil, tenofovir disoproxil hemifumarate or tenofovir disoproxil fumarate.

26. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

27. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a

second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

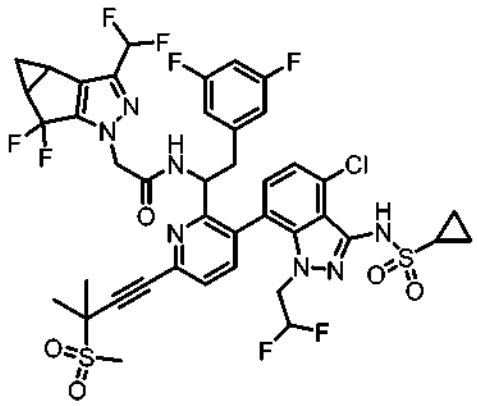
28. The compound for use according to claim 17, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

29. The pharmaceutical composition of claims 4 to 6, wherein the additional therapeutic agent is 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

30. The method of claims 10 to 12, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

31. The compound for use according to claims 17 to 22, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir, or a pharmaceutically acceptable salt thereof.

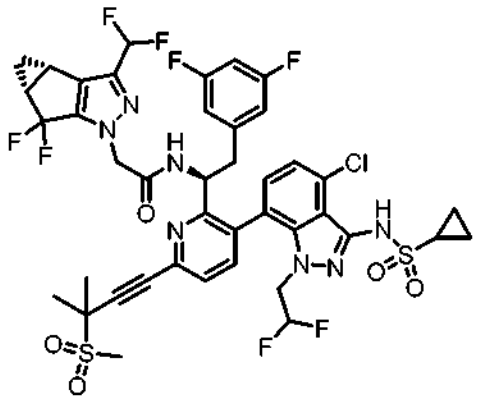
32. A compound of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 32, which is a compound of Formula (IIb)



(IIb)

or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

35. The pharmaceutical composition of claim 34, further comprising one, two, three, or four additional therapeutic agents.

36. The pharmaceutical composition of claim 35, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing

inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

37. The pharmaceutical composition of claim 35, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

38. The pharmaceutical composition of claims 35 to 37, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

39. The pharmaceutical composition of claims 35 to 38, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

40. A method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of a compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

41. The method of claim 40, wherein the method comprises administering the compound, or a pharmaceutically acceptable salt thereof, in combination with one, two, three, or four additional therapeutic agents.

42. The method of claim 41, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

43. The method of claim 41 or 42, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

44. The method of claims 41 to 43, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate.

45. The method of claims 41 to 44, wherein the additional therapeutic agents are selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate.

46. A compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, for use in therapy.

47. A compound of claim 32 or 33, or a pharmaceutically acceptable salt thereof, for use in a method of treating or preventing a human immunodeficiency virus (HIV) infection comprising administering a therapeutically effective amount of said compound to a subject in need thereof.

48. The compound for use according to claim 47, wherein said method comprises administering one, two, three or four additional therapeutic agents.

49. The compound for use as claimed in claim 48, wherein the additional therapeutic agents are administered simultaneously with the compound of formula (IIa) or (IIb), or a pharmaceutically acceptable salt thereof.

50. The compound for use as claimed in claim 49, wherein the compound of formula (IIa) or (IIb) is combined with the additional therapeutic agents in a unitary dosage form for simultaneous administration.

51. The compound for use as claimed in claim 48, wherein the compound of formula (IIa) or (IIb) is administered and the additional therapeutic agents are administered sequentially.

52. The compound for use according to claim 48, wherein the additional therapeutic agents are selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, and HIV vaccines, or any combinations thereof.

53. The compound for use according to claim 48, wherein the additional therapeutic agents are selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120

inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, pharmacokinetic enhancers, and other drugs for treating HIV, or any combinations thereof.

54. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

55. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir alafenamide, tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate.

56. The compound for use according to claim 48, wherein said compound is combined with 4′-ethynyl-2-fluoro-2′-deoxyadenosine, bictegravir or a pharmaceutically acceptable salt thereof, tenofovir disoproxil, tenofovir disoproxil hemifumarate or tenofovir disoproxil fumarate.

57. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

58. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

59. The compound for use according to claim 48, wherein said compound is combined with a first additional therapeutic agent selected from the group consisting of 4′-ethynyl-2-fluoro-2′-deoxyadenosine, tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir

disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

60. The pharmaceutical composition of any one of claims 3-8, 29, or 34-39, wherein the composition is a parenteral formulation.

61. The parenteral formulation according to claim 60, wherein the formulation is administered subcutaneously to a subject in need thereof.

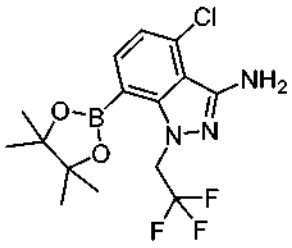
62. The parenteral formulation according to claim 60, wherein the formulation is administered intramuscularly to a subject in need thereof.

63. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises saline.

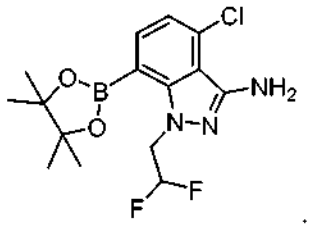
64. The parenteral formulation of any one of claims 60-63, wherein the formulation comprises a poloxamer.

65. The parenteral formulation of claim 64, wherein the poloxamer is poloxamer 338.

66. A compound selected from the group consisting of:

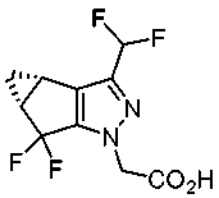


and

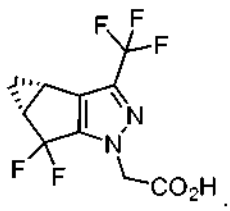


.

67. A compound selected from the group consisting of:

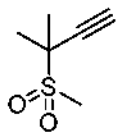


and



.

68. A compound of the formula:



69. The parenteral formulation of claim 64, wherein the poloxamer is poloxamer 188.

70. The parenteral formulation of claim 69, wherein the concentration of poloxamer 188 in saline is about 1 % to about 10%.

71. The parenteral formulation of claim 69 or 70, wherein the concentration of poloxamer 188 in saline is about 1 % to about 3%.

72. The parenteral formulation of claim 69, 70, or 71, wherein the concentration of poloxamer 188 in saline is about 2%.

73. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises N-methyl-2-pyrrolidone.

74. The parenteral formulation of any one of claims 60-62, wherein the formulation consists essentially of N-methyl-2-pyrrolidone.

75. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises dimethyl sulfoxide.

76. The parenteral formulation of any one of claims 60-62, wherein the formulation consists essentially of dimethyl sulfoxide.

77. The parenteral formulation of any one of claims 60-62, wherein the formulation comprises water.

78. The parenteral formulation of any one of claims 60-62 or 77, wherein the formulation further comprises an alcohol.

79. The parenteral formulation of claim 78, wherein the alcohol is ethanol.

80. The parenteral formulation of any one of claims 60-62 or 77 to 79, wherein the formulation further comprises polyethylene glycol.

81. The parenteral formulation of claim 80, wherein the polyethylene glycol has an average molecular weight of about 200 g/mol.

82. The parenteral formulation of any one of claims 77 to 81, further comprising an inorganic base.

83. The parenteral formulation of claim 82, wherein the inorganic base is sodium hydroxide.

84. The parenteral formulation of claims 60-62, and 77-83, wherein the formulation comprises about 5% to about 20% ethanol, about 5% to about 20% water, and about 60% to about 90% polyethylene glycol 200.

85. The parenteral formulation of claims 60-62, and 77-84, wherein the formulation comprises about 10% to about 15% ethanol, about 10% to about 15% water, and about 70% to about 80% polyethylene glycol 200.

86. The parenteral formulation of claims 60-62, and 77-85, wherein the formulation comprises about 10% ethanol, about 12% water, and about 78% polyethylene glycol 200.

87. The pharmaceutical composition of any one of claims 3-8, 29, or 34-39, wherein the composition is an oral formulation.

88. The formulation of any one of claims 60-65 and 69-87, wherein the compound is present as a sodium salt.

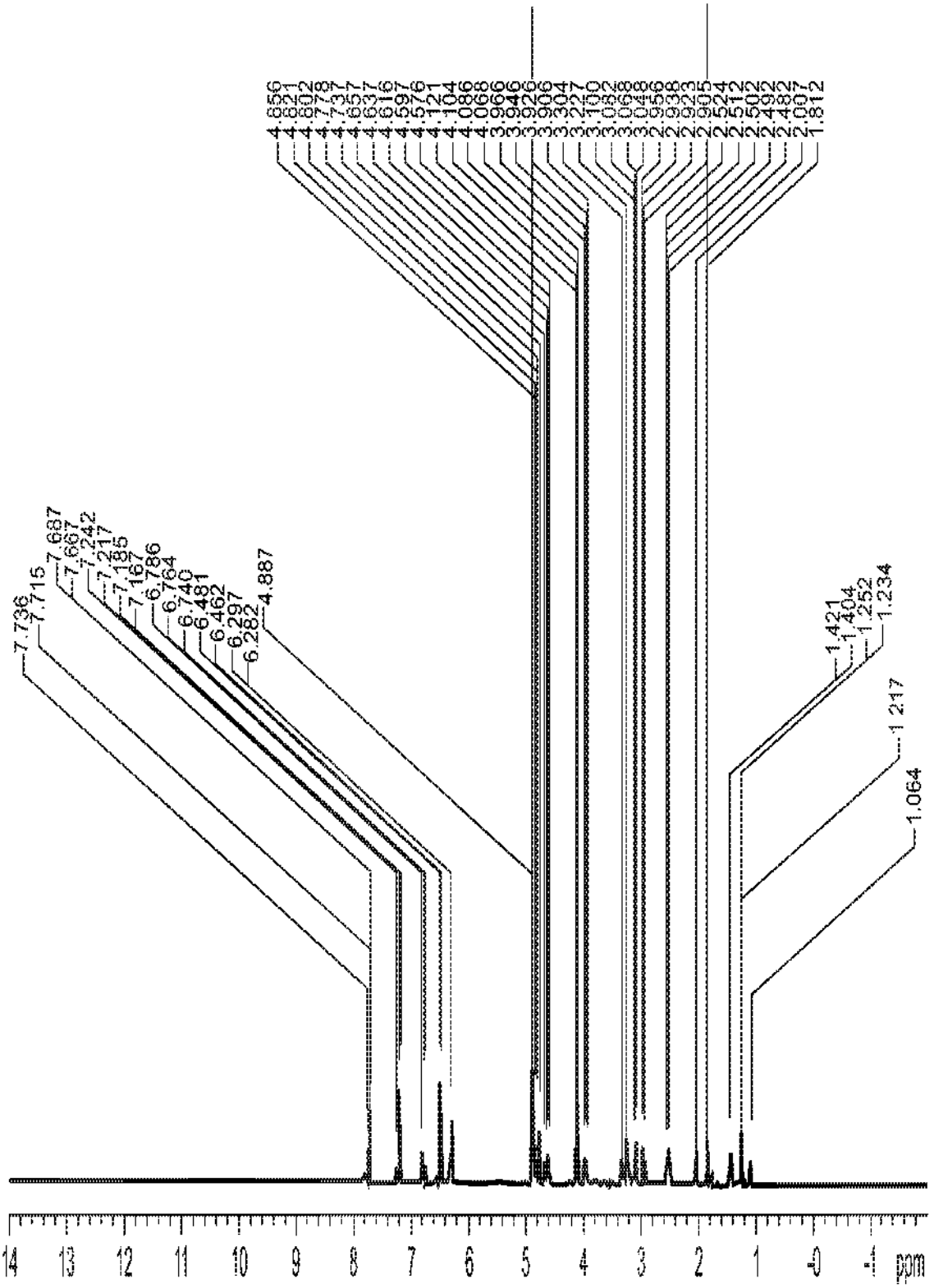

7.736
7.715
7.687
7.667
7.242
7.217
7.185
7.167
6.786
6.764
6.740
6.481
6.462
6.297
6.282
4.887
1.421
1.404
1.252
1.234
1.217
1.064
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

FIG. 1

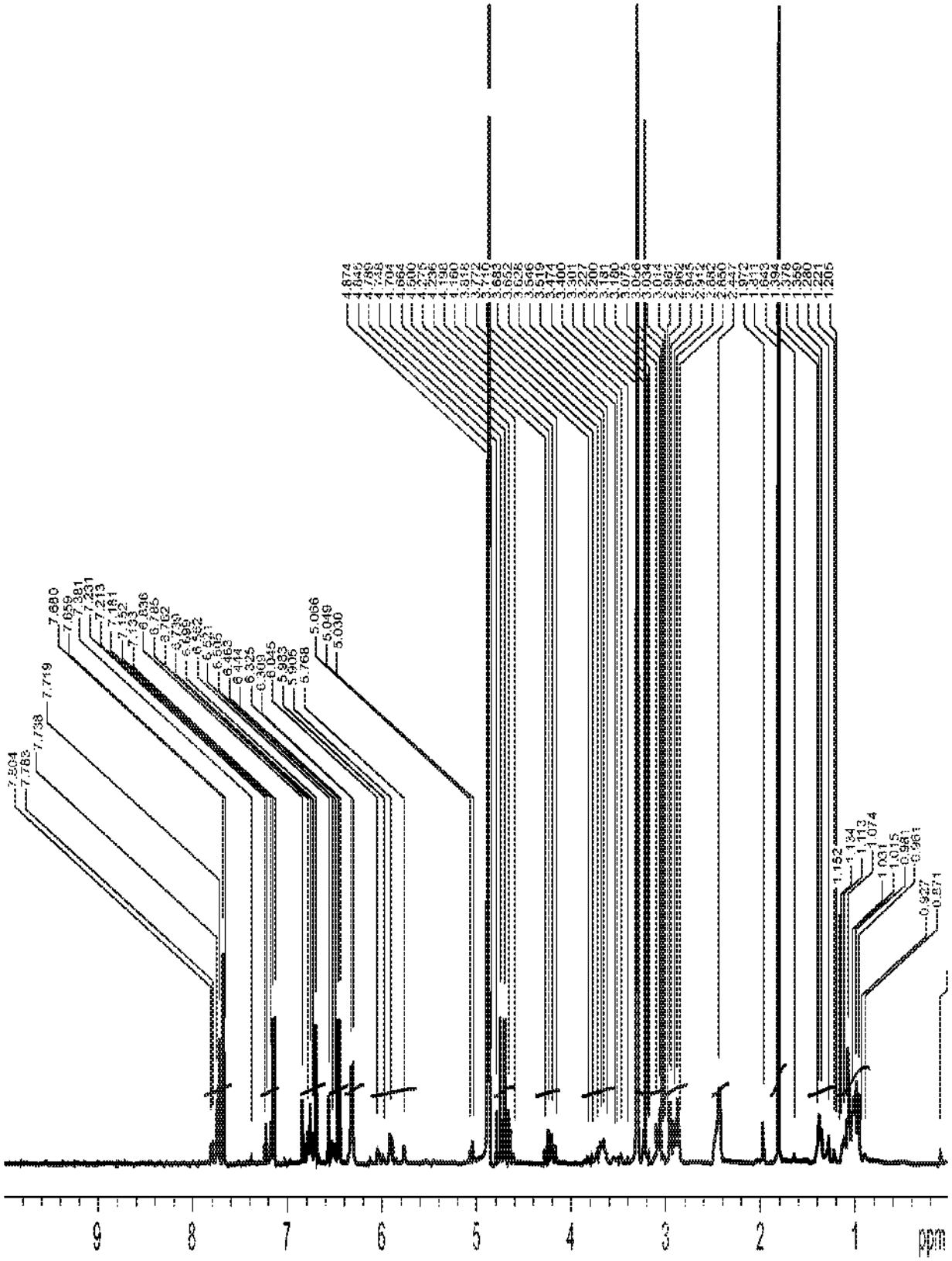

4.874
4.846
4.789
4.738
4.704
4.664
4.500
4.275
4.236
4.198
4.160
3.818
3.772
3.710
3.683
3.652
3.628
3.546
3.519
3.474
3.400
3.301
3.227
3.200
3.181
3.150
3.075
3.056
3.034
3.014
2.981
2.962
2.945
2.912
2.852
2.850
2.447
1.972
1.911
1.643
1.394
1.378
1.359
1.280
1.221
1.205
7.804
7.783
7.738
7.719
7.680
7.659
7.381
7.231
7.213
7.181
7.152
7.133
6.836
6.785
6.762
6.738
6.698
6.662
6.631
6.505
6.463
6.444
6.325
6.309
6.045
5.983
5.906
5.768
5.056
5.049
5.030
1.152
1.134
1.113
1.074
1.031
1.015
0.981
0.961
0.927
0.871
9
8
7
6
5
4
3
2
1
ppm

FIG. 2

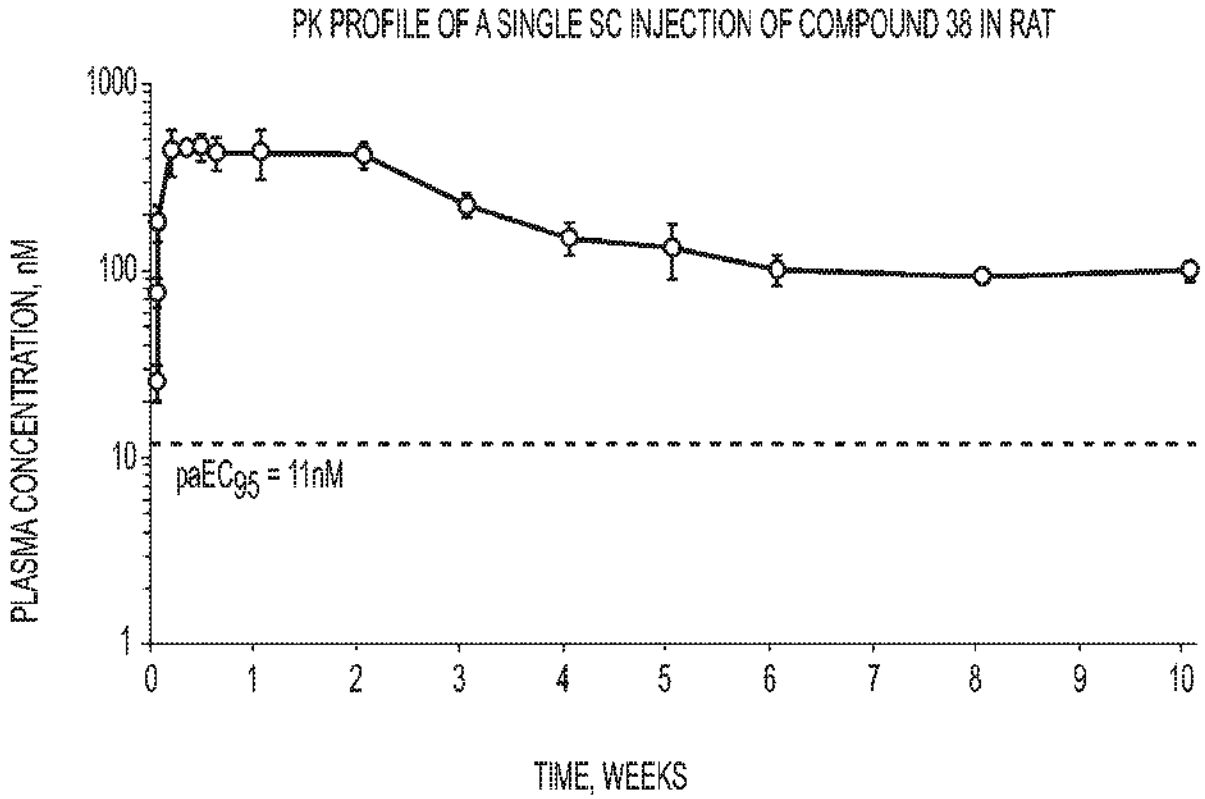

PK PROFILE OF A SINGLE SC INJECTION OF COMPOUND 38 IN RAT
PLASMA CONCENTRATION, nM
1000
100
10
1
paEC95 = 11nM
0
1
2
3
4
5
6
7
8
9
10
TIME, WEEKS

FIG. 3

Concentration over time of 200 mg/mL of Formula Ib free acid form suspended in 2% Poloxamer 188 in saline formulation after subcutaneous dosing in dogs at 6mg/kg

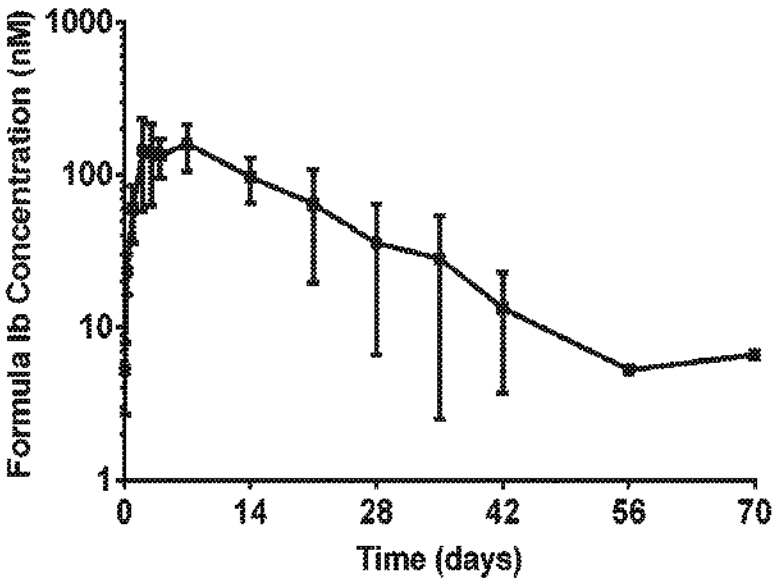


FIG. 4

Concentration over time of 100 mg/mL of Formula Ib free acid form suspended in 2% Poloxamer 188 in saline formulation after subcutaneous dosing in dogs at 6mg/kg

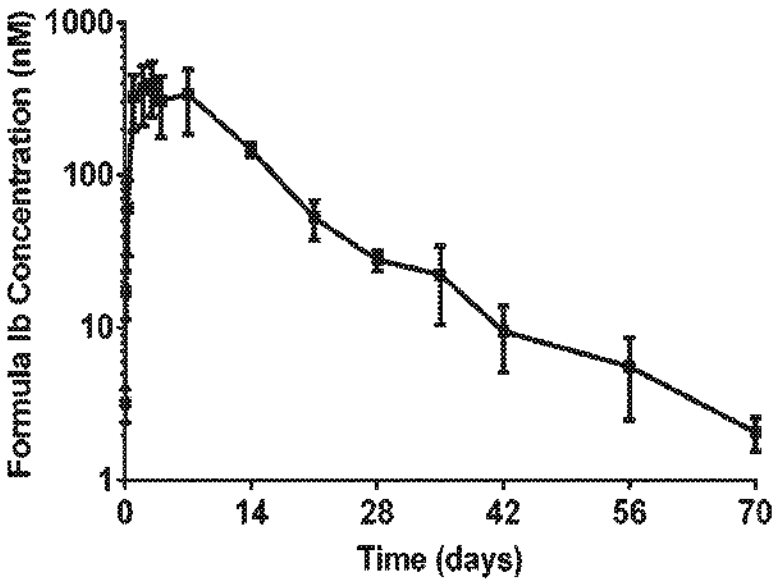


FIG. 5

Concentration over time of 200 mg/mL of Formula Ib, sodium salt form suspended in 2% Poloxamer 188 in saline formulation, after subcutaneous dosing in dogs at 6mg/kg

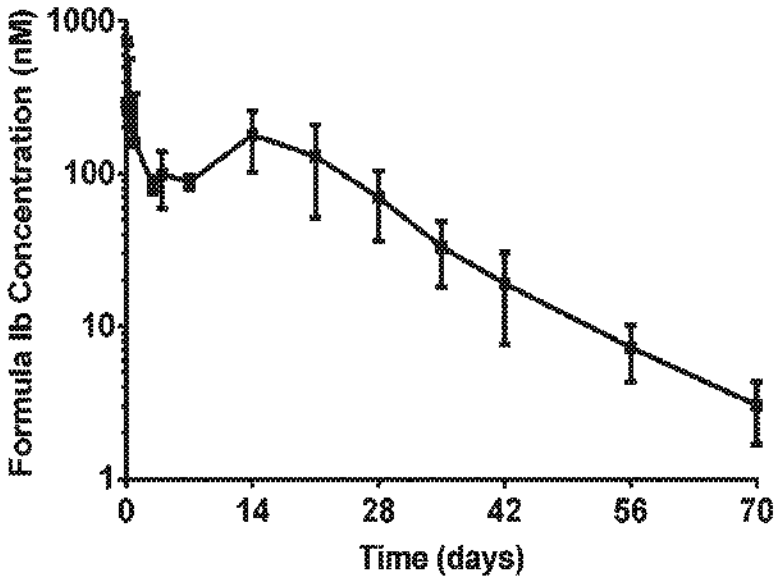


FIG. 6

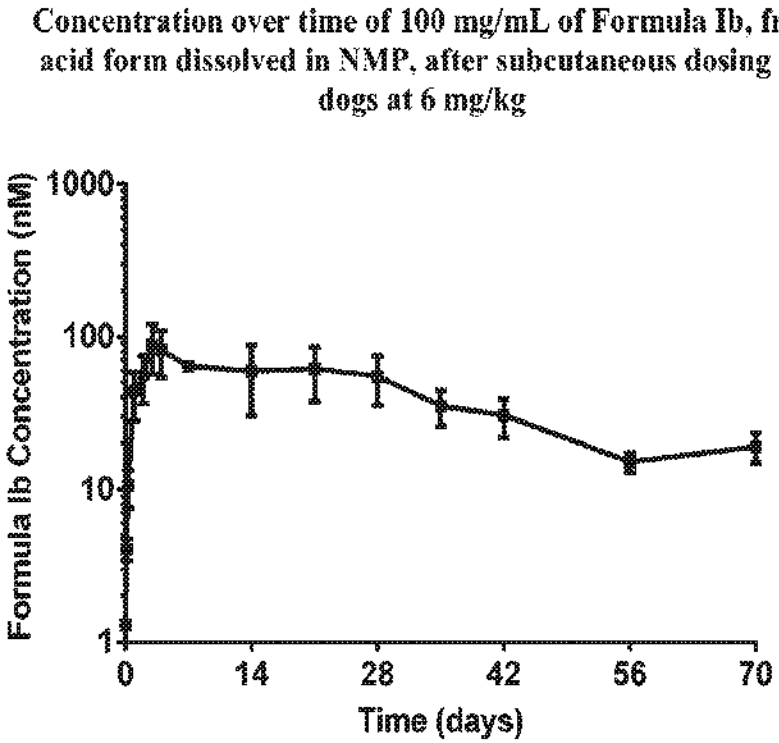

Concentration over time of 100 mg/mL of Formula Ib, free acid form dissolved in NMP, after subcutaneous dosing in dogs at 6 mg/kg
Formula Ib Concentration (nM)
1000
100
10
1
0
14
28
42
56
70
Time (days)

FIG. 7

Concentration over time of 200 mg/mL of Formula Ib, free acid form dissolved in NMP, after subcutaneous dosing in dogs at 6 mg/kg

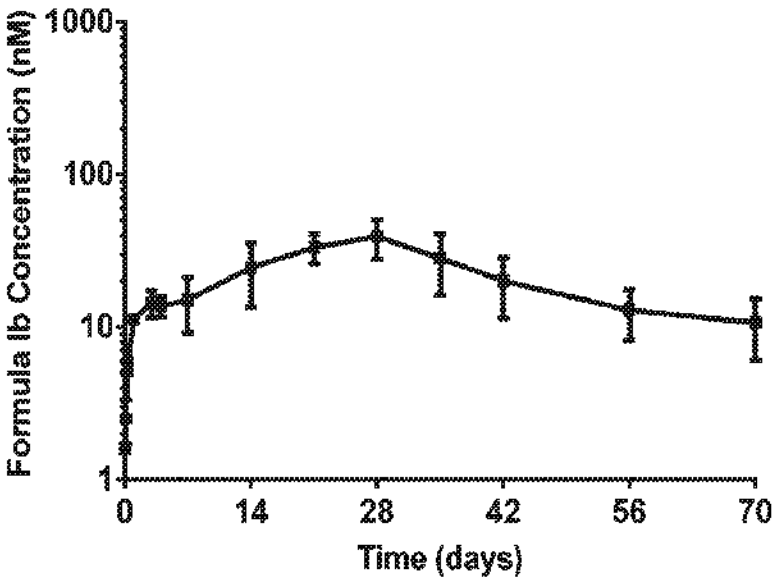


FIG. 8

Concentration over time of 200 mg/mL of Formula Ib, sodium salt form dissolved in NMP, after subcutaneous dosing in dogs at 6mg/kg

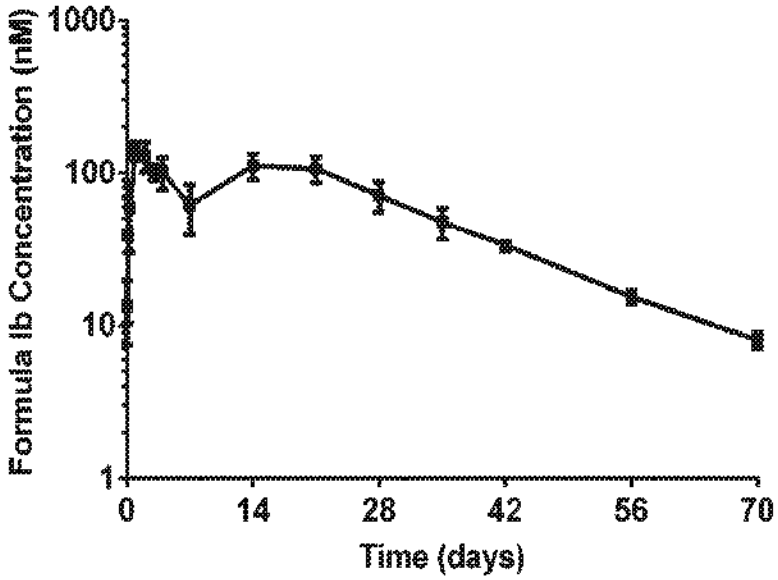


FIG. 9

Concentration over time of 200 mg/mL of Formula Ib free acid form dissolved in 10% ethanol, 12% water, and 78% PEG 200, after subcutaneous dosingin dogs at 6 mg/kg

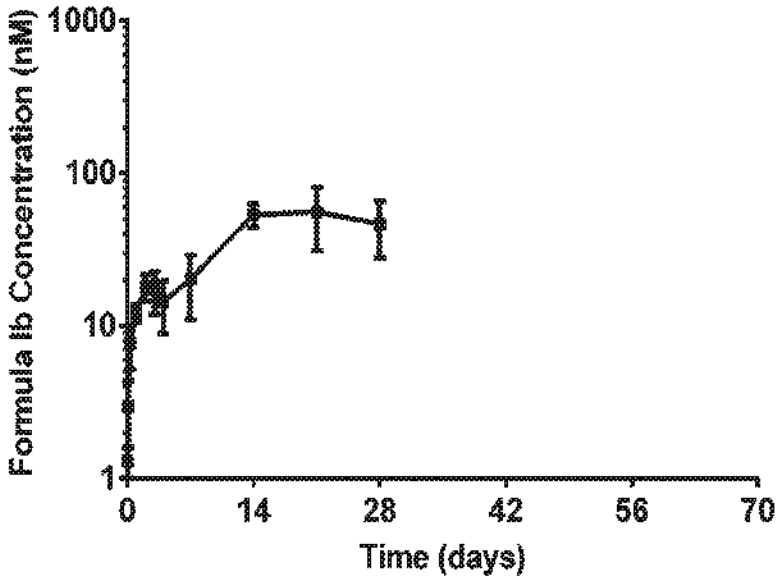


FIG. 10

Concentration over time of 200mg/mL of Formula Ib dissolved in 10% ethanol, 12% water, and 77% PEG 200, with 1.2 mol-eq sodium hydroxide, after subcutaneous dosing in dogs at 6 mg/kg

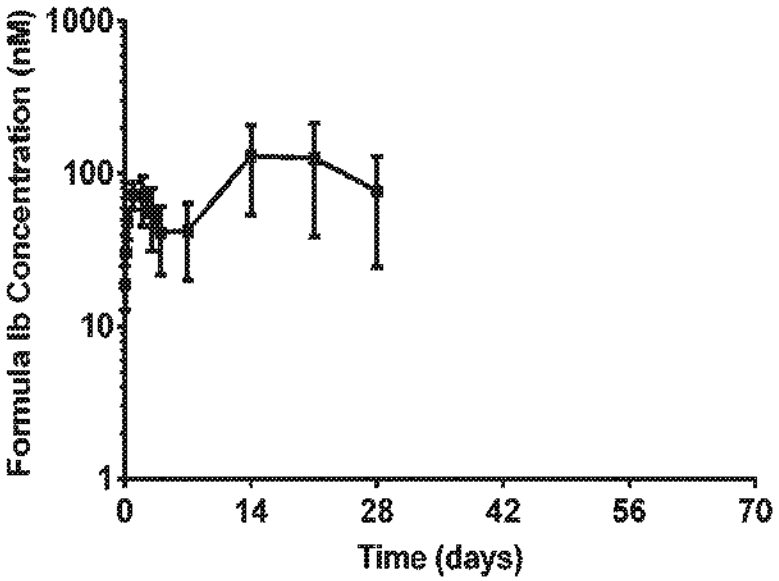


FIG. 11

Concentration over time of 200mg/mL of Formula Ib dissolved in 10% ethanol, 13% water, and 77% glycofurol, with 1.2 mol-eq NaOH, after subcutaneous dosing in dogs at 6mg/kg

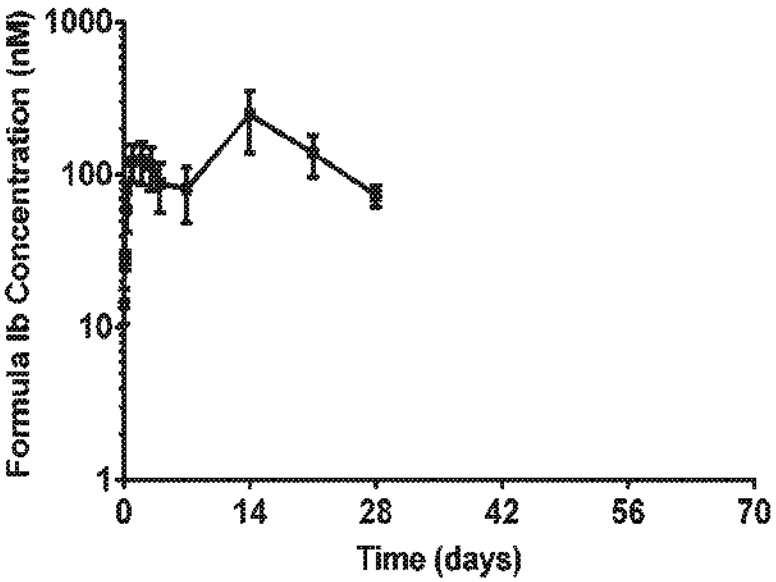


FIG. 12

Concentration over time of fixed 7.5mg oral dose of Formula Ib free acidform dissolved in 10% ethanol, 20% vitamin E TPGS, 70% Miglyol 812, after oral dosing in dogs

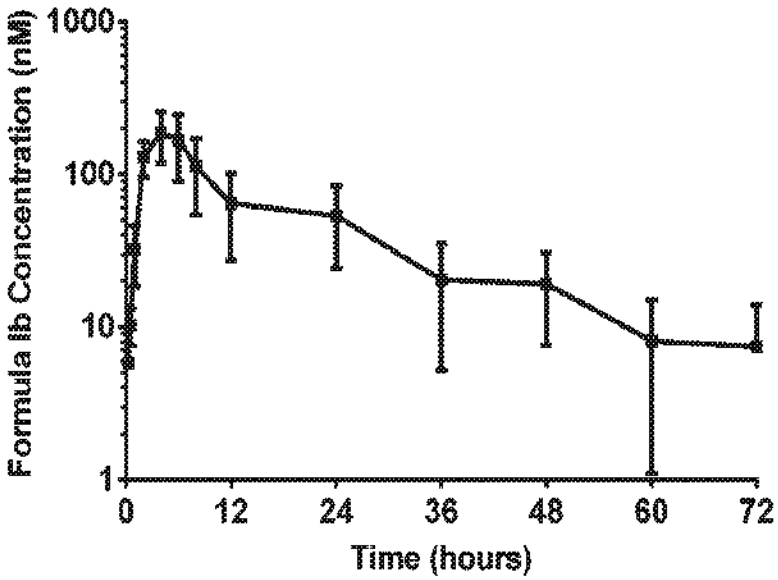


FIG. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/047416

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61P31/18 A61K31/4439
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/303164 A1 (BRIZGYS GEDIMINAS [US] ET AL) 9 October 2014 (2014-10-09) cited in the application	67
A	examples 19,33 claims 28, 46-50	1-65, 68-88
X,P	WO 2017/007689 A1 (GILEAD SCIENCES INC [US]) 12 January 2017 (2017-01-12) example 980	68

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2017	27/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fanni, Stefano

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/047416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014303164 A1	09-10-2014	AU 2014223973 A1	10-09-2015
		AU 2016262671 A1	08-12-2016
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		CR 20150454 A	20-11-2015
		CU 20150096 A7	29-07-2016
		EA 201591457 A1	31-03-2016
		EP 2961742 A2	06-01-2016
		HK 1222169 A1	23-06-2017
		JP 2016510038 A	04-04-2016
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		NZ 631754 A	24-02-2017
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		PH 12015501881 A1	11-01-2016
		SG 11201506929V A	29-10-2015
		TW 201446755 A	16-12-2014
		US 2014303164 A1	09-10-2014
		US 2016108030 A1	21-04-2016
		UY 35362 A	29-08-2014
		WO 2014134566 A2	04-09-2014
WO 2017007689 A1	12-01-2017	CA 2971640 A1	12-01-2017
		EP 3191470 A1	19-07-2017
		SG 11201702041P A	27-04-2017
		TW 201712005 A	01-04-2017
		US 2017008905 A1	12-01-2017
		US 2017152240 A1	01-06-2017
		UY 36771 A	31-01-2017
		WO 2017007689 A1	12-01-2017

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(19) World Intellectual Property Organization
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(43) International Publication Date
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WIPO | PCT

(10) International Publication Number
WO 2020/018459 A1

(51) International Patent Classification:
A61K 31/4427 (2006.01) *A61K 9/08* (2006.01)
A61K 31/4439 (2006.01) *A61K 9/20* (2006.01)
A61K 45/06 (2006.01) *A61K 9/48* (2006.01)
A61K 9/00 (2006.01) *A61P 31/18* (2006.01)

(21) International Application Number:
PCT/US2019/041880

(22) International Filing Date:
15 July 2019 (15.07.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/698,611 16 July 2018 (16.07.2018) US

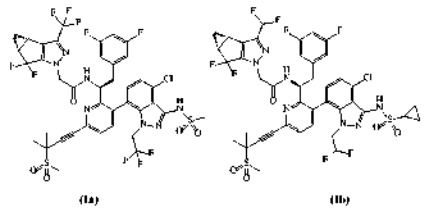
(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) Inventors: **BAUER, Laura Elizabeth**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **GORMAN, Eric M.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **MULATO, Andrew Stephen**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **RHEE, Martin Sunkwang**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **ROWE, Charles William**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **SELLERS, Scott P.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **STEFANIDIS, Dimitrios**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **TSE, Winston C.**; 801 Windblown Lane, Redwood City, California 94065 (US). **YANT, Stephen R.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **CHIU, Anna**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(74) Agent: **CHOI, Lydia B.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

(54) Title: CAPSID INHIBITORS FOR THE TREATMENT OF HIV



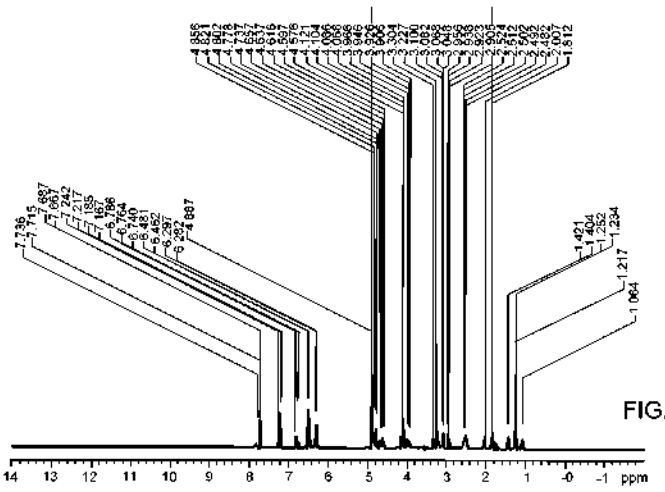


FIG. 1

(57) Abstract: The present disclosure relates to compounds of Formula (Ia) and (Ib) or a pharmaceutically acceptable salt thereof, which are useful in the treatment of an HIV infection in heavily treatment-experienced patients with multidrug resistant HIV infection.

WO 2020/018459 A1

[Continued on next page]

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

CAPSID INHIBITORS FOR THE TREATMENT OF HIV

CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims the benefit of U.S. Provisional Application No. 62/698,611, filed on July 16, 2018, the entire content of which is hereby incorporated by reference in its entirety.

FIELD

The present disclosure relates to methods for the treatment of a human immunodeficiency virus (HIV) infection in heavily treatment-experienced patients (e.g., patients with multidrug resistant HIV infection).

BACKGROUND

The viral capsid protein (CA) is essential for multiple stages of the HIV life cycle. During viral maturation following the processing of Gag polyprotein by the HIV protease, CA self-assembles into the conical shaped core characteristic of mature HIV-1 virions. Contained within this capsid core are the viral RNA, nucleocapsid, reverse transcriptase, and integrase. Failure to generate a suitable core precludes infectivity. In addition, CA contributes to multiple essential processes during the early stages of HIV replication, including important roles in regulating proper capsid core disassembly (uncoating) kinetics to ensure efficient and productive viral DNA synthesis via coupled reverse transcription, and contributes to the active transport of pre-integration complexes into the nuclear compartment to support viral DNA integration into transcriptionally active loci. Defects in the proper function of capsid ultimately inhibit efficient nuclear uptake and integration of viral DNA into the host genome.

There are currently a number of antiretroviral drugs available to combat HIV infection. These drugs can be divided into classes based on the viral protein they target or their mode of action. Used alone, these drugs are effective in reducing viral replication. However, the effect is only temporary as the virus readily develops resistance to all known agents used as monotherapy. Combination therapy has proven very effective at both reducing virus and suppressing the emergence of resistance in a number of patients. In the US, where combination therapy is widely available, the number of HIV-related deaths has dramatically declined (Palella, F. J.; Delany, K. M.; Moorman, A. C.; Loveless, M. O.; Furher, J.; Satten, G. A.; Aschman, D. J.; Holmberg, S. D.; *N. Engl. J. Med.* 1998, 338:853-860).

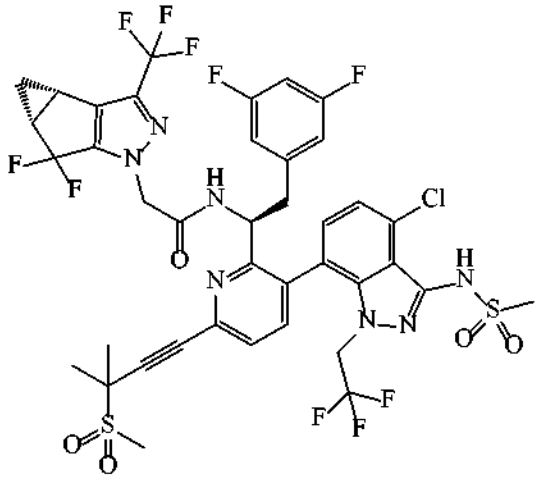
Despite the success of combination antiretroviral therapy, a significant proportion of patients experience a loss of virologic, immunologic, or clinical benefit from their current

regimens, leading to treatment failure and a rebound of the amount of HIV that can be measured in the blood. Initial studies suggest that approximately 30-50% of patients ultimately fail at least one drug in the suppressive combination. Treatment failure can be caused by the emergence of viral resistance. Viral resistance in turn can be caused by the replication rate of HIV-1 during the course of infection combined with the relatively high viral mutation rate associated with the viral polymerase and the lack of adherence of HIV-infected individuals in taking their prescribed medications. Because of structural similarities of the drugs within an antiretroviral class, cross resistance is commonly seen to the other members of that class (for example, virologic failure on a regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) will lead to cross resistance to the other first generation NNRTI agents). As patients experience repeated virologic failure on antiretroviral combination therapy, their viruses develop broad multi-class antiretroviral drug resistance which limits the effectiveness of the next round of antiretroviral therapy. Many heavily treatment-experienced patients have viral resistance to several classes of antiretroviral drugs and there are often not even two drugs that remain fully active to form the core of a new, effective antiretroviral drug regimen. Frequently, these patients have limited options for alternative treatment regimens and are at risk of significant morbidity and mortality.

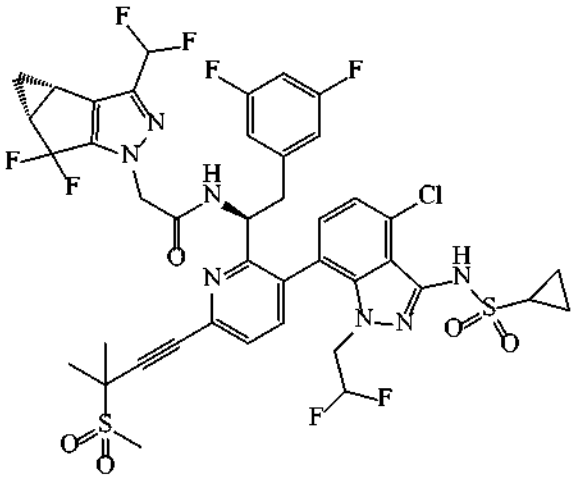
Thus, there is a need for safe and effective therapies for heavily treatment-experienced patients who have limited treatment options due to antiretroviral drug resistance.

SUMMARY

The present disclosure relates to methods of treating human immunodeficiency virus (HIV) infection in a heavily treatment-experienced patient. The method includes administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof.

In some embodiments, the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to one or more antiretroviral medications. In some embodiments, the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to two or more antiretroviral medications. In some embodiments, the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to three or more antiretroviral medications.

In some embodiments, the HIV-1 mutant is resistant to a protease inhibitor (PI), a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI). In certain embodiments, the HIV-1 mutant resistant to a protease inhibitor is selected from I50V, I84V/L90M, G48V/V82A/L90M, and G48V/V82S. In certain embodiments, the HIV-1 mutant resistant to a nucleoside or nucleotide reverse transcriptase inhibitor is selected from K65R, M184V, and 6TAMs. In certain embodiments, the HIV-1 mutant resistant to a non-nucleoside or non-nucleotide reverse transcriptase inhibitor is selected from K103N, Y181C, Y188L, L100I/K103N, and K103N/Y181C. In certain embodiments, the HIV-1 mutant resistant to a integrase strand transfer inhibitor is selected from Y143R, E138K/Q148K, G140S/Q148R, E92Q/N155H, N155H/Q148R, and R263K/M50I.

In some embodiments, the patient is infected with HIV-1 resistant to at least one antiretroviral medication. In some embodiments, the patient is infected with multidrug resistant HIV-1 which is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments, the patient is infected with multidrug resistant HIV-1 which is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

In some embodiments, the NRTI is selected from emtricitabine, lamivudine (3TC), zidovudine (azidothymidine (AZT)), didanosine (ddI), dideoxyinosine, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, stavudine (d4T), zalcitabine (dideoxycytidine, ddC), and abacavir.

In some embodiments, the NNRTI is selected from efavirenz, etravirine, rilpivirine, nevirapine, and delavirdine.

In some embodiments, the PI is selected from amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

In some embodiments, the INSTI is selected from raltegravir, elvitegravir, dolutegravir, and bictegravir.

In some embodiments of the method, the patient had been previously treated with at least one antiretroviral medication for at least 3 months, at least 6 months, at least 9 months, or at least 12 months.

In some embodiments, the patient failed a prior HIV treatment regimen including administration of at least one antiretroviral medication. In certain embodiments, the prior treatment regimen included administration of at least one antiretroviral medication from each of two different classes of antiretroviral medications. In certain embodiments, the prior treatment regimen included administration of at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

In certain embodiments of the method, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally, subcutaneously, intramuscularly, or intravenously.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally at a concentration of about 20 mg/mL to about 100 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a hard gelatin capsule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a soft gelatin capsule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a tablet.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously at a concentration of about 50 mg/mL to about 500 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a solution formulation. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as an aqueous suspension. In some embodiments, the compound of Formula **(Ia)** is a sodium salt. In some embodiments, the compound of Formula **(Ib)** is a trifluoroacetic acid salt.

In some embodiments of the method, the compound of Formula **(Ia)** or Formula **(Ib)** is formulated with one or more other compounds selected from HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV nucleoside reverse transcriptase translocation inhibitors, and

pharmacokinetic enhancers. In some embodiments, the HIV nucleoside reverse transcriptase translocation inhibitor is 4'-ethynyl-2-fluoro-2'-deoxyadenosine triphosphate (MK-8591).

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once daily. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, or 48 weeks.

In some embodiments of the method, the patient has a viral load of greater than about 200 copies of HIV-1 RNA/mL, greater than about 500 copies of HIV-1 RNA/mL, greater than about 750 copies of HIV-1 RNA/mL, greater than about 1000 copies of HIV-1 RNA/mL, or greater than about 2000 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the patient is failing an HIV treatment regimen including administration of at least one antiretroviral medication at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments of the method, administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, results in a decrease in the viral load in the patient. In some embodiments, the viral load is decreased by about 0.5 $\log_{10}$ to about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 0.5 $\log_{10}$, about 1 $\log_{10}$, about 1.5 $\log_{10}$, about 2 $\log_{10}$, or about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the viral load in the patient is about 200 copies of HIV-1 RNA/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks. In some embodiments, the viral load in the patient is about 50 copies of HIV-1 RNA/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks.

In some embodiments, the patient is concurrently treated with at least one additional antiretroviral medication. In some embodiments, the additional antiretroviral medication is

selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), an integrase strand transfer inhibitor (INSTI), a gp41 fusion inhibitor, a CCR5 co-receptor antagonist, and combinations thereof.

In some embodiments, the NRTI is selected from emtricitabine, lamivudine (3TC), zidovudine (azidothymidine (AZT)), didanosine (ddI), dideoxyinosine, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, stavudine (d4T), zalcitabine (dideoxycytidine, ddC), and abacavir.

In some embodiments, the NNRTI is selected from efavirenz, etravirine, rilpivirine, nevirapine, and delavirdine.

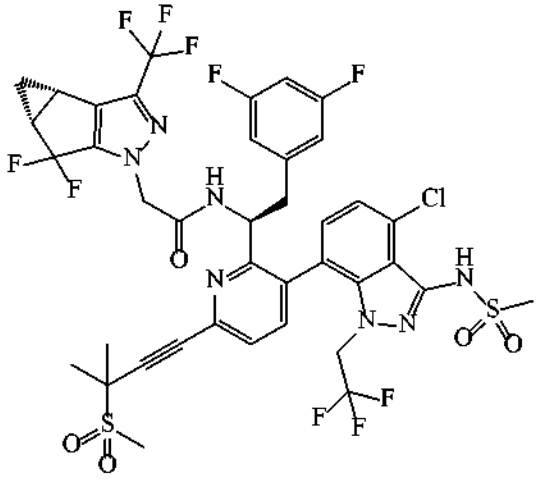
In some embodiments, the PI is selected from amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

In some embodiments, the INSTI is selected from raltegravir, elvitegravir, dolutegravir, and bictegravir.

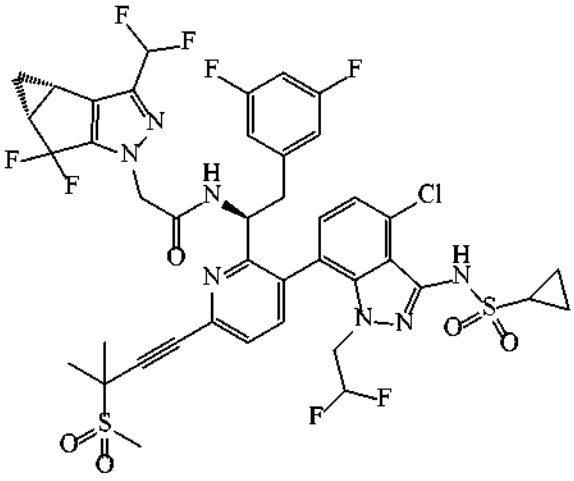
In some embodiments, the gp41 fusion inhibitor is selected from albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer, and sifuvirtide.

In some embodiments, the CCR5 co-receptor antagonist is selected from aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

Also included in the present disclosure is a method of treating human immunodeficiency virus-1 (HIV-1) infection in a heavily treatment-experienced patient with multidrug resistant HIV-1, the method including administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



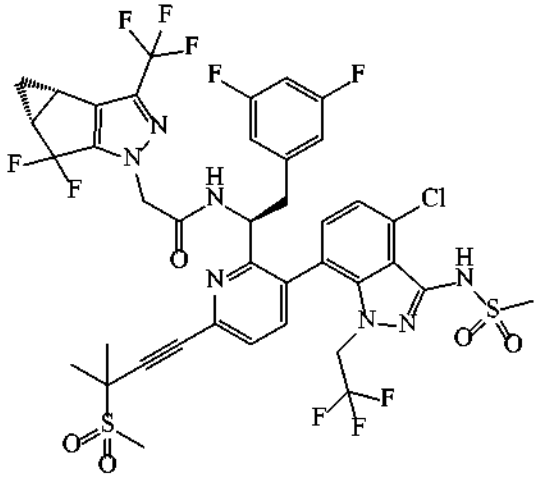
(Ib)

or a pharmaceutically acceptable salt thereof, where the patient had been previously treated with an HIV treatment regimen including administration of at least one antiretroviral medication and failed the treatment regimen; and administration of the compound results in a reduction in HIV viral load in the patient.

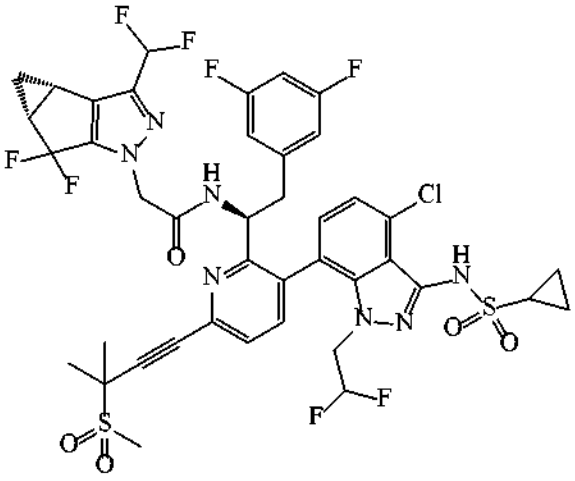
In some embodiments of the method, the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments of the method, the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiment, the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

In some embodiments, the patient had been previously treated with at least one antiretroviral medication for at least 3 months, at least 6 months, at least 9 months, or at least 12 months. In some embodiments, the prior treatment regimen included administration of at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments, the prior treatment regimen included administration of at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

Provided in the present disclosure is a method of treating human immunodeficiency virus-1 (HIV-1) infection in a heavily treatment-experienced patient with multidrug resistant HIV-1, the method including administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



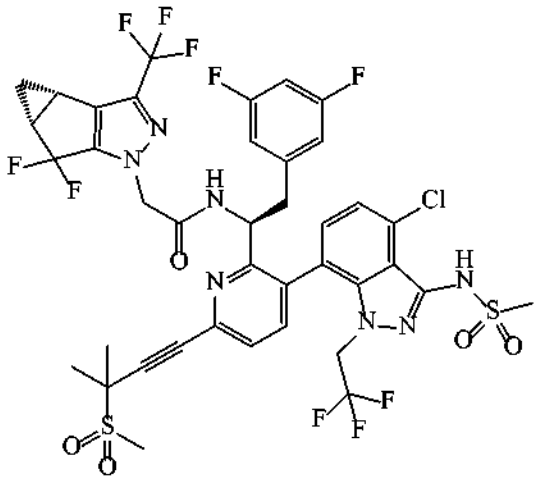
(Ia)



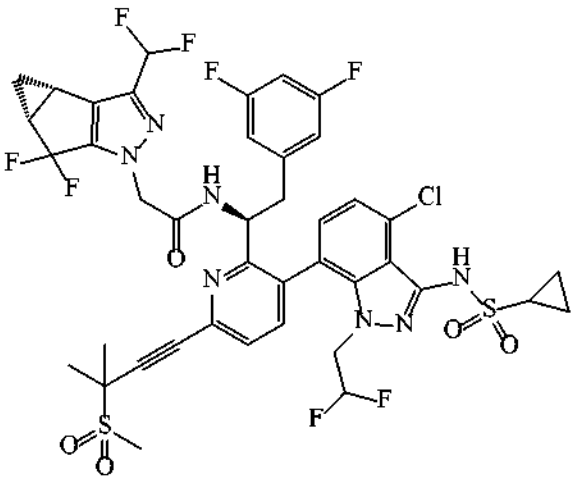
(Ib)

or a pharmaceutically acceptable salt thereof, where the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications, where the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI); the patient had been previously treated with an HIV treatment regimen including administration of at least one antiretroviral medication and failed the treatment regimen; the patient has a viral load of greater than about 200 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**; and administration of the compound results in a reduction in HIV viral load in the patient.

Also provided is a method of reducing the viral load associated with an HIV infection in a heavily treatment-experienced patient with multidrug resistant HIV, the method including administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof.

Additional embodiments of the current disclosure are disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the ^{1}H NMR (400 MHz, methanol-d_4) of the compound of Formula **(Ia)**: *N*-((*S*)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamide.

FIG. 2 shows the ^{1}H NMR (400 MHz, methanol-d_4) of the compound of Formula **(Ib)**: N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide.

FIG. 3 shows a plot of plasma concentration over time of 400 mg/mL of the compound of Formula **(Ia)** in 10% ethanol, 13% water, and 77% PEG 200 when dosed subcutaneously in dogs at 12 mg/kg and rats at 50 mg/kg.

FIG. 4 shows a plot of plasma concentration over time of 300 mg/mL of the compound of Formula **(Ia)** in 15% water and 85% PEG 300 when dosed subcutaneously in rats at 50 mg/kg.

FIG. 5 shows a plot of plasma concentration over time of 400 mg/mL of the compound of Formula **(Ia)** in 15% water and 85% PEG 300 when dosed subcutaneously in dogs at 12 mg/kg.

FIG. 6 shows a plot of plasma concentration over time of 300 mg/mL of the compound of Formula **(Ia)** sodium salt in a formulation of 22.6% water/50% PEG 300/1.1% NaOH/26.3% Formula **(Ia)** when dosed subcutaneously in dogs at 12 mg/kg.

FIGS. 7A and 7B show plots of the plasma concentration over time of 300 mg/ml of the compound of Formula **(Ia)** in a solution of 9.8 w/w% water, 65.0 w/w% PEG 300, and 25.2 w/w% of a compound of Formula **(Ia)** when dosed subcutaneously in rats at 50 mg/kg (FIG. 7A) and in dogs at 12 mg/kg (FIG. 7B).

FIGS. 8A and 8B show plots of the plasma concentration over time of 150 mg/ml of the compound of Formula **(Ia)** in a solution of 27.92 w/w% water, 58.04 w/w% PEG 300, 13.47 w/w% of a compound of Formula **(Ia)**, and 0.58 w/w% NaOH when dosed subcutaneously in rats at 50 mg/kg (FIG. 8A) and in dogs at 12 mg/kg (FIG. 8B).

FIGS. 9A and 9B show plots of the plasma concentration over time of 300 mg/ml of a compound of Formula **(Ia)** in a solution of 23.2 w/w% water, 50.0 w/w% PEG 300, 25.7 w/w% of a compound of Formula **(Ia)**, and 1.1 w/w% NaOH when dosed subcutaneously in rats at 50 mg/kg (FIG. 9A) and in dogs at 12 mg/kg (FIG. 9B).

FIGS. 10A and 10B show plots of the plasma concentration over time of 50 mg/ml of a compound of Formula (Ia) in a solution of 30.07 w/w% water, 64.40 w/w% PEG 300, 4.68 w/w% of a sodium salt of the compound of Formula **(Ia)**, and 0.85 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg (FIG. 10A) and in dogs at 6 mg/kg (FIG. 10B).

FIGS. 11A and 11B show plots of the plasma concentration over time of 75 mg/ml of a compound of Formula **(Ia)** in a solution of 29.21 w/w% water, 62.55 w/w% PEG 300, 6.97

w/w% of a sodium salt of the compound of Formula **(Ia)**, and 1.68 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg (FIG. 11A) and in dogs at 6 mg/kg (FIG. 11B).

FIGS. 12A and 12B show plots of the plasma concentration over time of 100 mg/ml of a compound of Formula **(Ia)** in a solution of 28.36 w/w% water, 60.73 w/w% PEG 300, 9.23 w/w% of a sodium salt of a compound of Formula **(Ia)**, and 1.68 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg (FIG. 12A) and in dogs at 6 mg/kg (FIG. 12B).

FIGS. 13A and 13B show plots of the plasma concentration over time of 125 mg/ml of a compound of Formula **(Ia)** in a solution of 27.51 w/w% water, 58.92 w/w% PEG 300, 11.48 w/w% of a sodium salt of the compound of Formula **(Ia)**, and 2.09 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg (FIG. 13A) and in dogs at 6 mg/kg (FIG. 13B).

FIG. 14A shows a plot of the plasma concentration over time of 150 mg/ml of the compound of Formula **(Ia)** in a solution of 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula **(Ia)**, 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg. FIG. 14B shows a plot of the plasma concentration over time of 150 mg/ml of the compound of Formula **(Ia)** in a solution of 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula **(Ia)**, 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 when dosed subcutaneously in dogs at 6 mg/kg.

FIGS. 15A and 15B show plots of the plasma concentration over time of 300 mg/ml of the compound of Formula **(Ia)** in a solution of 21.97 w/w% water, 47.05 w/w% PEG 300, 25.21 w/w% of a compound of Formula **(Ia)**, 1.08 w/w% of NaOH, and 4.69 w/w% poloxamer 188 when dosed subcutaneously in rats at 50 mg/kg (FIG. 15A) and in dogs at 6 mg/kg (FIG. 15B).

FIG. 16 shows a plot of the plasma concentration over time of a compound of Formula **(Ia)** in 100% glycerol monocaprylocaprate when orally administered in dogs as liquid-filled capsules at 7.5 mg fixed dose.

FIG. 17 shows a plot of the plasma concentration over time of a tablet prepared from a spray-dried dispersion of a sodium salt of the compound of Formula **(Ia)** (composition described in Table T with an outer film coating made of Opadry® II White 85F18422, wherein the outer film coating provides a 3% weight gain based on the uncoated tablet) when orally administered in dogs at 300 mg fixed dose.

DETAILED DESCRIPTION

The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience and are not to be construed to limit the claims in any

way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

When trade names are used herein, it is intended to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 8%. In other embodiments, the term "about" includes the indicated amount ± 5%. In other embodiments, the term "about" includes the indicated amount ± 3%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, the term "about X" includes description of "X".

As used herein and in the appended claims, the singular forms "a" and "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays, and so forth.

As an additional example, reference to "a pharmaceutically acceptable excipient" includes both a single pharmaceutically acceptable excipient and a plurality of pharmaceutically acceptable excipients.

As used herein, "HIV" or "Human Immunodeficiency Virus" refers to HIV-1 and/or to HIV-2.

As used herein, a "heavily treatment-experienced patient" refers to an HIV-infected patient who has limited treatment options due to a multidrug resistant HIV infection. For example, in some embodiments, the "heavily treatment-experienced patient" is a patient with HIV who has developed resistance to an antiretroviral medication from at least one class of antiretroviral medications selected from the group consisting of NRTIs, NNRTIs, PIs, and INSTIs.

In some embodiments, "multidrug resistant HIV infection" means resistance to an antiretroviral medication from at least one class of antiretroviral medications selected from the group consisting of NRTIs, NNRTIs, PIs, and INSTIs. In some embodiments, "multidrug resistant HIV infection" means resistance to at least one antiretroviral medication from two classes of antiretroviral medications selected from the group consisting of NRTIs, NNRTIs, PIs, and INSTIs. In some embodiments, "multidrug resistant HIV infection" means resistance to at least one antiretroviral medication from three classes of antiretroviral medications selected from

the group consisting of NRTIs, NNRTIs, PIs, and INSTIs. In some embodiments, "multidrug resistant HIV infection" means resistance to at least one antiretroviral medication from each of the four classes of antiretroviral medications selected from the group consisting of NRTIs, NNRTIs, PIs, and INSTIs.

As used herein, the term "NRTI(s)" refers to nucleoside reverse transcriptase inhibitor(s) or nucleotide reverse transcriptase inhibitor(s).

As used herein, the term "NNRTI(s)" refers to non-nucleoside reverse transcriptase inhibitor(s) or non-nucleotide reverse transcriptase inhibitor(s).

As used herein, the term "PI(s)" refers to protease inhibitor(s).

As used herein, the term "INSTI(s)" refers to integrase strand transfer inhibitor(s).

As used herein, the term "fail" or "failed" when referring to HIV therapy or an HIV treatment regimen means a treatment outcome which precludes the use of the same agent or class in the future in a patient with HIV. This could be due to inadequate initial viral response due to pre-existing viral resistance, viral rebound due to emergent viral resistance, or inability of a patient to continue a treatment due to intolerability or safety issues.

As used herein, the term "C_{max}" refers to the maximum observed plasma/serum concentration of drug.

"Pharmaceutically acceptable" refers to compounds, salts, compositions, dosage forms and other materials that are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

"Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trifluoroacetic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent

compound is replaced by either a metal ion, for example, an alkali metal ion (for example, a sodium or potassium), an alkaline earth ion (for example, calcium or magnesium), or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternary ammonium salts (e.g., quaternary ammonium salts containing the N,N,N-trimethylethanolammonium (choline) cation). Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

"Patient" and "patients" refer to humans, domestic animals (for example, dogs and cats), farm animals (for example, cattle, horses, sheep, goats and pigs), laboratory animals (for example, mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys), and the like.

As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment, "treatment" or "treating" includes one or more of the following: a) inhibiting the disease or condition (for example, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (for example, stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and/or c) relieving the disease or condition, for example, causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

As used herein, the term "therapeutically effective amount" or "effective amount" refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease or to an amount that is effective to protect against the contracting or onset of a disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the patient to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, for example, a single dose or multiple doses may be required to achieve the desired treatment outcome. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given

in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (for example, additive or synergistic effects) of the compounds.

Except as expressly defined otherwise, the present disclosure includes all tautomers of compounds detailed herein, even if only one tautomer is expressly represented (for example, both tautomeric forms are intended and described by the presentation of one tautomeric form where a pair of two tautomers may exist). For example, if reference is made to a compound containing an amide (for example, by structure or chemical name), it is understood that the corresponding imidic acid tautomer is included by this disclosure and described the same as if the amide were expressly recited either alone or together with the imidic acid. Where more than two tautomers may exist, the present disclosure includes all such tautomers even if only a single tautomeric form is depicted by chemical name and/or structure.

It is understood by one skilled in the art that this disclosure also includes any compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) that can be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^{2}H or D).

Disclosed are also compounds in which from 1 to n hydrogen atoms attached to a carbon atom can be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds can increase resistance to metabolism, and thus can be useful for increasing the half-life of the compounds when administered to a mammal. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example, by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in positron emission tomography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as

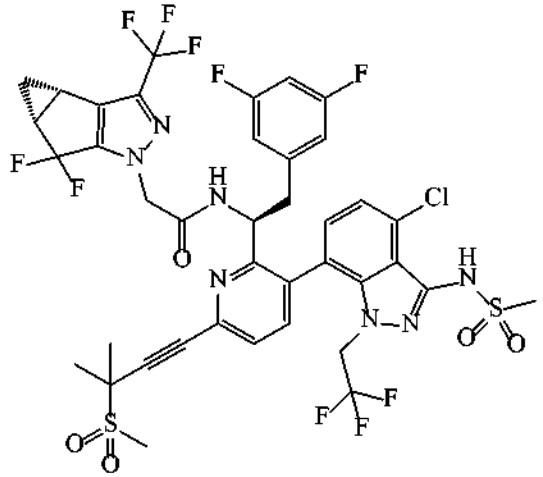
set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Compounds described herein can have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that all such optical, enantiomeric, diastereoisomeric and geometric isomers are encompassed. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s).

Also provided are also pharmaceutically acceptable hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein.

In an embodiment, the current disclosure relates to the use of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in treating an infection caused by the HIV virus comprising administering a therapeutically effective amount to a patient in need thereof, where the patient is a heavily treatment-experienced patient that has a multidrug resistant HIV infection.

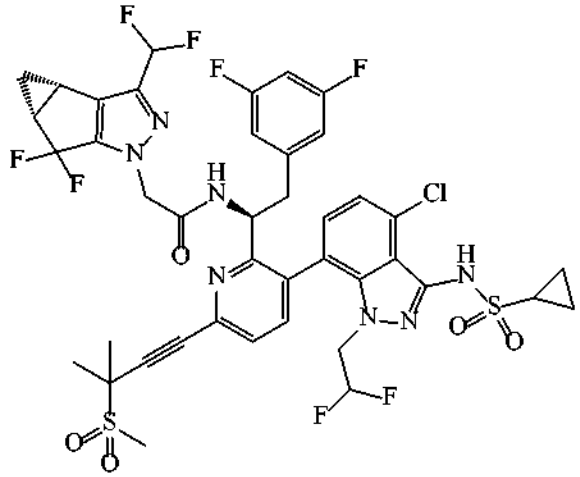
The present disclosure includes methods of using a compound of Formula **(Ia)**, N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide, having the following structure:



(Ia)

or pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in heavily treatment-experienced patients with multidrug resistant HIV infection.

The present disclosure also includes methods of using a compound of Formula **(Ib)**, N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide, having the following structure:



(Ib)

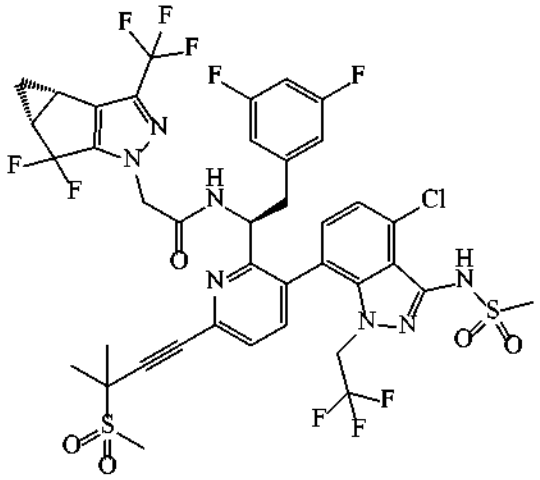
or pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in heavily treatment-experienced patients with multidrug resistant HIV infection.

In some embodiments, the compound is a pharmaceutically acceptable salt of the compound of Formula **(Ia)** or Formula **(Ib)**. Non-limiting examples of pharmaceutically acceptable salts of the compound of Formula **(Ia)** and Formula **(Ib)** include sodium salts and trifluoroacetic acid salts. In some embodiments, the compound of Formula **(Ia)** is a sodium salt. In some embodiments, the compound of Formula **(Ib)** is a trifluoroacetic acid salt.

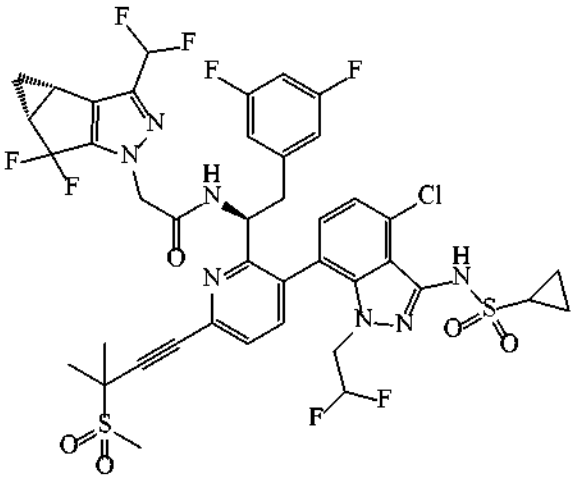
The compounds used in the methods disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) are active against major HIV-1 mutants selected by protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or integrase inhibitors (INSTIs).

Methods of Treatment

Provided in this disclosure is a method of treating human immunodeficiency virus (HIV) infection in a heavily treatment-experienced patient that includes administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof.

In the disclosed methods, the heavily treatment-experienced patient is infected with multidrug resistant HIV. In some embodiments, the heavily treatment-experienced patient has a multidrug resistant HIV infection and is on a failing HIV treatment regimen. In some embodiments, the heavily treatment-experienced patient has a viral load greater than about 1,000 copies of HIV RNA/mL.

In some embodiments, the HIV infection is an HIV-1 infection. In some embodiments, the HIV-1 infection is characterized by HIV-1 mutant resistance to an antiretroviral medication, for example, to one, two, three, four, or more classes of antiretroviral medications (e.g., PIs, NRTIs, NNRTIs, INSTIs, etc.). In some embodiments, the HIV-1 infection is characterized by HIV-1 mutant resistance to one or more classes of antiretroviral medications. In some embodiments, the HIV-1 infection is characterized by HIV-1 mutant resistance to two or more classes of antiretroviral medications. In some embodiments, the HIV-1 infection is characterized by HIV-1 mutant resistance to three or more classes of antiretroviral medications.

In some embodiments, the HIV-1 infection is characterized by an HIV-1 mutant that includes, but is not limited to:

(a) an HIV-1 mutant resistant to a PI (e.g., I50V, I84V/L90M, G48V/V82A/L90M, G48V/V82S, etc.);

(b) an HIV-1 mutant resistant to an NRTI (e.g., K65R, M184V, 6TAMs, etc.);

(c) an HIV-1 mutant resistant to an NNRTI (e.g., K103N, Y181C, Y188L, L100I/K103N, K103N/Y181C, etc.); and/or

(d) an HIV-1 mutant resistant to an INSTI (Y143R, E138K/Q148K, G140S/Q148R, E92Q/N155H, N155H/Q148R, R263K/M50I, etc.).

In some embodiments, the patient is infected with HIV-1 that is resistant to at least one antiretroviral medication. In some embodiments, the patient is infected with multidrug resistant HIV-1. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one, two, three, four, or more antiretroviral medications. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI). In some embodiments, the different classes of antiretroviral medications are selected from an NRTI, an NNRTI, and a PI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI and at least one NNRTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI and at least one PI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NNRTI and at least one PI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NNRTI and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one PI and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI, at least one NNRTI, and at least one PI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI, at least one NNRTI, and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI, at least one PI, and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NNRTI, at least one PI, and at least one INSTI. In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one NRTI, at least one NNRTI, at least one PI, and at least one INSTI.

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is an NRTI. Examples of NRTIs include, but are not limited to, emtricitabine (FTC; Emtriva®), lamivudine (3TC; Epivir®), zidovudine (azidothymidine (AZT); Retrovir®), didanosine (ddI; Videx-EC®), dideoxyinosine (Videx®),

tenofovir, tenofovir alafenamide (Vemlidy®), tenofovir disoproxil fumarate (Viread®), stavudine (d4T; Zerit®), zalcitabine (dideoxycytidine, ddC; Hivid®), and abacavir (Ziagen®).

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is an NNRTI. Examples of NNRTIs include, but are not limited to, efavirenz (Sustiva®), etravirine (Intelence®), rilpivirine (Edurant®), nevirapine (Viramune®), and delavirdine (Rescriptor®).

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is a PI. Examples of PIs include, but are not limited to, amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®, Lexiva®), indinavir (Crixivan®), lopinavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), and tipranavir (Aptivus®).

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is an INSTI. Examples of INSTIs include, but are not limited to, raltegravir (Isentress®), elvitegravir (Vitekta®), dolutegravir (Tivicay®), cabotegravir, and bictegravir.

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is a gp41 fusion inhibitor. Examples of gp41 fusion inhibitors include, but are not limited to, albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

In some embodiments, the patient is infected with multidrug resistant HIV-1 that is resistant to at least one antiretroviral medication that is a CCR5 co-receptor antagonist. Examples of CCR5 co-receptor antagonists include, but are not limited to, aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

In some embodiments of the disclosed methods, the patient has been previously treated with at least one antiretroviral medication before being treated with a compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 3 months, such as at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 3 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 6 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication

for at least 9 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 12 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 18 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 24 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 30 months. In some embodiments, the patient has been previously treated with at least one antiretroviral medication for at least 36 months.

In some embodiments of the disclosed methods, the patient has failed or is failing an HIV treatment regimen before being treated with a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the prior HIV treatment regimen included administering at least one antiretroviral medication. In some embodiments, the patient infected with HIV has relapsed after an initial response to the prior HIV treatment regimen, for example, antiretroviral therapy. In some embodiments, the patient has a viral load of greater than about 50 copies of HIV RNA/mL after about 48 weeks of therapy, for example, antiretroviral therapy, before being treated with a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI). In some embodiments, the different classes of antiretroviral medications are selected from an NRTI, an NNRTI, and a PI. In some embodiments, the prior treatment regimen includes administering at least one NRTI and at least one NNRTI. In some embodiments, the prior treatment regimen includes administering at least one NRTI and at least one PI. In some embodiments, the prior treatment regimen includes administering at least one NRTI and at least one INSTI. In some embodiments, the prior treatment regimen includes administering at least one NNRTI and at least one PI. In some embodiments, the prior treatment regimen includes administering at least one NNRTI and at least one INSTI. In some embodiments, the prior treatment regimen includes administering at least one PI and at least one INSTI. In some embodiments, the prior treatment regimen includes administering at least one NRTI, at least one NNRTI, and at least one PI. In some embodiments, the prior treatment regimen includes administering at least one NRTI, at least one NNRTI, and at least one INSTI. In some embodiments, the prior treatment regimen

includes administering at least one NRTI, at least one PI, and at least one INSTI. In some embodiments, the prior treatment regimen includes administering at least one NNRTI, at least one PI, and at least one INSTI.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is a gp41 fusion inhibitor.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is a CCR5 co-receptor antagonist.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is an NRTI. Examples of NRTIs include, but are not limited to, emtricitabine (FTC; Emtriva®), lamivudine (3TC; Epivir®), zidovudine (azidothymidine (AZT); Retrovir®), didanosine (ddI; Videx-EC®), dideoxyinosine (Videx®), tenofovir, tenofovir alafenamide (Vemlidy®), tenofovir disoproxil fumarate (Viread®), stavudine (d4T; Zerit®), zalcitabine (dideoxycytidine, ddC; Hivid®), and abacavir (Ziagen®).

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is an NNRTI. Examples of NNRTIs include, but are not limited to, efavirenz (Sustiva®), etravirine (Intelence®), rilpivirine (Edurant®), nevirapine (Viramune®), and delavirdine (Rescriptor®).

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is a PI. Examples of PIs include, but are not limited to, amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®, Lexiva®), indinavir (Crixivan®), lopinavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), and tipranavir (Aptivus®).

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is an INSTI. Examples of INSTIs include, but are not limited to, raltegravir (Isentress®), elvitegravir (Vitekta®), dolutegravir (Tivicay®), cabotegravir, and bictegravir.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is a gp41 fusion inhibitor. Examples of gp41 fusion inhibitors include, but are not limited to, albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

In some embodiments, the prior treatment regimen includes administering at least one antiretroviral medication that is a CCR5 co-receptor antagonist. Examples of CCR5 co-receptor antagonists include, but are not limited to, aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-

140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

In some embodiments of the disclosed methods, the heavily treatment-experienced patient infected with HIV has a viral load of about 200 copies of HIV-1 RNA/mL (c/mL) to about 1,000,000 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, such as a viral load of about 200 c/mL to about 500,000 c/mL, about 200 c/mL to about 250,000 c/mL, about 200 c/mL to about 100,000 c/mL, about 200 c/mL to about 50,000 c/mL, about 200 c/mL to about 25,000 c/mL, about 200 c/mL to about 10,000 c/mL, about 200 c/mL to about 5,000 c/mL, about 200 c/mL to about 3,000 c/mL, about 200 c/mL to about 2,000 c/mL, about 200 c/mL to about 1,000 c/mL, about 200 c/mL to about 750 c/mL, about 200 c/mL to about 500 c/mL, about 500 c/mL to about 1,000,000 c/mL, about 500 c/mL to about 500,000 c/mL, about 500 c/mL to about 250,000 c/mL, about 500 c/mL to about 100,000 c/mL, about 500 c/mL to about 50,000 c/mL, about 500 c/mL to about 25,000 c/mL, about 500 c/mL to about 10,000 c/mL, about 500 c/mL to about 5,000 c/mL, about 500 c/mL to about 3,000 c/mL, about 500 c/mL to about 2,000 c/mL, about 500 c/mL to about 1,000 c/mL, about 500 c/mL to about 750 c/mL, about 750 c/mL to about 1,000,000 c/mL, about 750 c/mL to about 500,000 c/mL, about 750 c/mL to about 250,000 c/mL, about 750 c/mL to about 100,000 c/mL, about 750 c/mL to about 50,000 c/mL, about 750 c/mL to about 25,000 c/mL, about 750 c/mL to about 10,000 c/mL, about 750 c/mL to about 5,000 c/mL, about 750 c/mL to about 3,000 c/mL, about 750 c/mL to about 2,000 c/mL, about 750 c/mL to about 1,000 c/mL, about 1,000 c/mL to about 1,000,000 c/mL, about 1,000 c/mL to about 500,000 c/mL, about 1,000 c/mL to about 250,000 c/mL, about 1,000 c/mL to about 100,000 c/mL, about 1,000 c/mL to about 50,000 c/mL, about 1,000 c/mL to about 25,000 c/mL, about 1,000 c/mL to about 10,000 c/mL, about 1,000 c/mL to about 5,000 c/mL, about 1,000 c/mL to about 3,000 c/mL, about 1,000 c/mL to about 2,000 c/mL, about 2,000 c/mL to about 1,000,000 c/mL, about 2,000 c/mL to about 500,000 c/mL, about 2,000 c/mL to about 250,000 c/mL, about 2,000 c/mL to about 100,000 c/mL, about 2,000 c/mL to about 50,000 c/mL, about 2,000 c/mL to about 25,000 c/mL, about 2,000 c/mL to about 10,000 c/mL, about 2,000 c/mL to about 5,000 c/mL, about 2,000 c/mL to about 3,000 c/mL, about 3,000 c/mL to about 1,000,000 c/mL, about 3,000 c/mL to about 500,000 c/mL, about 3,000 c/mL to about 250,000 c/mL, about 3,000 c/mL to about 100,000 c/mL, about 3,000 c/mL to about 50,000 c/mL, about 3,000 c/mL to about 25,000 c/mL, about 3,000 c/mL to about 10,000 c/mL, about 3,000 c/mL to about 5,000 c/mL, about 5,000 c/mL to about 1,000,000 c/mL, about 5,000 c/mL to about 500,000 c/mL, about 5,000 c/mL to about 250,000 c/mL, about 5,000 c/mL to about 100,000 c/mL, about 5,000 c/mL to about 50,000 c/mL, about 5,000 c/mL to about 25,000 c/mL, about 5,000 c/mL to about

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In some embodiments, the patient has a viral load of greater than about 200 copies of HIV-1 RNA/mL (c/mL) at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, such as a viral load greater than about 500 c/mL, about 750 c/mL, about 1,000 c/mL, about 2,000 c/mL, about 3,000 c/mL, about 5,000 c/mL, about 10,000 c/mL, about 25,000 c/mL, about 50,000 c/mL, about 100,000 c/mL, about 250,000 c/mL, about 500,000 c/mL, or greater than about 1,000,000 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a viral load of greater than about 200 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a viral load of greater than about 500 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a viral load of greater than about 750 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a viral load of greater than about 1,000 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient has a viral load of greater than about 2,000 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

The compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can be administered to a patient in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months,

at least about 6 months, or at least about 12 months, or longer. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered on a daily or intermittent schedule. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered weekly. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered bi-monthly (i.e., every two weeks). In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered monthly. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every two months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every three months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every four months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every five months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every 6 months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every five months. In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every 12 months.

In some embodiments, the compound of Formula (**Ia**) or Formula (**Ib**), or a pharmaceutically acceptable salt thereof, is administered every nine months.

In some embodiments of the disclosed methods, administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, results in a decrease in the viral load in the patient. In some embodiments, the viral load is decreased by about 0.5 $\log_{10}$ to about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for a certain amount of time as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. For example, the viral load is decreased by about 0.5 $\log_{10}$, about 1 $\log_{10}$, about 1.5 $\log_{10}$, about 2 $\log_{10}$, or about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for a certain amount of time as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 0.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning

administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 1 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 1.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 2 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof. In some embodiments, the viral load is decreased by about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof.

In some embodiments of the disclosed methods, the viral load in the patient is about 200 c/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for a certain amount of time, such as about 175 c/mL or less, about 150 c/mL or less, about 125 c/mL or less, about 100 c/mL or less, about 75 c/mL or less, or about 50 c/mL or less. In some embodiments, the viral load in the patient is about 200 c/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks. In some embodiments, the viral load in the patient is about 200 c/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks. In some embodiments, the viral load in the patient is about 100 c/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks. In some embodiments, the viral load in the patient is about 50 c/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib),** or a pharmaceutically acceptable salt thereof, for about 24 weeks.

In certain embodiments of the disclosed methods, the heavily treatment-experienced patient is concurrently being treated with at least one additional antiretroviral medication. In

some embodiments, the antiretroviral medication is selected from an NRTI, an NNRTI, a PI, an INSTI, a gp41 fusion inhibitor, and a CCR5 co-receptor antagonist.

In some embodiments, the patient is concurrently being treated with at least one NRTI. Examples of NRTIs include, but are not limited to, emtricitabine (FTC; Emtriva®), lamivudine (3TC; Epivir®), zidovudine (azidothymidine (AZT); Retrovir®), didanosine (ddI; Videx-EC®), dideoxyinosine (Videx®), tenofovir, tenofovir alafenamide (Vemlidy®), tenofovir disoproxil fumarate (Viread®), stavudine (d4T; Zerit®), zalcitabine (dideoxycytidine, ddC; Hivid®), and abacavir (Ziagen®).

In some embodiments, the patient is concurrently being treated with at least one NNRTI. Examples of NNRTIs include, but are not limited to, efavirenz (Sustiva®), etravirine (Intelence®), rilpivirine (Edurant®), nevirapine (Viramune®), and delavirdine (Rescriptor®).

In some embodiments, the patient is concurrently being treated with at least one PI. Examples of PIs include, but are not limited to, amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Telzir®, Lexiva®), indinavir (Crixivan®), lopinavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Invirase®), and tipranavir (Aptivus®).

In some embodiments, the patient is concurrently being treated with at least one INSTI. Examples of INSTIs include, but are not limited to, raltegravir (Isentress®), elvitegravir (Vitekta®), dolutegravir (Tivicay®), cabortegravir, and bictegravir.

In some embodiments, the patient is concurrently being treated with at least one gp41 fusion inhibitor. Examples of gp41 fusion inhibitors include, but are not limited to, albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer, and sifuvirtide.

In some embodiments, the patient is concurrently being treated with at least one CCR5 co-receptor antagonist. Examples of CCR5 co-receptor antagonists include, but are not limited to, aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

Also provided in this disclosure is a method of treating an HIV-1 infection in a heavily treatment-experienced patient with multidrug resistant HIV-1 that includes administering a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, to a patient that had been previously treated with an HIV treatment regimen that includes the administration of at least one antiretroviral medication and had failed the treatment regimen. In some embodiments, the HIV treatment regimen includes administration of at least one antiretroviral medication such as those described herein.

In some embodiments of the method, administration of the compound or Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, results in a reduction in HIV viral load in the patient.

Also disclosed is a method of treating an HIV-1 infection in a heavily treatment-experienced patient with multidrug resistant HIV-1 that includes administering a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, to a patient that had been previously treated with an HIV treatment regimen that includes the administration of at least one antiretroviral medication and had failed the treatment regimen, where the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from an NRTI, an NNRTI, a PI, and an INSTI. In some embodiments, the patient has a viral load of greater than about 200 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and administration of the compound results in a reduction in HIV viral load in the patient.

In some embodiments, disclosed is a method of treating an HIV-1 infection in a heavily treatment-experienced patient with multidrug resistant HIV-1 that includes administering a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, to a patient that had been previously treated with an HIV treatment regimen that includes the administration of at least one antiretroviral medication, and had failed the treatment regimen, where the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications. In some embodiments, the different classes of antiretroviral medications are selected from an NRTI, an NNRTI, a PI, and an INSTI. In some embodiments, the patient has a viral load of greater than about 200 c/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and administration of the compound results in a reduction in HIV viral load in the patient.

Pharmaceutical Compositions

Pharmaceutical compositions disclosed herein contain a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), together with one or more pharmaceutically acceptable excipients and optionally other therapeutic agents. Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration.

Pharmaceutical compositions comprising the compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), can be prepared with conventional carriers (for example, inactive ingredient or excipient material) which can be selected in accord with ordinary practice. Tablets can contain excipients including glidants, fillers, binders and the like. Aqueous compositions can be prepared in sterile form, and when intended for delivery by other than oral administration generally can be isotonic. All compositions can optionally contain excipients such as those set forth in the Rowe et al., Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

In some embodiments, tablets can contain excipients including glidants, fillers, binders, polymers and the like. Injectable solutions and suspensions can be prepared in sterile form, and when intended for delivery by other than oral administration generally can be isotonic. All compositions can optionally contain excipients such as those set forth in the Rowe et al., Handbook of Pharmaceutical Excipients, 5th edition, American Pharmacists Association, 1986. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

While it is possible for the active ingredient (for example, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) to be administered alone, it may be preferable to present the active ingredient as a pharmaceutical composition. The composition, both for veterinary and for human use, contains at least the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, together with one or more acceptable carriers and optionally other therapeutic ingredients. In one embodiment, the pharmaceutical composition comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents as defined herein. In some embodiments, the pharmaceutical composition comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic ingredient. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient thereof.

In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide hemifumarate, and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide hemifumarate and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and tenofovir alafenamide. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and tenofovir alafenamide hemifumarate. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable excipient and bictegravir.

In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide hemifumarate, and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide hemifumarate and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, a pharmaceutically acceptable excipient and tenofovir alafenamide. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, a pharmaceutically acceptable excipient and tenofovir alafenamide hemifumarate. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, a pharmaceutically acceptable excipient and bictegravir.

In some embodiments, the pharmaceutical compositions disclosed herein comprise a sodium salt of the compound of Formula **(Ia)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide hemifumarate, and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a sodium salt of the compound of Formula **(Ia)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group

consisting of tenofovir alafenamide hemifumarate and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a sodium salt of the compound of Formula **(Ia)**, a pharmaceutically acceptable excipient and tenofovir alafenamide. In some embodiments, the pharmaceutical compositions disclosed herein comprise a sodium salt of the compound of Formula **(Ia)**, a pharmaceutically acceptable excipient and tenofovir alafenamide hemifumarate. In some embodiments, the pharmaceutical compositions disclosed herein comprise a sodium salt of the compound of Formula **(Ia)**, a pharmaceutically acceptable excipient and bictegravir.

In some embodiments, the pharmaceutical compositions disclosed herein comprise a trifluoroacetic acid salt of the compound of Formula **(Ib)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide hemifumarate, and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a trifluoroacetic acid salt of the compound of Formula **(Ib)**, a pharmaceutically acceptable excipient and one other therapeutic agent selected from the group consisting of tenofovir alafenamide hemifumarate and bictegravir. In some embodiments, the pharmaceutical compositions disclosed herein comprise a trifluoroacetic acid salt of the compound of Formula **(Ib)**, a pharmaceutically acceptable excipient and tenofovir alafenamide. In some embodiments, the pharmaceutical compositions disclosed herein comprise a trifluoroacetic acid salt of the compound of Formula **(Ib)**, a pharmaceutically acceptable excipient and tenofovir alafenamide hemifumarate. In some embodiments, the pharmaceutical compositions disclosed herein comprise a trifluoroacetic acid salt of the compound of Formula **(Ib)**, a pharmaceutically acceptable excipient and bictegravir.

The compositions include those suitable for various administration routes. The compositions can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (for example, a compound of Formula **(Ia)** or Formula **(Ib)** or a pharmaceutically acceptable salt thereof) with one or more inactive ingredients (for example, a carrier, pharmaceutical excipient, etc.). The compositions can be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

Compositions described herein that are suitable for oral administration can be presented as discrete units (a unit dosage form) including, but not limited to, capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient.

When formulated for oral administration, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs can be prepared. Compositions intended for oral use can be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. Such compositions can contain one or more agents, including sweetening agents, flavoring agents, coloring agents, and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets can be uncoated or can be coated by known techniques that include microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

In some embodiments, disclosed herein are oral dosage forms (for example, tablets), which can be prepared from hot melt extrusion or spray-drying dispersion (SDD) technologies.

In some embodiments, disclosed herein are capsules filled with powder, beads, or granules containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. In some embodiments, the capsule is a hard capsule. In some embodiments, the capsule is a soft capsule.

In some embodiments, disclosed herein are hard or soft capsules filled with liquid or semi-solid mixtures containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of hard or soft capsules. These excipients can be, for example, solubilizing oils such as maize oil, sesame oil, or corn oil; medium chain triglycerides and related esters, such as, derivitized palm kernel oil or coconut oil; self-emulsifying lipid systems (SEDDS or SMEDDS), such as caprylic triglyceride or propylene glycol monocaprylate and polyethylene glycol esters of medium chain triglycerides; viscosity modifiers, such as, cetyl alcohol, steryl alcohol, glycerol stearate;

mixtures of medium chain mono- and di-glycerides; mixtures of monoglycerides, diglycerides, and triglycerides, such as caprylic/capric monoglycerides and diglycerides; and solubilizing agents and surfactants, such as polyethylene glycol, propylene glycol, glycerin, ethanol, polyethoxylated castor oil, poloxamers, or polysorbates. In some embodiments, the capsule is a hard capsule. In some embodiments, the capsule is a soft capsule.

In some embodiments, the hard or soft capsules comprise a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients. In some embodiments, the one or more pharmaceutically acceptable excipients of the hard or soft capsules disclosed herein are water-soluble and/or water-insoluble. Examples of water-soluble excipients include, but are not limited to, dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), ethanol, N-methyl-2-pyrrolidone (NMP), PEG 300, PEG 400, PEG 600, propylene glycol, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, glycerin, diethylene glycol monoethyl ether (e.g., Transcutol® HP), and phospholipids. Examples of phospholipids include, but are not limited to, hydrogenated soy phosphatidylcholine (HSPC), distearoylphosphatidylglycerol (DSPG), L-α-dimyristoylphosphatidyl-choline (DMPC), and L-α-dimyristoylphosphatidyl-glycerol (DMPG). Examples of water-insoluble excipients include, but are not limited to, beeswax, oleic acid, soy fatty acids, vitamin E, corn oil mono-di-tridiglycerides, medium chain C_{8-10} monoglycerides and diglycerides, propylene glycol dicaprylate/dicaprate, glyceryl monolinoleate, glyceryl monooleate, long-chain triglycerides, and medium-chain triglycerides. Examples of long-chain triglycerides include, but are not limited to, sesame oil, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, soybean oil, hydrogenated soybean oil, and hydrogenated vegetable oils. Examples of medium-chain triglycerides include, but are not limited to, caprylic/capric triglycerides derived from coconut oil or palm seed oil.

In some embodiments, the one or more pharmaceutically acceptable excipients of the hard or soft capsule disclosed herein include one or more surfactants. Examples of a surfactant include, but are not limited to, d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), polysorbate 20, polysorbate 80, polyoxyl 35 castor oil (e.g., Cremophor® EL), polyoxyl 40 hydrogenated castor oil (e.g., Cremophor® RH 40, Cremophor® RH 60), Solutol® HS-15, sorbitan monooleate (e.g., Span® 20), PEG 300 caprylic/capric glycerides (e.g., Softigen® 767), PEG 400 caprylic/capric glycerides (e.g., Labrasol®), PEG 300 oleic glycerides (e.g., Labrafil® M-1944CS), PEG 300 linoleic glycerides (e.g., Labrafil® M-2125CS), PEG 300 lauric glycerides (e.g., Labrafil® M2130CS), polyoxyl 8 stearate (e.g., PEG 400 monosterate),

polyoxyl 40 stearate (e.g., PEG 1750 monosterate), povidone K-90, polyoxyl stearate, Type I (e.g., Gelucire® 48/16), polyglyceryl-3 dioleate, propylene glycol monolaurate, Type I, propylene glycol monolaurate, Type II, propylene glycol monocaprylate, Type II (e.g., Capryol™ 90), propylene glycol monocaprylate, Type I (e.g., Capryol™ PGMC), lauroyl polyoxylglycerides (e.g., Gelucire® 44/14), stearoyl polyoxylglycerides (e.g., Gelucire® 50/13), poloxamer 124, poloxamer 188, and poloxamer 407.

The pharmaceutical compositions of the present disclosure can be in the form of a sterile injectable preparation, such as a solution or sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

In some embodiments, the sterile injectable preparation disclosed herein can also be a sterile injectable solution or suspension prepared from a reconstituted lyophilized powder in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents. In certain embodiments, the suspension is a microsuspension. In certain embodiments, the suspension is a nanosuspension.

In some embodiments, the pharmaceutical compositions of the present disclosure can be in the form of a solution formulation. In some embodiments, the solution comprises N-methyl-2-pyrrolidone (NMP), polyethylene glycol (PEG), water and/or glycofurol. In some embodiments, the solution comprises PEG 200, ethanol, and water. In some embodiments, the solution comprises PEG 300 and water. In some embodiments, the amount of water in the solution

comprising PEG 300 and water is about 25 w/w%, about 23 w/w%, about 20 w/w%, about 17 w/w%, about 15 w/w%, about 10 w/w%, about 9 w/w%, about 8 w/w%, or about 5 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising PEG 300 and water is about 90 w/w%, about 85 w/w%, about 80 w/w%, about 75 w/w%, about 70 w/w%, about 65 w/w%, about 60 w/w%, about 55 w/w%, about 50 w/w%, or about 45 w/w%. In some embodiments, the solution comprising PEG 300 and water comprises about 85 w/w% PEG 300 and about 15 w/w% water. In some embodiments, the solution comprising PEG 300 and water further comprises a base. In some embodiments, the solution comprising PEG 300 and water further comprises an inorganic base. In some embodiments, the inorganic base is sodium hydroxide or sodium ethoxide. In some embodiments, the sodium hydroxide or sodium ethoxide is in an amount of about 3 w/w%, about 2 w/w%, about 1 w/w%, or about 0.5 w/w%.

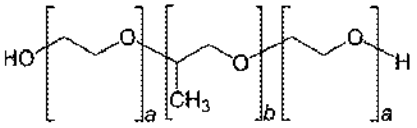
In some embodiments, formulations suitable for parenteral administration (for example, intramuscular (IM) and subcutaneous (SC) administration) will include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of parenteral formulation and can be found, for example, in the Handbook of Pharmaceutical Excipients (eds. Rowe, Sheskey & Quinn), 6th edition 2009.

Examples of solubilizing excipients in a parenteral formulation (for example, an SC or IM formulation) include, but are not limited to, polysorbates (such as polysorbate 20 or 80) and poloxamers (such as poloxamer 338, 188, or 207). In some embodiments, disclosed herein is a parenteral administration (for example, an SC or IM formulation) that comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and a poloxamer. In some embodiments, the poloxamer is poloxamer 338. In some embodiments, the poloxamer is poloxamer 188. In some embodiments, the amount of poloxamer in a parenteral administration disclosed herein is less than about 5%, such as less than about 3%, about 2%, about 1%, or about 0.5%.

In certain embodiments, excipients include N-methyl-2- pyrrolidone (NMP), dimethyl sulfoxide, polyethylene glycol and/or tetraglycol/glycofurol.

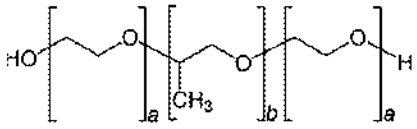
In general, poloxamers are synthetic non-ionic triblock of linear copolymers having a central hydrophobic chain of polyoxypropylene adjacent to two hydrophilic polypropylene oxide, in certain instances in a 4:2:4 weight ratio. Accordingly, in certain embodiments, the compositions disclosed herein include a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and a block copolymer comprised of one polyoxypropylene segment and two hydrophilic polypropylene oxide segments. In certain embodiments, the ratio of the polyoxypropylene segment to the two hydrophilic polypropylene

oxide segments is 4:2:4 (hydrophilic polypropylene oxide: polyoxypropylene: hydrophilic polypropylene oxide). Poloxamers are generally understood to have the following structure:



, where a and b are integers. For example, a is between about 2 and about 130 and b is between about 15 and about 67. Poloxamer 188, for example, is understood to have a molecular weight from about 7680 to about 9510 Daltons (where a is about 80 and b is about 27) (see, for example, International Journal of PharmTech Research, Vol.1, No.2, pp 299-303, April-June 2009). In some instances, poloxamer 188 has an average molecular weight of about 8400 Daltons. Poloxamer 338 has a molecular weight in the range of from about 12700 Da to about 17400 Da (where a is about 141 and b is about 44).

In some embodiments, poloxamers are synthetic non-ionic triblock of linear copolymers having a central hydrophobic chain of polypropylene oxide (PPO) adjacent to two hydrophilic chains of polyethylene oxide (PEO), in certain instances in a 4:2:4 weight ratio. Accordingly, in certain embodiments, the compositions disclosed herein include a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and a block copolymer comprised of one PPO segment and two PEO segments. In certain embodiments, the ratio of the PPO segment to the two PEO segments is 4:2:4 (PEO:PPO:PEO). Poloxamers are generally understood to have the following structure:



, where a and b are integers. For example, a is between about 2 and about 130 and b is between about 15 and about 67. Poloxamer 188, for example, is understood to have a molecular weight from about 7680 to about 9510 Daltons (where a is about 80 and b is about 27) (see, for example, International Journal of PharmTech Research, Vol.1, No.2, pp 299-303, April-June 2009). In some instances, poloxamer 188 has an average molecular weight of about 8400 Daltons. Poloxamer 338 has a molecular weight in the range of from about 12700 Da to about 17400 Da (where a is about 141 and b is about 44).

In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a poloxamer, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, poloxamer 188, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein do not comprise a poloxamer. In some embodiments, the pharmaceutical compositions

disclosed herein do not compromise poloxamer 188. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a poloxamer, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, poloxamer 188, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that do not comprise a poloxamer. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that do not comprise poloxamer 188.

Examples of excipients in a parenteral formulation (for example, an SC or an IM formulation) include polyethylene glycol. In general, polyethylene glycol (PEG) is a polyether having a general formula H-(O-CH_2-CH_2)$_n$-OH. In certain embodiments, the PEG may be "capped" by an alkyl group. In those embodiments, the capped PEG is of the formula alkyl-(O-CH_2-CH_2)$_n$-O-alkyl (for example, CH_3-(O-CH_2-CH_2)$_n$-OCH_3). The pharmaceutical compositions of the present disclosure can include PEG having an average molecular weight of about 100 to about 1000. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is about 100 to about 800. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is about 200 to about 600. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is about 400. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is about 300. In some embodiments, the average molecular weight of PEG within the pharmaceutical composition is about 200. In some embodiments of the pharmaceutical composition, different molecular weight PEG can be combined to obtain a desired property or properties (for example, viscosity). Specific examples of PEG include, but are not limited to, PEG 100, PEG 200, PEG 300, PEG 400, PEG 500, and PEG 600. PEG 100, for example, refers to a polyethylene glycol with an average molecular weight of about 100.

As noted above, in some embodiments, the pharmaceutical compositions comprising a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, disclosed herein are in the form of a solution.

In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of a compound of Formula

(Ia) or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 75 mg/ml to about 500 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 50 mg/ml to about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 75 mg/ml to about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 50 mg/ml, about 55 mg/ml, about 60 mg/ml, about 65 mg/ml, about 70 mg/ml, about 75 mg/ml, about 80 mg/ml, about 85 mg/ml, about 90 mg/ml, about 95 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about 120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, about 210 mg/ml, about 215 mg/ml, about 220 mg/ml, about 225 mg/ml, about 230 mg/ml, about 235 mg/ml, about 240 mg/ml, about 245 mg/ml, about 250 mg/ml, about 255 mg/ml, about 260 mg/ml, about 265 mg/ml, about 270 mg/ml, about 275 mg/ml, about 280 mg/ml, about 285 mg/ml, about 290 mg/ml, about 295 mg/ml, about 300 mg/ml, about 325 mg/ml, about 350 mg/ml, about 375 mg/ml, about 400 mg/ml, about 425 mg/ml, about 450 mg/ml, about 475 mg/ml, or about 500 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 50 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 75 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 100 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 125 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 150 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 175 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 200 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 225 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 250 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 275 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 325 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 350 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 375 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 425 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 450 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 475 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the solution disclosed herein is about 500 mg/ml.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, PEG 300, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, and water. In some embodiments, the solution disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water. In some embodiments, the solution disclosed herein comprises a trifluoroacetic acid salt of the compound

of Formula **(Ib)**, PEG 300, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, PEG 300, and water.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)**, PEG 300, and water. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml to about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 125 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 275 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 325 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is

about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 475 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 500 mg/ml.

In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 5 w/w% to about 15 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 5 w/w% to about 10 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 8 w/w% to about 12 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 9 w/w% to about 10 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 8.0 w/w%, about 8.1 w/w%, about 8.2 w/w%, about 8.3 w/w%, about 8.4 w/w%, about 8.5 w/w%, about 8.6 w/w%, about 8.7 w/w%, about 8.8 w/w%, about 8.9 w/w%, about 9.0 w/w%, about 9.1 w/w%, about 9.2 w/w%, about 9.3 w/w%, about 9.4 w/w%, about 9.5 w/w%, about 9.6 w/w%, about 9.7 w/w%, about 9.8 w/w%, about 9.9 w/w%, about 10.0 w/w%, about 10.1 w/w%, about 10.2 w/w%, about 10.3 w/w%, about 10.4 w/w%, about 10.5 w/w%, about 10.6 w/w%, about 10.7 w/w%, about 10.8 w/w%, about 10.9 w/w%, about 11.0 w/w%, about 11.1 w/w%, about 11.2 w/w%, about 11.3 w/w%, about 11.4 w/w%, about 11.5 w/w%, about 11.6 w/w%, about 11.7 w/w%, about 11.8 w/w%, about 11.9 w/w%, or about 12.0 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 9.0 w/w%, about 9.1 w/w%, about 9.2 w/w%, about 9.3 w/w%, about 9.4 w/w%, about 9.5 w/w%, about 9.6 w/w%, about 9.7 w/w%, about 9.8 w/w%, about 9.9 w/w%, or about 10.0 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 9.5 w/w%, about 9.6 w/w%, about 9.7 w/w%, about 9.8 w/w%, about 9.9 w/w%, or about 10.0 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula

(Ia), PEG 300, and water is about 9.8 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 10 w/w%.

In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 w/w% to about 85 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 60 w/w% to about 80 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 60 w/w% to about 70 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 50 w/w%, about 55 w/w%, about 60 w/w%, about 65 w/w%, about 70 w/w%, about 75 w/w%, about 80 w/w%, or about 85 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 65 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 65.0 w/w%.

In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 20 w/w% to about 35 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 24 w/w% to about 26 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, or about 25.5 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 25 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, and water is about 25.2 w/w%.

In some embodiments, the solution disclosed herein comprises about 5 w/w% to about 15 w/w% water, about 50 w/w% to about 85 w/w% PEG 300, and about 15 w/w% to about 35 w/w% of a compound of Formula **(Ia)**. In some embodiments, the solution comprises about 5 w/w% to about 10 w/w% water, about 60 w/w% to about 80 w/w% PEG 300, and about 20 w/w% to about 35 w/w% of a compound of Formula **(Ia)**. In some embodiments, the solution comprises about 8 w/w% to about 12 w/w% water, about 60 w/w% to about 70 w/w% PEG 300, and about 15 w/w% to about 35 w/w% of a compound of Formula **(Ia)**. In some embodiments,

the solution comprises about 9 w/w% to about 10 w/w% water, about 60 w/w% to about 70 w/w% PEG 300, and about 24 w/w% to about 26 w/w% of a compound of Formula **(Ia)**. In some embodiments, the solution comprises about 9.8 w/w% water, about 65.0 w/w% PEG 300, and about 25.2 w/w% of a compound of Formula **(Ia)**. In some embodiments, the solution comprises about 10 w/w% water, about 65.0 w/w% PEG 300, and about 25 w/w% of a compound of Formula **(Ia)**.

In some embodiments, the solution disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 125 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 275 mg/ml. In some embodiments, the concentration of the compound

of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 325 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 475 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 500 mg/ml.

In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 10 w/w% to about 40 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 20 w/w% to about 30 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 21 w/w% to about 29 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 23.4 w/w% to about 27.5 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 23.41 w/w% to about 27.47 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%,

about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 23.4 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 23.41 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 27.47 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 27.5 w/w%.

In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 35 w/w% to about 75 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 45 w/w% to about 65 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 48 w/w% to about 60 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50 w/w% to about 59 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50.1 w/w% to about 58.8 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50.13 w/w% to about 58.84 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 45 w/w%, about 46 w/w%, about 47 w/w%, about 48 w/w%, about 49 w/w%, about 50 w/w%, about 51 w/w%, about 52 w/w%, about 53 w/w%, about 54 w/w%, about 55 w/w%, about 56 w/w%, about 57 w/w%, about 58 w/w%, about 59 w/w%, about 60 w/w%, about 61 w/w%, about 62 w/w%, about 63 w/w%, about 64 w/w%, or

about 65 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50.1 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 50.13 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 58.8 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 58.84 w/w%.

In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 5 w/w% to about 35 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 10 w/w% to about 30 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 11 w/w% to about 28 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13 w/w% to about 27 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13.69 w/w% to about 26.46 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13.7 w/w% to about 26.5 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13.0 w/w%, about 13.1 w/w%, about 13.2 w/w%, about 13.3 w/w%, about 13.4 w/w%, about 13.5 w/w%, about 13.6 w/w%, about 13.7 w/w%, about 13.8 w/w%, about 13.9 w/w%, about 14.0 w/w%, about 14.1 w/w%, about 14.2 w/w%, about 14.3 w/w%, about 14.4 w/w%, about 14.5 w/w%, about 14.6 w/w%, about 14.7 w/w%, about 14.8 w/w%, about 14.9 w/w%, about 15.0 w/w%, about 15.1 w/w%, about 15.2 w/w%, about 15.3 w/w%, about 15.4 w/w%, about 15.5 w/w%, about 15.6 w/w%, about 15.7 w/w%, about 15.8 w/w%, about 15.9 w/w%, about 16.0 w/w%, about 16.1 w/w%, about 16.2 w/w%, about 16.3 w/w%, about 16.4 w/w%, about 16.5 w/w%, about 16.6 w/w%, about 16.7 w/w%, about 16.8 w/w%, about 16.9 w/w%, about 17.0 w/w%, about 17.1 w/w%, about 17.2 w/w%, about 17.3 w/w%, about 17.4 w/w%, about 17.5 w/w%, about 17.6 w/w%, about 17.7 w/w%, about 17.8 w/w%, about 17.9 w/w%, about 18.0 w/w%, about 18.1 w/w%, about 18.2 w/w%, about 18.3 w/w%, about 18.4

w/w%, about 18.5 w/w%, about 18.6 w/w%, about 18.7 w/w%, about 18.8 w/w%, about 18.9 w/w%, about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about 20.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3 w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13.69 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 13.7 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 26.46 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and water is about 26.5 w/w%.

In some embodiments, the solution disclosed herein comprises about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, and about 5 w/w% to about 35 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 15 w/w% to about 35 w/w% water, about 45 w/w% to about 65 w/w% PEG 300, and about 10 w/w% to about 30 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 20 w/w% to about 30 w/w% water, about

48 w/w% to about 60 w/w% PEG 300, and about 11 w/w% to about 28 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 21 w/w% to about 29 w/w% water, about 50 w/w% to about 59 w/w% PEG 300, and about 13 w/w% to about 27 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 23.4 w/w% to about 27.5 w/w% water, about 50.1 w/w% to about 58.8 w/w% PEG 300, and about 13.7 w/w% to about 26.5 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 23.41 w/w% to about 27.47 w/w% water, about 50.13 w/w% to about 58.84 w/w% PEG 300, and about 13.69 w/w% to about 26.46 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 27.5 w/w% water, about 58.8 w/w% PEG 300, and about 13.7 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 27.47 w/w% water, about 58.84 w/w% PEG 300, and about 13.69 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 23.4 w/w% water, about 50.1 w/w% PEG 300, and about 26.5 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the solution comprises about 23.41 w/w% water, about 50.13 w/w% PEG 300, and about 26.46 w/w% of a sodium salt of the compound of Formula **(Ia)**.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, PEG 300, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)**, PEG 300, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, PEG 300, poloxamer 188, and water.

In some embodiments, the solution disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 50 mg/ml to about 400 mg/ml. In some embodiments, the concentration of

the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 125 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 275 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 325 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer

188, and water is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 475 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 500 mg/ml.

In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 10 w/w% to about 45 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 20 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 20 w/w% to about 31 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 21.9 w/w% to about 30.1 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 21.87 w/w% to about 30.07 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about 20.0 w/w%, about 20.1 w/w%, about 20.2 w/w%, about 20.3 w/w%, about 20.4 w/w%, about 20.5 w/w%, about 20.6 w/w%, about 20.7 w/w%, about 20.8 w/w%, about 20.9 w/w%, about 21.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3 w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3

w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, about 29.0 w/w%, about 29.1 w/w%, about 29.2 w/w%, about 29.3 w/w%, about 29.4 w/w%, about 29.5 w/w%, about 29.6 w/w%, about 29.7 w/w%, about 29.8 w/w%, about 29.9 w/w%, about 30.0 w/w%, about 30.1 w/w%, about 30.2 w/w%, about 30.3 w/w%, about 30.4 w/w%, about 30.5 w/w%, about 30.6 w/w%, about 30.7 w/w%, about 30.8 w/w%, about 30.9 w/w%, about 31.0 w/w%, about 31.1 w/w%, about 31.2 w/w%, about 31.3 w/w%, about 31.4 w/w%, about 31.5 w/w%, about 31.6 w/w%, about 31.7 w/w%, about 31.8 w/w%, about 31.9 w/w%, about 32.0 w/w%, about 32.1 w/w%, about 32.2 w/w%, about 32.3 w/w%, about 32.4 w/w%, about 32.5 w/w%, about 32.6 w/w%, about 32.7 w/w%, about 32.8 w/w%, about 32.9 w/w%, or about 33.0 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 21.87 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 21.9 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 26.68 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 26.7 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, and poloxamer 188, and water is about 27.5 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 27.51 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 28.36 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 28.4 w/w%. In some embodiments, the amount of

water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 29.2 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 29.21 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 30.07 w/w%. In some embodiments, the amount of water in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 30.1 w/w%.

In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 30 w/w% to about 85 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 35 w/w% to about 75 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 40 w/w% to about 70 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 45 w/w% to about 68 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 46.8 w/w% to about 64.4 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 46.84 w/w% to about 64.40 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 40 w/w%, about 41 w/w%, about 42 w/w%, about 43 w/w%, about 44 w/w%, about 45 w/w%, about 46 w/w%, about 47 w/w%, about 48 w/w%, about 49 w/w%, about 50 w/w%, about 51 w/w%, about 52 w/w%, about 53 w/w%, about 54 w/w%, about 55 w/w%, about 56 w/w%, about 57 w/w%, about 58 w/w%, about 59 w/w%, about 60 w/w%, about 61 w/w%, about 62 w/w%, about 63 w/w%, about 64 w/w%, about 65 w/w%, about 66 w/w%, about 67 w/w%, about 68 w/w%, about 69 w/w%, or about 70 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 46.8 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 46.84 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 57.1 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound

of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 57.13 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 58.9 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 58.92 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 60.7 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 60.73 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 62.55 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 62.6 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 64.4 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 64.40 w/w%.

In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.5 w/w% to about 40 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1 w/w% to about 35 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1 w/w% to about 30 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 3 w/w% to about 28 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4 w/w% to about 27 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.68 w/w% to about 26.47 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.7 w/w% to about 26.5 w/w%. In some embodiments, the

amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 3.0 w/w%, about 3.1 w/w%, about 3.2 w/w%, about 3.3 w/w%, about 3.4 w/w%, about 3.5 w/w%, about 3.6 w/w%, about 3.7 w/w%, about 3.8 w/w%, about 3.9 w/w%, about 4.0 w/w%, about 4.1 w/w%, about 4.2 w/w%, about 4.3 w/w%, about 4.4 w/w%, about 4.5 w/w%, about 4.6 w/w%, about 4.7 w/w%, about 4.8 w/w%, about 4.9 w/w%, about 5.0 w/w%, about 5.1 w/w%, about 5.2 w/w%, about 5.3 w/w%, about 5.4 w/w%, about 5.5 w/w%, about 5.6 w/w%, about 5.7 w/w%, about 5.8 w/w%, about 5.9 w/w%, about 6.0 w/w%, about 6.1 w/w%, about 6.2 w/w%, about 6.3 w/w%, about 6.4 w/w%, about 6.5 w/w%, about 6.6 w/w%, about 6.7 w/w%, about 6.8 w/w%, about 6.9 w/w%, about 7.0 w/w%, about 7.1 w/w%, about 7.2 w/w%, about 7.3 w/w%, about 7.4 w/w%, about 7.5 w/w%, about 7.6 w/w%, about 7.7 w/w%, about 7.8 w/w%, about 7.9 w/w%, about 8.0 w/w%, about 8.1 w/w%, about 8.2 w/w%, about 8.3 w/w%, about 8.4 w/w%, about 8.5 w/w%, about 8.6 w/w%, about 8.7 w/w%, about 8.8 w/w%, about 8.9 w/w%, about 9.0 w/w%, about 9.1 w/w%, about 9.2 w/w%, about 9.3 w/w%, about 9.4 w/w%, about 9.5 w/w%, about 9.6 w/w%, about 9.7 w/w%, about 9.8 w/w%, about 9.9 w/w%, about 10.0 w/w%, about 10.1 w/w%, about 10.2 w/w%, about 10.3 w/w%, about 10.4 w/w%, about 10.5 w/w%, about 10.6 w/w%, about 10.7 w/w%, about 10.8 w/w%, about 10.9 w/w%, about 11.0 w/w%, about 11.1 w/w%, about 11.2 w/w%, about 11.3 w/w%, about 11.4 w/w%, about 11.5 w/w%, about 11.6 w/w%, about 11.7 w/w%, about 11.8 w/w%, about 11.9 w/w%, about 12.0 w/w%, about 12.1 w/w%, about 12.2 w/w%, about 12.3 w/w%, about 12.4 w/w%, about 12.5 w/w%, about 12.6 w/w%, about 12.7 w/w%, about 12.8 w/w%, about 12.9 w/w%, about 13.0 w/w%, about 13.1 w/w%, about 13.2 w/w%, about 13.3 w/w%, about 13.4 w/w%, about 13.5 w/w%, about 13.6 w/w%, about 13.7 w/w%, about 13.8 w/w%, about 13.9 w/w%, about 14.0 w/w%, about 14.1 w/w%, about 14.2 w/w%, about 14.3 w/w%, about 14.4 w/w%, about 14.5 w/w%, about 14.6 w/w%, about 14.7 w/w%, about 14.8 w/w%, about 14.9 w/w%, about 15.0 w/w%, about 15.1 w/w%, about 15.2 w/w%, about 15.3 w/w%, about 15.4 w/w%, about 15.5 w/w%, about 15.6 w/w%, about 15.7 w/w%, about 15.8 w/w%, about 15.9 w/w%, about 16.0 w/w%, about 16.1 w/w%, about 16.2 w/w%, about 16.3 w/w%, about 16.4 w/w%, about 16.5 w/w%, about 16.6 w/w%, about 16.7 w/w%, about 16.8 w/w%, about 16.9 w/w%, about 17.0 w/w%, about 17.1 w/w%, about 17.2 w/w%, about 17.3 w/w%, about 17.4 w/w%, about 17.5 w/w%, about 17.6 w/w%, about 17.7 w/w%, about 17.8 w/w%, about 17.9 w/w%, about 18.0 w/w%, about 18.1 w/w%, about 18.2 w/w%, about 18.3 w/w%, about 18.4 w/w%, about 18.5 w/w%, about 18.6 w/w%, about 18.7 w/w%, about 18.8 w/w%, about 18.9 w/w%, about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about

20.0 w/w%, about 20.1 w/w%, about 20.2 w/w%, about 20.3 w/w%, about 20.4 w/w%, about 20.5 w/w%, about 20.6 w/w%, about 20.7 w/w%, about 20.8 w/w%, about 20.9 w/w%, about 21.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3 w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.68 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.7 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 6.97 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 7 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 9.2 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 9.23 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 11.48 w/w%. In some embodiments, the amount of the

sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 11.5 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 13.7 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 13.70 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 26.47 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 26.5 w/w%.

In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.1 w/w% to about 10 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.3 w/w% to about 8 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.5 w/w% to about 7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.6 w/w% to about 7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.85 w/w% to about 4.82 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.9 w/w% to about 4.8 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.5 w/w%, about 0.6 w/w%, about 0.7 w/w%, about 0.8 w/w%, about 0.9 w/w%, about 1.0 w/w%, about 1.1 w/w%, about 1.2 w/w%, about 1.3 w/w%, about 1.4 w/w%, about 1.5 w/w%, about 1.6 w/w%, about 1.7 w/w%, about 1.8 w/w%, about 1.9 w/w%, about 2.0 w/w%, about 2.1 w/w%, about 2.2 w/w%, about 2.3 w/w%, about 2.4 w/w%, about 2.5 w/w%, about 2.6 w/w%, about 2.7 w/w%, about 2.8 w/w%, about 2.9 w/w%, about 3.0 w/w%, about 3.1 w/w%, about 3.2 w/w%, about 3.3 w/w%, about 3.4 w/w%, about 3.5 w/w%, about 3.6 w/w%, about 3.7 w/w%, about 3.8 w/w%, about 3.9 w/w%, about 4.0 w/w%, about 4.1 w/w%, about 4.2 w/w%, about 4.3 w/w%, about 4.4 w/w%, about 4.5 w/w%, about 4.6 w/w%, about 4.7 w/w%, about

4.8 w/w%, about 4.9 w/w%, about 5.0 w/w%, about 5.1 w/w%, about 5.2 w/w%, about 5.3 w/w%, about 5.4 w/w%, about 5.5 w/w%, about 5.6 w/w%, about 5.7 w/w%, about 5.8 w/w%, about 5.9 w/w%, about 6.0 w/w%, about 6.1 w/w%, about 6.2 w/w%, about 6.3 w/w%, about 6.4 w/w%, about 6.5 w/w%, about 6.6 w/w%, about 6.7 w/w%, about 6.8 w/w%, about 6.9 w/w%, or about 7.0 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.85 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 0.9 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1.27 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1.3 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1.68 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 1.7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 2.09 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 2.1 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 2.49 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 2.5 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.8 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a sodium salt of the compound of Formula **(Ia)**, PEG 300, poloxamer 188, and water is about 4.82 w/w%.

In some embodiments, the solution disclosed herein comprises about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about 0.5 w/w% to about 40 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.1 w/w% to about 10 w/w% of poloxamer 188. In some embodiments, the solution comprises about 15 w/w% to about 35 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, about 1 w/w% to about 35 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.3 w/w% to about 8 w/w% of

poloxamer 188. In some embodiments, the solution comprises about 20 w/w% to about 35 w/w% water, about 40 w/w% to about 70 w/w% PEG 300, about 1 w/w% to about 30 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.5 w/w% to about 7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 20 w/w% to about 31 w/w% water, about 45 w/w% to about 68 w/w% PEG 300, about 3 w/w% to about 28 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.6 w/w% to about 7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 21.9 w/w% to about 30.1 w/w% water, about 46.8 w/w% to about 64.4 w/w% PEG 300, about 4.7 w/w% to about 26.5 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.9 w/w% to about 4.8 w/w% of poloxamer 188. In some embodiments, the solution comprises about 21.87 w/w% to about 30.07 w/w% water, about 46.84 w/w% to about 64.40 w/w% PEG 300, about 4.68 w/w% to about 26.47 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.85 w/w% to about 4.82 w/w% of poloxamer 188. In some embodiments, the solution comprises about 30.1 w/w% water, about 64.4 w/w% PEG 300, about 4.7 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.9 w/w% of poloxamer 188. In some embodiments, the solution comprises about 30.07 w/w% water, about 64.40 w/w% PEG 300, about 4.68 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.85 w/w% of poloxamer 188. In some embodiments, the solution comprises about 29.2 w/w% water, about 62.6 w/w% PEG 300, about 7 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 1.3 w/w% of poloxamer 188. In some embodiments, the solution comprises about 29.21 w/w% water, about 62.55 w/w% PEG 300, about 6.97 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 1.27 w/w% of poloxamer 188. In some embodiments, the solution comprises about 28.4 w/w% water, about 60.7 w/w% PEG 300, about 9.2 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 1.7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 28.36 w/w% water, about 60.73 w/w% PEG 300, about 9.23 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 1.68 w/w% of poloxamer 188. In some embodiments, the solution comprises about 27.5 w/w% water, about 58.9 w/w% PEG 300, about 11.5 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 2.1 w/w% of poloxamer 188. In some embodiments, the solution comprises about 27.51 w/w% water, about 58.92 w/w% PEG 300, about 11.48 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 2.09 w/w% of poloxamer 188. In some embodiments, the solution comprises about 26.7 w/w% water, about 57.1 w/w% PEG 300, about 13.7 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 2.5 w/w% of poloxamer 188. In some embodiments, the solution comprises about 26.68 w/w% water, about 57.13 w/w% PEG 300, about 13.70 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 2.49 w/w% of poloxamer 188. In some embodiments, the solution

comprises about 21.9 w/w% water, about 46.8 w/w% PEG 300, about 26.5 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 4.8 w/w% of poloxamer 188. In some embodiments, the solution comprises about 21.87 w/w% water, about 46.84 w/w% PEG 300, about 26.47 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 4.82 w/w% of poloxamer 188.

In some embodiments, the parenteral formulation (for example, an SC or IM formulation) disclosed herein is an aqueous suspension. In some embodiments, the parenteral formulation (for example, an SC or IM formulation) disclosed herein is an aqueous suspension that includes a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and saline. In some embodiments, the parenteral formulation (for example, an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, saline, and a suspending agent. In some embodiments, the parenteral formulation (for example, an SC or IM formulation) disclosed herein is an aqueous suspension that comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, saline, and a poloxamer (such as poloxamer 338, 188, or 207).

In some embodiments, a suspension comprising a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in a poloxamer and saline is provided. In some embodiments, the concentration of poloxamer in saline is from about 0.1% to about 20%. In some embodiments, the concentration of poloxamer in saline is from about 0.1% to about 10%. In some embodiments, the concentration of poloxamer in saline is about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%. In certain embodiments, the concentration of poloxamer in saline is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula **(Ia)**. In certain embodiments, the compound is a sodium salt of the compound of Formula **(Ia)**. In certain embodiments, the compound is a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula **(Ib)**. In certain embodiments, the compound is a trifluoroacetic acid salt of the compound of Formula **(Ib)**.

In some embodiments, a suspension comprising a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in a poloxamer and mannitol is provided. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1% to about 20%. In some embodiments, the concentration of poloxamer in mannitol is from about 0.1% to

about 10%. In some in embodiments, the concentration of poloxamer in mannitol is about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2,%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%. In certain embodiments, the concentration of poloxamer in mannitol is about 2%. In certain embodiments, the poloxamer is poloxamer 188. In certain embodiments, the compound is a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula **(Ia)**. In certain embodiments, the compound is a sodium salt of the compound of Formula **(Ia)**. In certain embodiments, the compound is a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound of Formula **(Ib)**. In certain embodiments, the compound is a trifluoroacetic acid salt of the compound of Formula **(Ib)**.

In certain embodiments, the composition is formulated as a solid dosage form. In some embodiments, the solid dosage form is a solid injectable dosage form, such as a solid depot form.

In certain embodiments, the active ingredient (for example, a compound of Formula **(Ia)** or Formula **(Ib)**) is present as a free acid. In certain embodiments, the active ingredient (for example, a compound of Formula **(Ia)** or Formula **(Ib)**) is present as a sodium salt. In certain embodiments, the active ingredient (for example, a compound of Formula **(Ia)** or Formula **(Ib)**) is present as a trifluoroacetic acid salt. In some embodiments, the active ingredient is a compound of Formula **(Ia)**. In some embodiments, the active ingredient is a compound of Formula **(Ib)**.

In certain embodiments, the pharmaceutical composition disclosed herein is a parenteral formulation. In certain embodiments, the formulation is administered subcutaneously to a patient in need thereof. In certain embodiments, the formulation is administered intramuscularly to a patient in need thereof.

In certain embodiments, the parenteral formulation comprises N-methyl-2-pyrrolidone (NMP). In certain embodiments, the parenteral formulation consists essentially of N-methyl-2-pyrrolidone. In certain embodiments, the parenteral formulation comprises dimethyl sulfoxide (DMSO). In some embodiments, the parenteral formulation comprises polyethylene glycol (PEG) or glycofurol. In some embodiments, the solution comprises PEG 200, ethanol, and water. In some embodiments, the solution comprises PEG 300 and water. In some embodiments, the solution comprises poloxamer in saline. In some embodiments, the solution comprises 2% poloxamer 188 in normal saline.

In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and water. In certain

embodiments, the parenteral formulation comprises a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof, and water. In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and water. In certain embodiments, the parenteral formulation further contains an alcohol. In certain embodiments, the alcohol is ethanol. In certain embodiments, the parenteral formulation further contains polyethylene glycol. In certain embodiments, the polyethylene glycol has an average molecular weight of about 200 g/mol (for example, polyethylene glycol 200). In certain embodiments, the parenteral formulation further contains an inorganic base. In certain embodiments, the inorganic base is sodium hydroxide (NaOH). In certain embodiments, the inorganic base is sodium ethoxide (NaOEt). In certain embodiments, the formulation comprises from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 0.75 molar equivalents to about 1.2 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises about 1.0 molar equivalents inorganic base. In certain embodiments, the formulation comprises about 1.2 molar equivalents inorganic base. In some embodiments, the inorganic base is NaOH or NaOEt.

In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof, water and polyethylene glycol PEG 300. In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, water, and polyethylene glycol PEG 300.

In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof, water, and polyethylene glycol PEG 300 (polyethylene glycol with an average molecular weight of 300 g/mol), and NaOH. In certain embodiments, the parenteral formulation comprises a compound of Formula **(Ia)**, or a pharmaceutically acceptable salt thereof, water, and polyethylene glycol (PEG) 300, and NaOEt. In certain embodiments, the formulation includes from about 0.1 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation includes from about 0.5 molar equivalents to about 1.5 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation includes from about 0.75 molar equivalents to about 1.2 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation comprises about 1.0 molar equivalents of NaOH or NaOEt. In certain embodiments, the formulation includes about 1.2 molar equivalents of NaOH or NaOEt.

In certain embodiments, the parenteral formulation is a solution formulation that includes a mixture of ethanol, water, and polyethylene glycol. In certain embodiments, the parenteral

formulation is a solution formulation that includes a mixture of ethanol, water, and PEG 200. In certain embodiments, the solution formulation includes about 5% to about 20% ethanol, about 5% to about 20% water, and about 60% to about 90% PEG 200. In certain embodiments, the solution formulation comprises about 10% to about 15% ethanol, about 10% to about 15% water, and about 70% to about 80% PEG 200. In certain embodiments, the solution formulation includes about 10% ethanol, about 12% water, and about 78% PEG 200. In certain embodiments, the solution formulation further includes an inorganic base. In certain embodiments, the solution formulation includes about 10% ethanol, about 13% water, and about 77% PEG 200. In certain embodiments, the solution formulation further includes an inorganic base. In certain embodiments, the formulation includes from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 1.0 molar equivalents to about 1.2 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises about 1.2 molar equivalents inorganic base. In certain embodiments, the inorganic base is sodium hydroxide or sodium ethoxide. In certain embodiments, the inorganic base is sodium hydroxide.

In certain embodiments, the parenteral formulation is a solution formulation that includes a mixture of water and polyethylene glycol. In certain embodiments, the parenteral formulation is a solution formulation that includes a mixture of water and PEG 300. In certain embodiments, the solution formulation includes about 5% w/w to about 25% w/w water, and about 75% w/w to about 95% w/w PEG 300. In some embodiments, the solution formulation further includes an inorganic base. In certain embodiments, the formulation includes from about 0.1 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 0.5 molar equivalents to about 1.5 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises from about 0.75 molar equivalents to about 1.2 molar equivalents of the inorganic base. In certain embodiments, the formulation comprises about 1.0 molar equivalents inorganic base. In certain embodiments, the formulation comprises about 1.2 molar equivalents inorganic base. In certain embodiments, the inorganic base is sodium hydroxide or sodium ethoxide. In certain embodiments, the inorganic base is sodium hydroxide.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, and

water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, and water. In some embodiments, the solution disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water. In some embodiments, the solution disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)**, PEG 300, sodium hydroxide, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, PEG 300, sodium hydroxide, and water.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50 mg/ml to about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 125 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in

the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 275 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 325 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 475 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 500 mg/ml.

In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 10 w/w% to about 40 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 20 w/w% to about 30 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 21 w/w% to about 29 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 23.2 w/w% to about 27.9 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 23.2 w/w% to about 27.92 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is

about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 23.2 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 27.9 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 27.92 w/w%.

In some embodiments, the amount of PEG 300 in the solution comprising compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 35 w/w% to about 75 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 45 w/w% to about 65 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 48 w/w% to about 60 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 49 w/w% to about 59 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50.0 w/w% to about 58.0 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50.0 w/w% to about 58.04 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 45 w/w%, about 46 w/w%, about 47 w/w%, about 48 w/w%, about 49 w/w%, about 50 w/w%, about 51 w/w%, about 52 w/w%, about 53

w/w%, about 54 w/w%, about 55 w/w%, about 56 w/w%, about 57 w/w%, about 58 w/w%, about 59 w/w%, about 60 w/w%, about 61 w/w%, about 62 w/w%, about 63 w/w%, about 64 w/w%, or about 65 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 50.0 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 58.0 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 58.04 w/w%.

In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 5 w/w% to about 35 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 10 w/w% to about 30 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 11 w/w% to about 28 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13 w/w% to about 27 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13.5 w/w% to about 25.7 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13.47 w/w% to about 25.7 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13.0 w/w%, about 13.1 w/w%, about 13.2 w/w%, about 13.3 w/w%, about 13.4 w/w%, about 13.5 w/w%, about 13.6 w/w%, about 13.7 w/w%, about 13.8 w/w%, about 13.9 w/w%, about 14.0 w/w%, about 14.1 w/w%, about 14.2 w/w%, about 14.3 w/w%, about 14.4 w/w%, about 14.5 w/w%, about 14.6 w/w%, about 14.7 w/w%, about 14.8 w/w%, about 14.9 w/w%, about 15.0 w/w%, about 15.1 w/w%, about 15.2 w/w%, about 15.3 w/w%, about 15.4 w/w%, about 15.5 w/w%, about 15.6 w/w%, about 15.7 w/w%, about 15.8 w/w%, about 15.9 w/w%, about 16.0 w/w%, about 16.1 w/w%, about 16.2 w/w%, about 16.3 w/w%, about 16.4 w/w%, about 16.5 w/w%, about 16.6 w/w%, about 16.7 w/w%, about 16.8 w/w%, about 16.9 w/w%, about 17.0 w/w%, about 17.1 w/w%, about 17.2 w/w%, about 17.3 w/w%, about 17.4 w/w%, about 17.5 w/w%, about 17.6 w/w%, about 17.7 w/w%, about 17.8 w/w%, about 17.9 w/w%, about 18.0 w/w%, about 18.1 w/w%, about 18.2 w/w%, about 18.3 w/w%, about 18.4 w/w%, about 18.5 w/w%, about 18.6 w/w%, about 18.7 w/w%, about 18.8 w/w%, about 18.9 w/w%,

about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about 20.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3 w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13.47 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 13.5 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 25.7 w/w%.

In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.05 w/w% to about 2 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.1 w/w% to about 1.5 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.3 w/w% to about 1.3 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.5 w/w% to about 1.2 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.6 w/w% to about

1.1 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.58 w/w% to about 1.1 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.1 w/w%, about 0.2 w/w%, about 0.3 w/w%, about 0.4 w/w%, about 0.5 w/w%, about 0.6 w/w%, about 0.7 w/w%, about 0.8 w/w%, about 0.9 w/w%, about 1.0 w/w%, about 1.1 w/w%, about 1.2 w/w%, about 1.3 w/w%, about 1.4 w/w%, about 1.5 w/w%, about 1.6 w/w%, about 1.7 w/w%, about 1.8 w/w%, about 1.9 w/w%, or about 2.0 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.58 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 0.6 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water is about 1.1 w/w%. In some embodiments, the solution disclosed herein comprises about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, about 5 w/w% to about 35 w/w% of a compound of Formula **(Ia)**, and about 0.05 w/w% to about 2 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 15 w/w% to about 35 w/w% water, about 45 w/w% to about 65 w/w% PEG 300, about 10 w/w% to about 30 w/w% of a compound of Formula **(Ia)**, and about 0.1 w/w% to about 1.5 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 20 w/w% to about 30 w/w% water, about 48 w/w% to about 60 w/w% PEG 300, about 11 w/w% to about 28 w/w% of a compound of Formula **(Ia)**, and about 0.3 w/w% to about 1.3 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 21 w/w% to about 29 w/w% water, about 49 w/w% to about 59 w/w% PEG 300, about 13 w/w% to about 27 w/w% of a compound of Formula **(Ia)**, and about 0.5 w/w% to about 1.2 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 23.2 w/w% to about 27.9 w/w% water, about 50 w/w% to about 58 w/w% PEG 300, about 13.5 w/w% to about 25.7 w/w% of a compound of Formula **(Ia)**, and about 0.6 w/w% to about 1.1 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 23.2 w/w% to about 27.92 w/w% water, about 50.0 w/w% to about 58.04 w/w% PEG 300, about 13.47 w/w% to about 25.7 w/w% of a compound of Formula **(Ia)**, and about 0.58 w/w% to about 1.1 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 27.9 w/w% water, about 58 w/w% PEG 300, about 13.5 w/w% of a compound of Formula **(Ia)**, and about 0.6 w/w% of sodium hydroxide. In some embodiments, the solution comprises about 27.92 w/w% water, about 58.04 w/w% PEG 300, about 13.47 w/w% of a compound of Formula **(Ia)**, and about 0.58 w/w% of sodium hydroxide. In some embodiments, the solution comprises

about 23.2 w/w% water, about 50.0 w/w% PEG 300, about 25.7 w/w% of a compound of Formula **(Ia)**, and about 1.1 w/w% of sodium hydroxide.

In some embodiments, the compound of Formula **(Ia)** becomes ionized in situ to a sodium salt of the compound of Formula **(Ia)** in the presence of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water. Thus, in some embodiments, the compound of Formula **(Ia)** is present as a sodium salt of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, and water.

In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a poloxamer, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, poloxamer 188, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, a poloxamer, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions disclosed herein are solutions that comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, poloxamer 188, and a pharmaceutically acceptable excipient.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, PEG 300, sodium hydroxide, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water. In some embodiments, the solution disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)**, PEG 300, sodium hydroxide, poloxamer 188, and water.

In some embodiments, the solution disclosed herein comprises a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 50 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in

the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 50 mg/ml to about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 125 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 275 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 325 mg/ml. In some embodiments, the concentration of the compound of

Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 475 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 500 mg/ml.

In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 10 w/w% to about 45 w/w%. In some embodiments, the amount of water in the solution comprising a of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 20 w/w% to about 35 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 20 w/w% to about 31 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 22 w/w% to about 30.1 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 21.97 w/w% to about 30.07 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about 20.0 w/w%, about 20.1 w/w%, about 20.2 w/w%, about 20.3 w/w%, about 20.4 w/w%, about 20.5 w/w%, about 20.6 w/w%, about 20.7 w/w%, about 20.8 w/w%, about 20.9 w/w%, about 21.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3

w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, about 29.0 w/w%, about 29.1 w/w%, about 29.2 w/w%, about 29.3 w/w%, about 29.4 w/w%, about 29.5 w/w%, about 29.6 w/w%, about 29.7 w/w%, about 29.8 w/w%, about 29.9 w/w%, about 30.0 w/w%, about 30.1 w/w%, about 30.2 w/w%, about 30.3 w/w%, about 30.4 w/w%, about 30.5 w/w%, about 30.6 w/w%, about 30.7 w/w%, about 30.8 w/w%, about 30.9 w/w%, about 31.0 w/w%, about 31.1 w/w%, about 31.2 w/w%, about 31.3 w/w%, about 31.4 w/w%, about 31.5 w/w%, about 31.6 w/w%, about 31.7 w/w%, about 31.8 w/w%, about 31.9 w/w%, about 32.0 w/w%, about 32.1 w/w%, about 32.2 w/w%, about 32.3 w/w%, about 32.4 w/w%, about 32.5 w/w%, about 32.6 w/w%, about 32.7 w/w%, about 32.8 w/w%, about 32.9 w/w%, or about 33.0 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 21.97 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 22 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 30.07 w/w%. In some embodiments, the amount of water in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 30.1 w/w%.

In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 30 w/w% to about 85 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a

compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 35 w/w% to about 75 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 40 w/w% to about 70 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 45 w/w% to about 68 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 47.1 w/w% to about 64.4 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 47.05 w/w% to about 64.41 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 40 w/w%, about 41 w/w%, about 42 w/w%, about 43 w/w%, about 44 w/w%, about 45 w/w%, about 46 w/w%, about 47 w/w%, about 48 w/w%, about 49 w/w%, about 50 w/w%, about 51 w/w%, about 52 w/w%, about 53 w/w%, about 54 w/w%, about 55 w/w%, about 56 w/w%, about 57 w/w%, about 58 w/w%, about 59 w/w%, about 60 w/w%, about 61 w/w%, about 62 w/w%, about 63 w/w%, about 64 w/w%, about 65 w/w%, about 66 w/w%, about 67 w/w%, about 68 w/w%, about 69 w/w%, or about 70 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 47.05 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 47.1 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 64.4 w/w%. In some embodiments, the amount of PEG 300 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 64.41 w/w%.

In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.5 w/w% to about 40 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 1 w/w% to about 35 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 1 w/w% to about 30 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide,

poloxamer 188, and water is about 3 w/w% to about 28 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4 w/w% to about 26 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.6 w/w% to about 25.2 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.57 w/w% to about 25.21 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 3.0 w/w%, about 3.1 w/w%, about 3.2 w/w%, about 3.3 w/w%, about 3.4 w/w%, about 3.5 w/w%, about 3.6 w/w%, about 3.7 w/w%, about 3.8 w/w%, about 3.9 w/w%, about 4.0 w/w%, about 4.1 w/w%, about 4.2 w/w%, about 4.3 w/w%, about 4.4 w/w%, about 4.5 w/w%, about 4.6 w/w%, about 4.7 w/w%, about 4.8 w/w%, about 4.9 w/w%, about 5.0 w/w%, about 5.1 w/w%, about 5.2 w/w%, about 5.3 w/w%, about 5.4 w/w%, about 5.5 w/w%, about 5.6 w/w%, about 5.7 w/w%, about 5.8 w/w%, about 5.9 w/w%, about 6.0 w/w%, about 6.1 w/w%, about 6.2 w/w%, about 6.3 w/w%, about 6.4 w/w%, about 6.5 w/w%, about 6.6 w/w%, about 6.7 w/w%, about 6.8 w/w%, about 6.9 w/w%, about 7.0 w/w%, about 7.1 w/w%, about 7.2 w/w%, about 7.3 w/w%, about 7.4 w/w%, about 7.5 w/w%, about 7.6 w/w%, about 7.7 w/w%, about 7.8 w/w%, about 7.9 w/w%, about 8.0 w/w%, about 8.1 w/w%, about 8.2 w/w%, about 8.3 w/w%, about 8.4 w/w%, about 8.5 w/w%, about 8.6 w/w%, about 8.7 w/w%, about 8.8 w/w%, about 8.9 w/w%, about 9.0 w/w%, about 9.1 w/w%, about 9.2 w/w%, about 9.3 w/w%, about 9.4 w/w%, about 9.5 w/w%, about 9.6 w/w%, about 9.7 w/w%, about 9.8 w/w%, about 9.9 w/w%, about 10.0 w/w%, about 10.1 w/w%, about 10.2 w/w%, about 10.3 w/w%, about 10.4 w/w%, about 10.5 w/w%, about 10.6 w/w%, about 10.7 w/w%, about 10.8 w/w%, about 10.9 w/w%, about 11.0 w/w%, about 11.1 w/w%, about 11.2 w/w%, about 11.3 w/w%, about 11.4 w/w%, about 11.5 w/w%, about 11.6 w/w%, about 11.7 w/w%, about 11.8 w/w%, about 11.9 w/w%, about 12.0 w/w%, about 12.1 w/w%, about 12.2 w/w%, about 12.3 w/w%, about 12.4 w/w%, about 12.5 w/w%, about 12.6 w/w%, about 12.7 w/w%, about 12.8 w/w%, about 12.9 w/w%, about 13.0 w/w%, about 13.1 w/w%, about 13.2 w/w%, about 13.3 w/w%, about 13.4 w/w%, about 13.5 w/w%, about 13.6 w/w%, about 13.7 w/w%, about 13.8 w/w%, about 13.9 w/w%, about 14.0 w/w%, about 14.1 w/w%, about 14.2 w/w%, about 14.3 w/w%, about 14.4 w/w%, about 14.5 w/w%, about 14.6 w/w%, about 14.7 w/w%, about 14.8 w/w%, about 14.9 w/w%, about 15.0 w/w%, about 15.1 w/w%, about 15.2 w/w%, about 15.3 w/w%, about 15.4 w/w%, about 15.5 w/w%, about 15.6 w/w%, about 15.7 w/w%, about 15.8 w/w%, about 15.9 w/w%,

about 16.0 w/w%, about 16.1 w/w%, about 16.2 w/w%, about 16.3 w/w%, about 16.4 w/w%, about 16.5 w/w%, about 16.6 w/w%, about 16.7 w/w%, about 16.8 w/w%, about 16.9 w/w%, about 17.0 w/w%, about 17.1 w/w%, about 17.2 w/w%, about 17.3 w/w%, about 17.4 w/w%, about 17.5 w/w%, about 17.6 w/w%, about 17.7 w/w%, about 17.8 w/w%, about 17.9 w/w%, about 18.0 w/w%, about 18.1 w/w%, about 18.2 w/w%, about 18.3 w/w%, about 18.4 w/w%, about 18.5 w/w%, about 18.6 w/w%, about 18.7 w/w%, about 18.8 w/w%, about 18.9 w/w%, about 19.0 w/w%, about 19.1 w/w%, about 19.2 w/w%, about 19.3 w/w%, about 19.4 w/w%, about 19.5 w/w%, about 19.6 w/w%, about 19.7 w/w%, about 19.8 w/w%, about 19.9 w/w%, about 20.0 w/w%, about 21.1 w/w%, about 21.2 w/w%, about 21.3 w/w%, about 21.4 w/w%, about 21.5 w/w%, about 21.6 w/w%, about 21.7 w/w%, about 21.8 w/w%, about 21.9 w/w%, about 22.0 w/w%, about 22.1 w/w%, about 22.2 w/w%, about 22.3 w/w%, about 22.4 w/w%, about 22.5 w/w%, about 22.6 w/w%, about 22.7 w/w%, about 22.8 w/w%, about 22.9 w/w%, about 23.0 w/w%, about 23.1 w/w%, about 23.2 w/w%, about 23.3 w/w%, about 23.4 w/w%, about 23.5 w/w%, about 23.6 w/w%, about 23.7 w/w%, about 23.8 w/w%, about 23.9 w/w%, about 24.0 w/w%, about 24.1 w/w%, about 24.2 w/w%, about 24.3 w/w%, about 24.4 w/w%, about 24.5 w/w%, about 24.6 w/w%, about 24.7 w/w%, about 24.8 w/w%, about 24.9 w/w%, about 25.0 w/w%, about 25.1 w/w%, about 25.2 w/w%, about 25.3 w/w%, about 25.4 w/w%, about 25.5 w/w%, about 25.6 w/w%, about 25.7 w/w%, about 25.8 w/w%, about 25.9 w/w%, about 26.0 w/w%, about 26.1 w/w%, about 26.2 w/w%, about 26.3 w/w%, about 26.4 w/w%, about 26.5 w/w%, about 26.6 w/w%, about 26.7 w/w%, about 26.8 w/w%, about 26.9 w/w%, about 27.0 w/w%, about 27.1 w/w%, about 27.2 w/w%, about 27.3 w/w%, about 27.4 w/w%, about 27.5 w/w%, about 27.6 w/w%, about 27.7 w/w%, about 27.8 w/w%, about 27.9 w/w%, about 28.0 w/w%, about 28.1 w/w%, about 28.2 w/w%, about 28.3 w/w%, about 28.4 w/w%, about 28.5 w/w%, about 28.6 w/w%, about 28.7 w/w%, about 28.8 w/w%, about 28.9 w/w%, or about 29.0 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.57 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.6 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 25.2 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 25.21 w/w%.

In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about

0.01 w/w% to about 3.0 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.01 w/w% to about 2.0 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.05 w/w% to about 1.5 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.05 w/w% to about 1.2 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.1 w/w% to about 1.1 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.10 w/w% to about 1.08 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.01 w/w%, about 0.02 w/w%, about 0.03 w/w%, about 0.04 w/w%, about 0.05 w/w%, about 0.06 w/w%, about 0.07 w/w%, about 0.08 w/w%, about 0.09 w/w%, about 0.1 w/w%, about 0.2 w/w%, about 0.3 w/w%, about 0.4 w/w%, about 0.5 w/w%, about 0.6 w/w%, about 0.7 w/w%, about 0.8 w/w%, about 0.9 w/w%, about 1.0 w/w%, about 1.1 w/w%, about 1.2 w/w%, about 1.3 w/w%, about 1.4 w/w%, about 1.5 w/w%, about 1.6 w/w%, about 1.7 w/w%, about 1.8 w/w%, about 1.9 w/w%, or about 2.0 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.1 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.10 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 1.08 w/w%. In some embodiments, the amount of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 1.1 w/w%.

In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.1 w/w% to about 10 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.3 w/w% to about 8 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.5 w/w% to about 7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300,

sodium hydroxide, poloxamer 188, and water is about 0.6 w/w% to about 7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.85 w/w% to about 4.69 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.9 w/w% to about 4.7 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.5 w/w%, about 0.6 w/w%, about 0.7 w/w%, about 0.8 w/w%, about 0.9 w/w%, about 1.0 w/w%, about 1.1 w/w%, about 1.2 w/w%, about 1.3 w/w%, about 1.4 w/w%, about 1.5 w/w%, about 1.6 w/w%, about 1.7 w/w%, about 1.8 w/w%, about 1.9 w/w%, about 2.0 w/w%, about 2.1 w/w%, about 2.2 w/w%, about 2.3 w/w%, about 2.4 w/w%, about 2.5 w/w%, about 2.6 w/w%, about 2.7 w/w%, about 2.8 w/w%, about 2.9 w/w%, about 3.0 w/w%, about 3.1 w/w%, about 3.2 w/w%, about 3.3 w/w%, about 3.4 w/w%, about 3.5 w/w%, about 3.6 w/w%, about 3.7 w/w%, about 3.8 w/w%, about 3.9 w/w%, about 4.0 w/w%, about 4.1 w/w%, about 4.2 w/w%, about 4.3 w/w%, about 4.4 w/w%, about 4.5 w/w%, about 4.6 w/w%, about 4.7 w/w%, about 4.8 w/w%, about 4.9 w/w%, about 5.0 w/w%, about 5.1 w/w%, about 5.2 w/w%, about 5.3 w/w%, about 5.4 w/w%, about 5.5 w/w%, about 5.6 w/w%, about 5.7 w/w%, about 5.8 w/w%, about 5.9 w/w%, about 6.0 w/w%, about 6.1 w/w%, about 6.2 w/w%, about 6.3 w/w%, about 6.4 w/w%, about 6.5 w/w%, about 6.6 w/w%, about 6.7 w/w%, about 6.8 w/w%, about 6.9 w/w%, or about 7.0 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.85 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 0.9 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.69 w/w%. In some embodiments, the amount of poloxamer 188 in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water is about 4.7 w/w%.

In some embodiments, the solution disclosed herein comprises about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about 0.5 w/w% to about 40 w/w% of a compound of Formula **(Ia)**, about 0.01 w/w% to about 3.0 w/w% of sodium hydroxide, and about 0.1 w/w% to about 10 w/w% of poloxamer 188. In some embodiments, the solution comprises about 15 w/w% to about 35 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, about 1 w/w% to about 35 w/w% of a compound of Formula **(Ia)**, about 0.01 w/w% to about 2.0 w/w% of sodium hydroxide, and about 0.3 w/w% to about 8 w/w% of

poloxamer 188. In some embodiments, the solution comprises about 20 w/w% to about 35 w/w% water, about 40 w/w% to about 70 w/w% PEG 300, about 1 w/w% to about 30 w/w% of a compound of Formula **(Ia)**, about 0.05 w/w% to about 1.5 w/w% of sodium hydroxide, and about 0.5 w/w% to about 7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 20 w/w% to about 31 w/w% water, about 45 w/w% to about 68 w/w% PEG 300, about 3 w/w% to about 28 w/w% of a compound of Formula **(Ia)**, about 0.05 w/w% to about 1.2 w/w% of sodium hydroxide, and about 0.6 w/w% to about 7 w/w% of poloxamer 188.

In some embodiments, the solution comprises about 22 w/w% to about 30.1 w/w% water, about 47.1 w/w% to about 64.4 w/w% PEG 300, about 4.6 w/w% to about 25.2 w/w% of a compound of Formula **(Ia)**, about 0.1 w/w% to about 1.1 w/w% of sodium hydroxide, and about 0.9 w/w% to about 4.7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 21.97 w/w% to about 30.07 w/w% water, about 47.05 w/w% to about 64.41 w/w% PEG 300, about 4.57 w/w% to about 25.21 w/w% of a compound of Formula **(Ia)**, about 0.10 w/w% to about 1.08 w/w% of sodium hydroxide, and about 0.85 w/w% to about 4.69 w/w% of poloxamer 188. In some embodiments, the solution comprises about 30.1 w/w% water, about 64.4 w/w% PEG 300, about 4.6 w/w% of a compound of Formula **(Ia)**, about 0.1 w/w% of sodium hydroxide, and about 0.9 w/w% of poloxamer 188. In some embodiments, the solution comprises about 30.07 w/w% water, about 64.41 w/w% PEG 300, about 4.57 w/w% of a compound of Formula **(Ia)**, about 0.10 w/w% of sodium hydroxide, and about 0.85 w/w% of poloxamer 188. In some embodiments, the solution comprises about 22 w/w% water, about 47.1 w/w% PEG 300, about 25.2 w/w% of a compound of Formula **(Ia)**, about 1.1 w/w% of sodium hydroxide, and about 4.7 w/w% of poloxamer 188. In some embodiments, the solution comprises about 21.97 w/w% water, about 47.05 w/w% PEG 300, about 25.21 w/w% of a compound of Formula **(Ia)**, about 1.08 w/w% of sodium hydroxide, and about 4.69 w/w% of poloxamer 188.

In some embodiments, the compound of Formula **(Ia)** becomes ionized in situ to a sodium salt of the compound of Formula **(Ia)** in the presence of sodium hydroxide in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water. Thus, in some embodiments, the compound of Formula **(Ia)** is present as a sodium salt of the compound of Formula **(Ia)** in the solution comprising a compound of Formula **(Ia)**, PEG 300, sodium hydroxide, poloxamer 188, and water.

In some embodiments, the solution formulation comprises about 50 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 75 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some

embodiments, the solution formulation comprises about 125 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 175 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 225 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 250 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 275 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 325 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 350 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 375 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the solution formulation comprises about 100 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 150 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 200 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 300 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 400 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the solution formulation comprises about 425 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 450 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 475 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the solution formulation comprises about 500 mg/mL of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the solutions disclosed herein are administered through subcutaneous injection. In some embodiments, the solutions disclosed herein are administered through intramuscular injection.

In certain embodiments, an oral formulation of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and at least one excipient is provided. Excipients can include ethanol, medium chain triglycerides, vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), glycerol monocaprylocaprate, glycerin, and/or pharmaceutically acceptable oils. Examples of suitable medium chain triglycerides include, but are not limited to, MIGLYOL 810, MIGLYOL 821, and MIGLYOL 840. Examples of suitable pharmaceutically acceptable oils include, but are not limited to, sesame oil, castor oil, safflower oil, vegetable oil, and soybean oil. Oral formulations disclosed herein can include any combination of one or more suitable excipients. Excipients taken together can be present in greater than about 65% by weight of the total oral formulation, greater than about 70% by weight of the total oral formulation, greater than about 80% by weight of the total oral formulation, greater than about 90% by weight of the total oral formulation, or greater than about 95% by weight of the total oral formulation.

In some embodients, the oral formulation of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and at least one excipient as disclosed herein is prepared in hard or soft capsules. In some embodiments, the hard or soft capsules comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and one or more excipients selected from the group consisting of ethanol, propylene glycol, glycerine, d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), polyoxyl 35 castor oil (e.g., Kolliphor® EL), glycerol monocapryolocaprate (e.g., Capmul® MCM), PEG 400 caprylic/capric glycerides (e.g., Labrasol®), PEG 400, diethylene glycol monoethyl ether (e.g., Transcutol®), propylene glycol monocaprylate, Type II (e.g., Capryol® 90), glyceryl monooleate, Type 40 (e.g., Peceol™), medium chain triglycerides (e.g., Miglyol® 812N), glyceryl monolinoleate (e.g., Maisine®), and polysorbate 80. In some embodiments, the hard or soft capsules comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and one or more excipients selected from the group consisting of ethanol, medium chain triglycerides (e.g., Miglyol® 812N), d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), glycerol monocapryolocaprate (e.g., Capmul® MCM), PEG 400 caprylic/capric glycerides (e.g., Labrasol®), and PEG 400.

In some embodiments, the hard or soft capsules further comprise a capsule shell. In some embodiments, the capsule shell comprises one or more pharmaceutically acceptable

excipients. In some embodiments, the one or more pharmaceutically acceptable excipients of the capsule shell is selected from the group consisting of a gelatin shell, a plasticizer, an opacifier, and a colorant. Plasticizers, opacifiers, and colorants are well-known in the art. In some embodiments, the capsule shell comprises one or more pharmaceutically acceptable excipients selected from the group consisting of gelatin, glycerin, titanium dioxide, and iron oxide. In some embodiments, the iron oxide comprises iron oxide (yellow).

In some embodiments, an oral formulation of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is provided. In certain embodiments, the oral formulation comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and glycerol monocaprylocaprate. In certain embodiments, the oral formulation includes a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, about 5% to about 20% ethanol, about 10% to about 30% vitamin E TPGS, and about 50% to about 85% MIGLYOL 812. In some embodiments, the oral formulation includes a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, about 8% to about 15% ethanol, about 15% to about 25% vitamin E TPGS, and about 60% to about 77% MIGLYOL 812. In certain embodiments, the oral formulation includes a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in about 10% ethanol, about 20% vitamin E TPGS, and about 70% MIGLYOL 812. In certain embodiments, the oral formulation is prepared in hard gelatin capsules. In certain embodiments, the oral formulation is prepared in soft gelatin capsules.

In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient as disclosed herein. In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and glycerol monocaprylocaprate. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 10 mg/ml to about 500 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 10 mg/ml to about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 50 mg/ml to about 200 mg/ml. In

some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 50 mg/ml to about 100 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 30 mg/ml, about 40 mg/ml, about 45 mg/ml, about 50 mg/ml, about 55 mg/ml, about 60 mg/ml, about 65 mg/ml, about 70 mg/ml, about 75 mg/ml, about 80 mg/ml, about 85 mg/ml, about 90 mg/ml, about 95 mg/ml, about 100 mg/ml, about 105 mg/ml, about 110 mg/ml, about 115 mg/ml, about 120 mg/ml, about 125 mg/ml, about 130 mg/ml, about 135 mg/ml, about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, 205 mg/ml, about 210 mg/ml, about 215 mg/ml, about 220 mg/ml, about 225 mg/ml, about 230 mg/ml, about 235 mg/ml, about 240 mg/ml, about 245 mg/ml, about 250 mg/ml, about 255 mg/ml, about 260 mg/ml, about 265 mg/ml, about 270 mg/ml, about 275 mg/ml, about 280 mg/ml, about 285 mg/ml, about 290 mg/ml, about 295 mg/ml, about 300 mg/ml, about 305 mg/ml, about 310 mg/ml, about 315 mg/ml, about 320 mg/ml, about 325 mg/ml, about 330 mg/ml, about 335 mg/ml, about 340 mg/ml, about 345 mg/ml, about 350 mg/ml, about 355 mg/ml, about 360 mg/ml, about 365 mg/ml, about 370 mg/ml, about 375 mg/ml, about 380 mg/ml, about 385 mg/ml, about 390 mg/ml, about 395 mg/ml, about 400 mg/ml, about 405 mg/ml, about 410 mg/ml, about 415 mg/ml, about 420 mg/ml, about 425 mg/ml, about 430 mg/ml, about 435 mg/ml, about 440 mg/ml, about 445 mg/ml, about 450 mg/ml, about 455 mg/ml, about 460 mg/ml, about 465 mg/ml, about 470 mg/ml, about 475 mg/ml, about 480 mg/ml, about 485 mg/ml, about 490 mg/ml, about 495 mg/ml, or about 500 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 10 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 20 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 30 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 40 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft

gelatin capsule disclosed herein is about 50 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 75 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 100 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 125 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 150 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 175 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 200 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 225 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 250 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 275 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 325 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 350 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 375 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft

gelatin capsule disclosed herein is about 425 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 450 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 475 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the hard gelatin or soft gelatin capsule disclosed herein is about 500 mg/ml.

In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and glycerol monocaprylocaprate. In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)** and glycerol monocaprylocaprate.

In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a compound of Formula **(Ia)** and glycerol monocaprylocaprate. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml to about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml to about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml to about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 20 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in

the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 30 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 40 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 100 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 125 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 150 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 175 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 200 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 225 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 250 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 275 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 300 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 325 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 350 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is

about 375 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 400 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 425 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 450 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 475 mg/ml. In some embodiments, the concentration of a compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 500 mg/ml.

In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 30 w/w% to about 85 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 40 w/w% to about 80 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 w/w% to about 80 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 60 w/w% to about 70 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 65.9 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 65.94 w/w%.

In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 1 w/w% to about 40 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 1 w/w% to about 35 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 2 w/w% to about 30 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol

monocaprylocaprate is about 3 w/w% to about 28 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 3.4 w/w%. In some embodiments, the amount of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 3.42 w/w%.

In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises a capsule shell. In some embodiments, the capsule shell comprises one or more pharmaceutically acceptable excipients. In some embodiments, the one or more pharmaceutically acceptable excipients of the capsule shell is selected from the group consisting of a gelatin shell, a plasticizer, an opacifier, and a colorant. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises one or more of a pharmaceutically acceptable excipient selected from the group consisting of gelatin, glycerin, titanium dioxide, and iron oxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises glycerin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises titanium dioxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises iron oxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin and glycerin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin, glycerin, and titanium dioxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin, glycerin, titanium dioxide, and iron oxide. In some embodiments, the iron oxide of the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide comprises iron oxide (yellow).

In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10 w/w% to about 40 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is

about 10 w/w% to about 30 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 15 w/w% to about 25 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 18 w/w% to about 22 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 19.6 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 19.60 w/w%.

In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 3 w/w% to about 25 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 5 w/w% to about 20 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 5 w/w% to about 15 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 8 w/w% to about 12 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10.8 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10.80 w/w%.

In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 2 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.05 w/w% to about 1.5 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide,

and iron oxide is about 0.1 w/w% to about 1.0 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.1 w/w% to about 0.5 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.2 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.22 w/w%.

In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 1 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.5 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.15 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.1 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.02 w/w%.

In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 30 w/w% to about 85 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 40 w/w% of a compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 40 w/w% to about 80 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 35 w/w% of a compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 50 w/w% to about 80 w/w% of glycerol monocaprylocaprate and about 2 w/w% to about 30 w/w% of a compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 60 w/w% to about 70 w/w% of glycerol monocaprylocaprate and about 3 w/w% to about 28 w/w% of a compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 65.9 w/w% of glycerol monocaprylocaprate and about 3.4 w/w% of a compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule

disclosed herein comprises about 65.94 w/w% of glycerol monocaprylocaprate and about 3.42 w/w% of a compound of Formula **(Ia)**.

In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 30 w/w% to about 85 w/w% of glycerol monocaprylocaprate, about 1 w/w% to about 40 w/w% of a compound of Formula **(Ia)**, about 10 w/w% to about 40 w/w% of gelatin, about 3 w/w% to about 25 w/w% of glycerin, about 0.01 w/w% to about 2 w/w% of titanium dioxide, and about 0.01 w/w% to about 1 w/w% of iron oxide. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 40 w/w% to about 80 w/w% of glycerol monocaprylocaprate, about 1 w/w% to about 35 w/w% of a compound of Formula **(Ia)**, about 10 w/w% to about 30 w/w% of gelatin, about 5 w/w% to about 20 w/w% of glycerin, about 0.05 w/w% to about 1.5 w/w% of titanium dioxide, and about 0.01 w/w% to about 0.5 w/w% of iron oxide. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 50 w/w% to about 80 w/w% of glycerol monocaprylocaprate, about 2 w/w% to about 30 w/w% of a compound of Formula **(Ia)**, about 15 w/w% to about 25 w/w% of gelatin, about 5 w/w% to about 15 w/w% of glycerin, about 0.1 w/w% to about 1.0 w/w% of titanium dioxide, and about 0.01 w/w% to about 0.15 w/w% of iron oxide. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 60 w/w% to about 70 w/w% of glycerol monocaprylocaprate, about 3 w/w% to about 28 w/w% of a compound of Formula **(Ia)**, about 18 w/w% to about 22 w/w% of gelatin, about 8 w/w% to about 12 w/w% of glycerin, about 0.1 w/w% to about 0.5 w/w% of titanium dioxide, and about 0.01 w/w% to about 0.1 w/w% of iron oxide. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 65.9 w/w% of glycerol monocaprylocaprate, about 3.4 w/w% of a compound of Formula **(Ia)**, about 19.6 w/w% of gelatin, about 10.8 w/w% of glycerin, about 0.2 w/w% of titanium dioxide, and about 0.02 w/w% of iron oxide. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 65.94 w/w% of glycerol monocaprylocaprate, about 3.42 w/w% of a compound of Formula **(Ia)**, about 19.60 w/w% of gelatin, about 10.80 w/w% of glycerin, about 0.22 w/w% of titanium dioxide, and about 0.02 w/w% of iron oxide.

In some embodiments, the iron oxide in the hard gelatin or soft gelatin capsule comprising a compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide comprises iron oxide (yellow). In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 65.9 w/w% of glycerol monocaprylocaprate, about 3.4 w/w% of a compound of Formula **(Ia)**, about 19.6 w/w% of gelatin, about 10.8 w/w% of glycerin, about 0.2 w/w% of titanium dioxide, and about 0.02 w/w% of iron oxide (yellow). In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 65.94 w/w% of glycerol monocaprylocaprate, about 3.42 w/w% of a

compound of Formula **(Ia)**, about 19.60 w/w% of gelatin, about 10.80 w/w% of glycerin, about 0.22 w/w% of titanium dioxide, and about 0.02 w/w% of iron oxide (yellow).

In some embodiments, the hard gelatin or soft gelatin capsule disclosed herein comprises a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml to about 500 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml to about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 75 mg/ml to about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 10 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 20 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 30 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 40 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 75 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 100 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 125 mg/ml. In some embodiments, the

concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 150 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 175 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 200 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 225 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 250 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 275 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 300 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 325 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 350 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 375 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 400 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 425 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 450 mg/ml. In some embodiments, the concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 475 mg/ml. In some embodiments, the

concentration of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 500 mg/ml.

In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 30 w/w% to about 99 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 50 w/w% to about 99 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 60 w/w% to about 99 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 75 w/w% to about 98 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 80.09 w/w% to about 94.85 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 80.1 w/w% to about 94.9 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 80.09 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 80.1 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 94.85 w/w%. In some embodiments, the amount of glycerol monocaprylocaprate in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 94.9 w/w%.

In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 1 w/w% to about 40 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 1 w/w% to about 35 w/w%. In some embodiments, the amount of

the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 2 w/w% to about 30 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 3 w/w% to about 28 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 5.15 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 5.2 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 19.9 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate is about 19.91 w/w%.

In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises a capsule shell. In some embodiments, the capsule shell comprises one or more pharmaceutically acceptable excipients. In some embodiments, the one or more pharmaceutically acceptable excipients of the capsule shell is selected from the group consisting of a gelatin shell, a plasticizer, an opacifier, and a colorant. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises one or more of a pharmaceutically acceptable excipient selected from the group consisting of gelatin, glycerin, titanium dioxide, and iron oxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises glycerin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises titanium dioxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises iron oxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin and

glycerin. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin, glycerin, and titanium dioxide. In some embodiments, the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)** and glycerol monocaprylocaprate further comprises gelatin, glycerin, titanium dioxide, and iron oxide. In some embodiments, the iron oxide of the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide comprises iron oxide (yellow).

In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10 w/w% to about 40 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10 w/w% to about 30 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 15 w/w% to about 25 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 18 w/w% to about 22 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 19.6 w/w%. In some embodiments, the amount of gelatin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 19.60 w/w%.

In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 3 w/w% to about 25 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 5 w/w% to about 20 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia)**, glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 5 w/w% to about 15 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of

Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 8 w/w% to about 12 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10.8 w/w%. In some embodiments, the amount of glycerin in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 10.80 w/w%.

In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 2 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.05 w/w% to about 1.5 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.1 w/w% to about 1.0 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.1 w/w% to about 0.5 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.2 w/w%. In some embodiments, the amount of titanium dioxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.22 w/w%.

In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 1 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.5 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.15 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule

comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.01 w/w% to about 0.1 w/w%. In some embodiments, the amount of iron oxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide is about 0.02 w/w%.

In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 30 w/w% to about 99 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 40 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 50 w/w% to about 99 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 35 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 60 w/w% to about 99 w/w% of glycerol monocaprylocaprate and about 2 w/w% to about 30 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 75 w/w% to about 98 w/w% of glycerol monocaprylocaprate and about 3 w/w% to about 28 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 80.09 w/w% to about 94.85 w/w% of glycerol monocaprylocaprate and about 5.15 w/w% to about 19.91 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 80.1 w/w% to about 94.9 w/w% of glycerol monocaprylocaprate and about 5.2 w/w% to about 19.9 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 94.85 w/w% of glycerol monocaprylocaprate and about 5.15 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 94.9 w/w% of glycerol monocaprylocaprate and about 5.2 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 80.09 w/w% of glycerol monocaprylocaprate and about 19.91 w/w% of a sodium salt of the compound of Formula **(Ia)**. In some embodiments, the hard gelatin or soft capsule disclosed herein comprises about 80.1 w/w% of glycerol monocaprylocaprate and about 19.9 w/w% of a sodium salt of the compound of Formula **(Ia)**.

In some embodiments, the iron oxide in the hard gelatin or soft gelatin capsule comprising a sodium salt of the compound of Formula **(Ia),** glycerol monocaprylocaprate, gelatin, glycerin, titanium dioxide, and iron oxide comprises iron oxide (yellow).

In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein may be taken with food. In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein

exhibit an increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 2-10 fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 2-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 3-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 4-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 5-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 6-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 7-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein exhibit about a 8-fold increase in C_{max} when taken with food (compared to when taken without food).

In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein comprises any food that is ranging from low in fat to high in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein comprises any food that is low in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein comprises any food that is moderate in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein comprises any food that is high in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein is low in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein is moderate in fat. In some embodiments, the food taken with the hard gelatin or soft gelatin capsules disclosed herein is high in fat.

In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein are hard gelatin capsules. In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein are soft gelatin capsules.

In some embodiments, the oral formulation of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, disclosed herein is a tablet prepared from a spray-dried dispersion of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of a compound of Formula **(Ia)** or

Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 5 mg to about 500 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 25 mg to about 500 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 25 mg to about 400 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 25 mg to about 300 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 50 mg to about 500 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 75 mg to about 500 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 50 mg to about 400 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 50 mg to about 300 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 75 mg to about 400 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 75 mg to about 300 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455

mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, or about 500 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 5 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 10 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 20 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 25 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 30 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 40 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 50 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 75 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 100 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 125 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 150 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 175 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 200 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 225 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 250 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 275 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 300 mg.

In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 325 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 350 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 375 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 400 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 425 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 450 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 475 mg. In some embodiments, the amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in the tablet disclosed herein is about 500 mg.

In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)** and one or more pharmaceutically acceptable excipients. In some embodiments, the tablet disclosed herein comprises a sodium salt of the compound of Formula **(Ia)** and one or more pharmaceutically acceptable excipients. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ib)** and one or more pharmaceutically acceptable excipients. In some embodiments, the tablet disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)** and one or more pharmaceutically acceptable excipients.

The pharmaceutically acceptable excipients of the tablets disclosed herein should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of tablet formulation and may be found *e.g.* in *Handbook of Pharmaceutical Excipients* (eds. Rowe, Sheskey & Quinn), 6th edition **2009**. As used herein the term "excipients" is intended to refer to *inter alia* basifying agents, solubilisers, glidants, fillers, binders, lubricant, diluents, preservatives, surface active agents, dispersing agents and the like. The term also includes

agents such as sweetening agents, flavoring agents, coloring agents and preserving agents. Such components will generally be present in admixture within the tablet.

Examples of solubilisers include, but are not limited to, surfactants (including both ionic and non-ionic surfactants) such as sodium lauryl sulphate, cetyltrimethylammonium bromide, polysorbates (such as polysorbate 20 or 80), poloxamers (such as poloxamer 188 or 207), and macrogols. Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP, sodium starch glycolate, croscarmellose sodium, and the like. Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. Examples of binders include, but are not limited to, cross-linked PVP, HPMC, microcrystalline cellulose, sucrose, starches, and the like.

In some embodiments, the tablets disclosed herein comprise a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients selected from the group consisting of a matrix former, a surfactant, a filler, a disintegrant, and a lubricant. In some embodiments, the tablet comprises about 1 w/w% to about 10 w/w% of a matrix former. In some embodiments, the matrix former comprises copovidone. In some embodiments, the tablet comprises about 0.01 w/w% to about 10 w/w% of a surfactant. In some embodiments, the surfactant comprises poloxamer 407. In some embodiments, the tablet comprises about 25-85 w/w% of one or more fillers. In some embodiments, the one or more fillers comprises microcrystalline cellulose and/or mannitol. In some embodiments, the tablet comprises about 1 w/w% to about 30 w/w% of a disintegrant. In some embodiments, the disintegrant comprises croscarmellose sodium. In some embodiments, the tablet comprises about 0.01 w/w% to about 10 w/w% of a lubricant. In some embodiments, the lubricant comprises magnesium stearate.

The tablets disclosed herein may be uncoated or coated (in which case they include an outer film coat). Although uncoated tablets may be used, it is more usual to provide a coated tablet, in which case a conventional non-enteric coating may be used. Film coatings are known in the art and can be composed of hydrophilic polymer materials, but are not limited to, polysaccharide materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-co-ethylene glycol) and other water soluble polymers. Though the water soluble material included in the film coating of the tablets disclosed herein may include a single polymer material, it may also be formed using a mixture of more than one polymer. The coating may be white or colored.

Suitable coatings include, but are not limited to, polymeric film coatings such as those comprising polyvinyl alcohol *e.g.* 'Opadry® II' (which includes part-hydrolysed PVA, titanium dioxide, macrogol 3350 and talc, with optional colouring such as iron oxide or indigo carmine or iron oxide yellow or FD&C yellow #6). The amount of coating will generally be between about 1-8% of the uncoated tablet's weight.

In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In some embodiments, the one or more pharmaceutically acceptable excipients is selected from the group consisting of copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone. In some embodiments, the one or more pharmaceutically acceptable excipient comprises poloxamer 407. In some embodiments, the one or more pharmaceutically acceptable excipient comprises microcrystalline cellulose. In some embodiments, the one or more pharmaceutically acceptable excipient comprises mannitol. In some embodiments, the one or more pharmaceutically acceptable excipient comprises croscarmellose sodium. In some embodiments, the one or more pharmaceutically acceptable excipient comprises magnesium stearate. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone and poloxamer 407. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone, poloxamer 407, and microcrystalline cellulose. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone, poloxamer 407, microcrystalline cellulose, and mannitol. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone, poloxamer 407, microcrystalline cellulose, mannitol, and croscarmellose sodium. In some embodiments, the one or more pharmaceutically acceptable excipient comprises copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate.

In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)** or a pharmaceutically acceptable salt thereof, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the tablet disclosed herein comprises a trifluoroacetic acid salt of the compound of Formula **(Ib)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ia)**, copovidone,

poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the tablet disclosed herein comprises a compound of Formula **(Ib)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate.

In some embodiments, the tablet disclosed herein comprises a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 5 mg to about 500 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 25 mg to about 500 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 25 mg to about 400 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 25 mg to about 300 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 50 mg to about 300 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 5 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 10 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 20 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 25 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet

comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 30 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 40 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 50 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 75 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 100 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 125 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 150 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 175 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 200 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 225 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 250 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about

275 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 300 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 325 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 350 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 375 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 400 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 425 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 450 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 475 mg. In some embodiments, the amount of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 500 mg.

In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 5 w/w% to about 45 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 10 w/w% to about 40 w/w%. In some embodiments, the

amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 15 w/w% to about 25 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 20.46 w/w%. In some embodiments, the amount of the sodium salt of the compound of Formula **(Ia)** in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 20.5 w/w%.

In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1 w/w% to about 10 w/w%. In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 2 w/w% to about 10 w/w%. In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 3 w/w% to about 8 w/w%. In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 3 w/w% to about 6 w/w%. In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 4.88 w/w%. In some embodiments, the amount of copovidone in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 4.9 w/w%.

In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.01 w/w% to about 10 w/w%. In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium

salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.05 w/w% to about 8 w/w%. In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.5 w/w% to about 4 w/w%. In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.5 w/w% to about 3.0 w/w%. In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1.3 w/w%. In some embodiments, the amount of poloxamer 407 in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1.33 w/w%.

In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 5 w/w% to about 45 w/w%. In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 10 w/w% to about 40 w/w%. In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 15 w/w% to about 35 w/w%. In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 18 w/w% to about 30 w/w%. In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 21.28 w/w%. In some embodiments, the amount of microcrystalline cellulose in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 21.3 w/w%.

In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose,

mannitol, croscarmellose sodium, and magnesium stearate is about 15 w/w% to about 70 w/w%. In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 20 w/w% to about 60 w/w%. In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 30 w/w% to about 55 w/w%. In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 40 w/w% to about 50 w/w%. In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 42.55 w/w%. In some embodiments, the amount of mannitol in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 42.6 w/w%.

In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1 w/w% to about 30 w/w%. In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1 w/w% to about 20 w/w%. In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 4 w/w% to about 16 w/w%. In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 6 w/w% to about 10 w/w%. In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 8.0 w/w%. In some embodiments, the amount of croscarmellose sodium in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 8.00 w/w%.

In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.01 w/w% to about 10 w/w%. In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.05 w/w% to about 8 w/w%. In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 0.5 w/w% to about 4 w/w%. In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1.0 w/w% to about 3.0 w/w%. In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1.5 w/w%. In some embodiments, the amount of magnesium stearate in the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate is about 1.50 w/w%.

In some embodiments, the tablet disclosed herein comprises about 5 w/w% to about 45 w/w% of a sodium salt of the compound of Formula **(Ia)**, about 1 w/w% to about 10 w/w% of copovidone, about 0.01 w/w% to about 10 w/w% of poloxamer 407, about 5 w/w% to about 45 w/w% of microcrystalline cellulose, about 15 w/w% to about 70 w/w% of mannitol, about 1 w/w% to about 30 w/w% of croscarmellose sodium, and about 0.01 w/w% to about 10 w/w% of magnesium stearate. In some embodiments, the tablet disclosed herein comprises about 10 w/w% to about 40 w/w% of a sodium salt of the compound of Formula **(Ia)**, about 2 w/w% to about 10 w/w% of copovidone, about 0.05 w/w% to about 8 w/w% of poloxamer 407, about 10 w/w% to about 40 w/w% of microcrystalline cellulose, about 20 w/w% to about 60 w/w% of mannitol, about 1 w/w% to about 20 w/w% of croscarmellose sodium, and about 0.05 w/w% to about 8 w/w% of magnesium stearate. In some embodiments, the tablet disclosed herein comprises about 15 w/w% to about 35 w/w% of a sodium salt of the compound of Formula **(Ia)**, about 3 w/w% to about 8 w/w% of copovidone, about 0.5 w/w% to about 4 w/w% of poloxamer 407, about 15 w/w% to about 35 w/w% of microcrystalline cellulose, about 30 w/w% to about 55 w/w% of mannitol, about 4 w/w% to about 16 w/w% of croscarmellose sodium, and about 0.5 w/w% to about 4 w/w% of magnesium stearate. In some embodiments, the tablet disclosed herein comprises about 15 w/w% to about 25 w/w% of a sodium salt of the compound of

Formula **(Ia)**, about 3 w/w% to about 6 w/w% of copovidone, about 0.5 w/w% to about 3.0 w/w% of poloxamer 407, about 18 w/w% to about 30 w/w% of microcrystalline cellulose, about 40 w/w% to about 50 w/w% of mannitol, about 6 w/w% to about 10 w/w% of croscarmellose sodium, and about 1.0 w/w% to about 3.0 w/w% of magnesium stearate. In some embodiments, the tablet disclosed herein comprises about 20.5 w/w% of a sodium salt of the compound of Formula **(Ia)**, about 4.9 w/w% of copovidone, about 1.3 w/w% of poloxamer 407, about 21.3 w/w% of microcrystalline cellulose, about 42.6 w/w% of mannitol, about 8.0 w/w% of croscarmellose sodium, and about 1.5 w/w% of magnesium stearate. In some embodiments, the tablet disclosed herein comprises about 20.46 w/w% of a sodium salt of the compound of Formula **(Ia)**, about 4.88 w/w% of copovidone, about 1.33 w/w% of poloxamer 407, about 21.28 w/w% of microcrystalline cellulose, about 42.55 w/w% of mannitol, about 8.00 w/w% of croscarmellose sodium, and about 1.50 w/w% of magnesium stearate.

In some embodiments, the tablet disclosed herein further comprises an outer film coat. In some embodiments, the tablet comprising a sodium salt of the compound of Formula **(Ia)**, copovidone, poloxamer 407, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate further comprises an outer film coat. In some embodiments, the outer film coat provides from about 1% to about 8% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides from about 2% to about 6% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides from about 2% to about 4% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides from about 4% to about 6% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, or about 8% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 1% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 2% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 3% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 4% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 5% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 6% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 7% weight gain based on the uncoated tablet. In some embodiments, the outer film coat provides about 8% weight gain based on the uncoated tablet. In some embodiments, the outer film coat comprises Opadry® II. In some embodiments, the outer film coat comprises Opadry® II White. In some embodiments, the outer film coat comprises Opadry® II White 85F18422.

In some embodiments, the tablets disclosed herein may be taken with food. In some embodiments, the tablets disclosed herein exhibit an increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 2-10 fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 2-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 3-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 4-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 5-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 6-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 7-fold increase in C_{max} when taken with food (compared to when taken without food). In some embodiments, the tablets disclosed herein exhibit about a 8-fold increase in C_{max} when taken with food (compared to when taken without food).

In some embodiments, the food taken with the tablets disclosed herein comprises any food that is ranging from low in fat to high in fat. In some embodiments, the food taken with the tablets disclosed herein comprises any food that is low in fat. In some embodiments, the food taken with the tablets disclosed herein comprises any food that is moderate in fat. In some embodiments, the food taken with the tablets disclosed herein comprises any food that is high in fat. In some embodiments, the food taken with the tablets disclosed herein is low in fat. In some embodiments, the food taken with the tablets disclosed herein is moderate in fat. In some embodiments, the food taken with the tablets disclosed herein is high in fat.

The amount of active ingredient that can be combined with the inactive ingredients to produce a dosage form can vary depending upon the intended treatment patient and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans can contain approximately 1 mg to about 1000 mg of active material formulated with an appropriate and convenient amount of carrier material (for example, inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5% to about 95% of the total weight of the composition.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions of these embodiments can include other agents conventional in the art having regard to the type of composition in question. For example, those suitable for oral administration can include flavoring agents.

In certain embodiments, a composition comprising an active ingredient disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) in one variation does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that compositions containing a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in certain embodiments do not comprise an agent that would affect (for example, slow, hinder, or retard) the metabolism of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, or any other active ingredient administered separately, sequentially, or simultaneously with a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in certain embodiments do not contain an agent that would affect (for example, slow, hinder, or retard) the metabolism of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, or any other active ingredient administered separately, sequentially, or simultaneously with a compound of any one of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In one aspect, disclosed herein are methods for preparing the suspensions, solutions, hard gelatin or soft gelatin capsules, and tablets disclosed herein. Methods of preparing suspensions, solutions, hard gelatin or soft gelatin capsules, and tablets (prepared from spray-dried dispersion technology) are well known in the art.

In some embodiments, the solutions disclosed herein may be prepared by mixing the individual ingredients together and heating the resulting mixture.

In some embodiments, the hard gelatin or soft gelatin capsules disclosed herein may be prepared by mixing the individual ingredients together and homogenizing the mixture. The homogenized mixture may be deaerated, heated, and then dispensed into gelatin capsules while being heated.

In some embodimnets, the tablets disclosed herein may be prepared by mixing the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable excipients and spray drying the mixture into a powder, which is then dried. The dried powder may be combined with one or more additional pharmaceutically acceptable excipients. The resulting mixture may be milled and compressed into tablets.

Routes of Administration

The compound of the Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can be administered by any route appropriate to the condition to be treated. Suitable

routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route can vary with, for example, the condition of the recipient. In certain embodiments, the compounds disclosed are dosed parenterally. In certain embodiments, the compounds disclosed are dosed intravenously, subcutaneously, or intramuscularly. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered intravenously. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered intramuscularly. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally.

In some embodiments, the compound of the Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered via injection, using an injection device. In some embodiments, the injection device is or includes a syringe, which can be employed manually, or as part of a syringe-containing injection device. A wide variety of injection devices can be used, including, but not limited to, a handheld or wearable autoinjector, a handheld or wearable manual injector, an on-body injector, a syrette, a jet injector, or a pen injector, each of which can be reusable or disposable.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can be administered with a syringe suitable for administration of the compound. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can be administered with an auto-injector comprising a syringe. In some embodiments, the syringe is disposable. In some embodiments, the syringe is reusable. In some embodiments, the syringe is pre-filled with the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for subcutaneous administration. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a solution or suspension. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a solution for subcutaneous administration. In some embodiments, the compound of Formula **(Ia)**

or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a suspension for subcutaneous administration. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 50 mg/mL to about 500 mg/mL, such as about 50 mg/mL to about 400 mg/mL, about 50 mg/mL to about 300 mg/mL, about 50 mg/mL to about 200 mg/mL, about 50 mg/mL to about 150 mg/mL, about 50 mg/mL to about 100 mg/mL, about 100 mg/mL to about 500 mg/mL, about 100 mg/mL to about 400 mg/mL, about 100 mg/mL to about 300 mg/mL, about 100 mg/mL to about 200 mg/mL, about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 300 mg/mL, about 300 mg/mL to about 500 mg/mL, about 300 mg/mL to about 400 mg/mL, or about 400 mg/mL to about 500 mg/mL, or about 50 mg/mL, about 100 mg/mL, about 150 mg/mL, about 200 mg/mL, about 300 mg/mL, about 400 mg/mL, or about 500 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 100 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 150 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 300 mg/mL.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 50 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 75 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 125 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 175 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 200 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 225 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 250 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 275 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 325 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is

formulated at a concentration of about 350 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 375 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 400 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 425 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 450 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 475 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 500 mg/mL.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a hard gelatin capsule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a soft gelatin capsule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a hard gelatin capsule for oral administration. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a soft gelatin capsule for oral administration. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated at a concentration of about 20 mg/mL to about 100 mg/mL, such as about 20 mg/mL to about 75 mg/mL, about 20 mg/mL to about 50 mg/mL, about 20 mg/mL to about 30 mg/mL, about 30 mg/mL to about 100 mg/mL, about 30 mg/mL to about 75 mg/mL, about 30 mg/mL to about 50 mg/mL, about 50 mg/mL to about 100 mg/mL, about 50 mg/mL to about 75 mg/mL, or about 75 mg/mL to about 100 mg/mL, or about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, or about 100 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 30 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 50 mg/mL.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 10 mg/ml to about 500 mg/mL.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 10 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 25 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 75 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 100 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 125 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 150 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 175 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 200 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 225 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 250 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 275 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 300 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 325 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 350 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 375 mg/mL. In some embodiments, the compound of

Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 400 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 425 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 450 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 475 mg/mL. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated for oral administration at a concentration of about 500 mg/mL.

Dosing Regimen

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered to a patient in accordance with an effective dosing regimen for a desired period of time or duration. In some embodiments, the dosing regimen includes administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for at least about 1 week, about 2 weeks, about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, or about 48 weeks, or longer.

In some embodiments, the dosing regimen includes administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for at least about 1 year, 2 years, 3 years, 4 years, 5 years, 10 years, or longer. In some embodiments, the dosing regimen includes a permanent administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered on a daily or intermittent schedule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once daily. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered on a monthly schedule. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once about every 1 week, about every 2 weeks, about every 4 weeks, about every 8 weeks, about every 12 weeks, about every 16 weeks, about every 20 weeks, about every 24 weeks, or once about every 48 weeks. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable

salt thereof, is administered once every 4 weeks (or monthly). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 8 weeks (or 2 months). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 12 weeks (or three months). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 16 weeks (or four months). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 20 weeks (or five months). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every 24 weeks (or 6 months). In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every 52 weeks (or yearly).

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously administered to a patient for at least about one month. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously or intramuscularly administered to a patient for at least about 2 months, at least about 3 months, at least about 4 months, or at least about 6 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously administered to a patient once about every month. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously or intramuscularly administered to a patient once about every 3 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously or intramuscularly administered to a patient once about every 6 months.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is intramuscularly administered to a patient once about every month. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously administered to a patient once about every 3 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is intramuscularly administered to a patient once about every 3 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is subcutaneously administered to a patient once about every 6 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is intramuscularly administered to a patient once about every 6 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof, is subcutaneously administered to a patient once about every year. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is intramuscularly administered to a patient once about every year.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once daily. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every 1 week, about every 2 weeks, about every 4 weeks, about every 8 weeks, about every 12 weeks, about every 16 weeks, about every 20 weeks, about every 24 weeks, about every 48 weeks, or about every year. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every 1 week. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every month. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every 3 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every 6 months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is orally administered to a patient once about every year.

The dosage or dosing frequency of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, can be adjusted over the course of the treatment, based on the judgment of the administering physician.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered to a patient (for example, a human) in a therapeutically effective amount. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once daily. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every two months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every three months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every four months. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every six months. In

some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered yearly.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a dosage amount that is effective. In some embodiments, the dosage is from about 1 mg to about 1000 mg of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage amount is about 1 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, or about 150 mg of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage amount is about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the dosage amount is about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 2000 mg, about 2050 mg, or about 3000 mg of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 1 mg to about 2500 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 2400 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 2000 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 1500 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 1200 mg. In some

embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 1000 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 500 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 300 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 200 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 100 mg. In some embodiments, the dosage amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 50 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg to about 1500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 5 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 100 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 200 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 300 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 500 mg to about 1200 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg to about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 5 mg to about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 10 mg to about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 50 mg to about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 100 mg to about 200 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, or about 1500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 5 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 10 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 15 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 20 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 25 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 50 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 75 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 125 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is

administered in a once daily dose of about 150 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 175 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 300 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 600 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 700 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 800 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 900 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1300 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose of about 1500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg to about 2400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 300 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 500 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 800 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1000 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 150 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 200 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 300 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 500 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 600 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 800 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1000 mg to about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100

mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, or about 2500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 150 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 175 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 300 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 600 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 700 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 800 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 900 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1300 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1600 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1700 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1800 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 1900 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2300 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered weekly at a dose of about 2500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg to about 3000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg to about 2400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 300 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 500 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 800 mg to about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1000 mg to about 2500 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 200 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 300 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 400 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 500 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 800 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1000 mg to about 2000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, or about 3000 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 100 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 150 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 200 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 300 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 800 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1000 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 1800 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2000 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2100 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2200 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2300 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2400 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2500 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2600 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2700 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable

salt thereof, is administered monthly at a dose of about 2800 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 2900 mg. In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered monthly at a dose of about 3000 mg.

In some embodiments, the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered every 6 months at a dose of about 600 mg.

In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally or parenterally. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered through one or more tablets as disclosed herein. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered through one or more capsules as disclosed herein. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered through one or more hard gelatin or soft gelatin capsules as disclosed herein.

In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered parenterally. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered through an injection. In some embodiments, the dosage and/or dose amounts disclosed herein of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered through a subcutaneous injection.

Combination Therapy

In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), in combination

with a therapeutically effective amount of one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

In some embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents.

In one embodiment, pharmaceutical compositions comprising a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) in combination with one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

In some embodiments, pharmaceutical compositions comprising a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) in combination with one or more (for example, one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) in combination with a therapeutically

effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a heavily treatment-experienced patient in need thereof a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection in a heavily treatment-experienced patient. In some embodiments, the heavily treatment-experienced patients are patients with multidrug resistant HIV infection.

In certain embodiments, the present disclosure provides a method for treating an HIV infection in a heavily treatment-experienced patient, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof).

In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with two additional

therapeutic agents. In other embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HIV Combination Therapy

In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), and the one or more additional therapeutic agents are both present in the body of the patient. When administered sequentially, the combination may be administered in two or more administrations.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), and the one or more additional therapeutic agents are both present in the body of the patient. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration includes administration of unit dosages of the compounds disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or pharmaceutically acceptable salts thereof), before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is administered first, followed, after a period of hours (for example, 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (for example, 1-12 hours), by administration of a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof).

In some embodiments, co-administration includes administration of unit dosages of the compounds disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), before or after administration of unit dosages of one or more additional therapeutic agents. For example, the compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), may be administered within seconds, minutes, or hours of the administration of the one or more additional therapeutic agents. In some embodiments, a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) within seconds or minutes. In other embodiments, a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is administered first, followed, after a period of hours (for example, 1-12 hours), by

administration of a unit dose of one or more additional therapeutic agents. In yet other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (for example, 1-12 hours), by administration of a unit dose of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof).

For the avoidance of doubt, co-administration of a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, with one or more additional therapeutic agents, may refer to co-administration with one or more of the therapeutic agents described herein.

In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient. In certain embodiments, such a unitary dosage form can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the unitary dosage form can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the unitary dosage form is orally bioavailable and can be dosed orally. In certain embodiments, the unitary dosage form can be a solid dosage form for oral administration.

The compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), in combination with one or more additional therapeutic agents can be administered by any route appropriate to the condition to be treated.

Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

The compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), in combination with one or more additional therapeutic agents can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In certain embodiments, the compounds disclosed can be dosed parenterally. In certain embodiments, the compounds disclosed can be dosed intravenous, subcutaneous, or intramuscular. In certain embodiments, the compounds disclosed are orally bioavailable and can be dosed orally.

In certain embodiments, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV nucleoside reverse transcriptase translocation inhibitors, pharmacokinetic enhancers, and combinations thereof.

In certain embodiments, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a solution formulation, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the solution can contain one or more other compounds useful for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV nucleoside reverse transcriptase translocation inhibitors, pharmacokinetic enhancers, and combinations thereof.

In certain embodiments, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a suspension, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the suspension can contain one or more other compounds useful for treating HIV, such as HIV

protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV nucleoside reverse transcriptase translocation inhibitors, pharmacokinetic enhancers, and combinations thereof.

In certain embodiments, such tablets are suitable for once daily dosing.

HIV Combination Therapy

In some embodiments, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered with a therapeutically effective amount of at least one additional therapeutic agent.

In the above embodiments, the additional therapeutic agent can be an anti-HIV agent selected from the group consisting of combination drugs for treating HIV, other drugs for treating HIV, HIV nucleoside reverse transcriptase translocation inhibitors, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV vaccines, and combinations thereof.

In some embodiments, the additional therapeutic agent is selected from immunomodulators, immunotherapeutic agents, antibody-drug conjugates, gene modifiers, gene editors (such as CRISPR/Cas9, zinc finger nucleases, homing nucleases, synthetic nucleases,

TALENs), and cell therapies such as chimeric antigen receptor T-cell, CAR-T (e.g., YESCARTA® (axicabtagene ciloleucel)), and engineered T cell receptors, TCR-T.

In some embodiments, the additional therapeutic agent is selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV nucleoside reverse transcriptase translocation inhibitors, HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry (fusion) inhibitors, HIV maturation inhibitors, latency reversing agents, capsid inhibitors, immune-based therapies, PI3K inhibitors, HIV antibodies, and bispecific antibodies, and "antibody-like" therapeutic proteins, and combinations thereof.

HIV Combination Drugs

Examples of combination drugs include ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF+FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide); darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat; efavirenz, lamivudine, and tenofovir disoproxil fumarate; lamivudine and tenofovir disoproxil fumarate; tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); KALETRA® (ALUVIA®; lopinavir and ritonavir); TRIUMEQ® (dolutegravir, abacavir, and lamivudine); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); atazanavir and cobicistat; atazanavir sulfate and cobicistat; atazanavir sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; cabotegravir and rilpivirine; cabotegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dolutegravir + lamivudine; lamivudine + abacavir + zidovudine; lamivudine + abacavir; lamivudine + tenofovir disoproxil fumarate; lamivudine + zidovudine + nevirapine; lopinavir + ritonavir; lopinavir + ritonavir + abacavir + lamivudine; lopinavir + ritonavir + zidovudine + lamivudine; tenofovir + lamivudine;

and tenofovir disoproxil fumarate + emtricitabine + rilpivirine hydrochloride; lopinavir , ritonavir, zidovudine and lamivudine; Vacc-4x and romidepsin; and APH-0812.

Other HIV Drugs

Examples of other drugs for treating HIV include acemannan, alisporivir, BanLec, deferiprone, Gamimune, metenkefalin, naltrexone, Prolastin, REP 9, RPI-MN, VSSP, H1viral, SB-728-T, 1,5-dicaffeoylquinic acid, rHIV7-shl-TAR-CCR5RZ, AAV-eCD4-Ig gene therapy, MazF gene therapy, BlockAide, ABX-464, AG-1105, APH-0812, BIT-225, CYT-107, HGTV-43, HPH-116, HS-10234, IMO-3100, IND-02, MK-1376, MK-8507, MK-8591, NOV-205, PA-1050040 (PA-040), PGN-007, SCY-635, SB-9200, SCB-719, TR-452, TEV-90110, TEV-90112, TEV-90111, TEV-90113, RN-18, Immuglo, and VIR-576.

HIV nucleoside reverse transcriptase translocation inhibitors

Examples of HIV nucleoside reverse transcriptase translocation inhibitors ("NRTTIs") include 4'-ethynyl-2-fluoro-2'-deoxyadenosine triphosphate (also known as MK-8591 and EFdA).

HIV Protease Inhibitors

Examples of HIV protease inhibitors include amprenavir, atazanavir, brecanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, tipranavir, DG-17, TMB-657 (PPL-100), T-169, BL-008, and TMC-310911.

HIV Reverse Transcriptase Inhibitors

Examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, rilpivirine, AIC-292, KM-023, and VM-1500. Further examples of non-nucleoside reverse transcriptase inhibitors are disclosed in U.S. Patent Publication No. US 2016/0250215.

Examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddI), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753,

tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, and KP-1461.

In some embodiments, examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, VIDEX® and VIDEX EC® (didanosine, ddl), abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, CMX-157, dapivirine, doravirine, etravirine, OCR-5753, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, GS-9131, GS-9148, KP-1461, and 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

HIV Integrase Inhibitors

Examples of HIV integrase inhibitors include elvitegravir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, dolutegravir, JTK-351, bictegravir, AVX-15567, diketo quinolin-4-1 derivatives, integrase-LEDGF inhibitor, ledgins, M-522, M-532, NSC-310217, NSC-371056, NSC-48240, NSC-642710, NSC-699171, NSC-699172, NSC-699173, NSC-699174, stilbenedisulfonic acid, T-169 and cabotegravir.

Examples of HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) include CX-05045, CX-05168, and CX-14442.

HIV Entry Inhibitors

Examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, gp120 inhibitors, and CXCR4 inhibitors.

Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

Examples of gp41 inhibitors include albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer and sifuvirtide.

Examples of CD4 attachment inhibitors include ibalizumab and CADA analogs

Examples of gp120 inhibitors include Radha-108 (receptol) 3B3-PE38, BanLec, bentonite-based nanomedicine, fostemsavir tromethamine, IQP-0831, and BMS-663068

Examples of CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

HIV Maturation Inhibitors

Examples of HIV maturation inhibitors include BMS-955176 and GSK-2838232.

Latency Reversing Agents

Examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors such as velcade, protein kinase C (PKC) activators, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA (suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), IL-15, JQ1, disulfram, amphotericin B, and ubiquitin inhibitors such as largazole analogs, and GSK-343.

Examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

Examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

Capsid Inhibitors

Examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide, HIV p24 capsid protein inhibitors, AVI-621, AVI-101, AVI-201, AVI-301, and AVI-CAN1-15 series.

Immune-based Therapies

Examples of immune-based therapies include toll-like receptors modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; DermaVir; interleukin-7; plaquenil (hydroxychloroquine); proleukin (aldesleukin, IL-2); interferon alfa; interferon alfa-2b; interferon alfa-n3; pegylated interferon alfa; interferon gamma; hydroxyurea; mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF); ribavirin; rintatolimod, polymer polyethyleneimine (PEI); gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, RPI-MN, GS-9620, and IR-103.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

Examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib, puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, taselisib, AMG-319, AZD-8186, BAY-1082439, CLR-1401, CLR-457, CUDC-907, DS-7423, EN-3342, GSK-2126458, GSK-2269577, GSK-2636771, INCB-040093, LY-3023414, MLN-1117, PQR-309, RG-7666, RP-6530, RV-1729, SAR-245409, SAR-260301, SF-1126, TGR-1202, UCB-5857, VS-5584, XL-765, and ZSTK-474.

HIV Antibodies, Bispecific Antibodies, and "Antibody-like" Therapeutic Proteins

Examples of HIV antibodies, bispecific antibodies, and "antibody-like" therapeutic proteins include DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, bnABs (broadly neutralizing HIV-1 antibodies), BMS-936559, TMB-360, and those targeting HIV gp120 or gp41, antibody-Recruiting Molecules targeting HIV, anti-CD63 monoclonal antibodies , anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs (PGT-121), ibalizumab, Immuglo, MB-66

Examples of those targeting HIV in such a manner include bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117, PGT145, PGT121, MDX010 (ipilimumab), VRC01, A32, 7B2, 10E8, VRC-07-523, VRC-HIVMAB080-00-AB, MGD-014 and VRC07.

Pharmacokinetic Enhancers

Examples of pharmacokinetic enhancers include cobicistat and ritonavir.

Additional Therapeutic Agents

Examples of additional therapeutic agents include the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), WO 2013/159064 (Gilead Sciences), WO 2014/100323 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US 2014/0221378 (Japan Tobacco), US 2014/0221380 (Japan Tobacco), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/006792 (Pharma

Resources), US 20140221356 (Gilead Sciences), US 20100143301 (Gilead Sciences) and WO 2013/091096 (Boehringer Ingelheim).

HIV Vaccines

Examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, ad35-Grin/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-UGR7C, EN41-FPA2, PreVaxTat, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, DNA-Ad5 gag/pol/nef/nev (HVTN505), MVATG-17401, ETV-01, CDX-1401, rcAD26.MOS1.HIV-Env, Ad26.Mod.HIV vaccine, AGS-004, AVX-101, AVX-201, PEP-6409, SAV-001, ThV-01, TL-01, TUTI-16, VGX-3300, IHV-001, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, GI-2010, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine (HIV infection), NCI, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, Vacc-4x + romidepsin, variant gp120 polypeptide vaccine, rAd5 gag-pol env A/B/C vaccine.

HIV Combination Therapy

In a particular embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and

emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA® (KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir; elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; and abacavir sulfate.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with one, two, three, four or more additional therapeutic agents selected from ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); COMPLERA® (EVIPLERA®; rilpivirine, tenofovir disoproxil fumarate, and emtricitabine); STRIBILD® (elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine); TRUVADA® (tenofovir disoproxil fumarate and emtricitabine; TDF +FTC); DESCOVY® (tenofovir alafenamide and emtricitabine); ODEFSEY® (tenofovir alafenamide, emtricitabine, and rilpivirine); GENVOYA® (tenofovir alafenamide, emtricitabine, cobicistat, and elvitegravir); adefovir; adefovir dipivoxil; cobicistat; emtricitabine; tenofovir; tenofovir disoproxil; tenofovir disoproxil fumarate; tenofovir alafenamide; tenofovir alafenamide hemifumarate; TRIUMEQ® (dolutegravir, abacavir, and lamivudine); dolutegravir, abacavir sulfate, and lamivudine; raltegravir; raltegravir and lamivudine; maraviroc; enfuvirtide; ALUVIA® (KALETRA®; lopinavir and ritonavir); COMBIVIR® (zidovudine and lamivudine; AZT+3TC); EPZICOM® (LIVEXA®; abacavir sulfate and lamivudine; ABC+3TC); TRIZIVIR® (abacavir sulfate, zidovudine, and lamivudine; ABC+AZT+3TC); rilpivirine; rilpivirine hydrochloride; atazanavir sulfate and cobicistat; atazanavir and cobicistat; darunavir and cobicistat; atazanavir; atazanavir sulfate; dolutegravir;

elvitegravir; ritonavir; atazanavir sulfate and ritonavir; darunavir; lamivudine; prolastin; fosamprenavir; fosamprenavir calcium efavirenz; etravirine; nelfinavir; nelfinavir mesylate; interferon; didanosine; stavudine; indinavir; indinavir sulfate; tenofovir and lamivudine; zidovudine; nevirapine; saquinavir; saquinavir mesylate; aldesleukin; zalcitabine; tipranavir; amprenavir; delavirdine; delavirdine mesylate; Radha-108 (receptol); lamivudine and tenofovir disoproxil fumarate; efavirenz, lamivudine, and tenofovir disoproxil fumarate; phosphazid; lamivudine, nevirapine, and zidovudine; abacavir; abacavir sulfate; 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA); and bictegravir, or a pharmaceutically acceptable salt thereof.

It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with at least one HIV nucleoside reverse transcriptase translocation inhibitor. In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with at least one HIV nucleoside or nucleotide inhibitor of reverse transcriptase. In a specific embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with at least one HIV nucleoside or nucleotide inhibitor of reverse transcriptase and at least one HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with

one or two HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In a specific embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

In a particular embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)** or a pharmaceutically acceptable salt thereof), is combined with at least one HIV nucleoside reverse transcriptase translocation inhibitor. In some embodiments, the HIV nucleoside reverse transcriptase translocation inhibitor is 4'-ethynyl-2-fluoro-2'-deoxyadenosine triphosphate.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a HIV integrase inhibitor. In some embodiments, the HIV integrase inhibitor is bictegravir.

In a particular embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a nucleotide reverse transcriptase inhibitor. In some embodiments, the nucleotide reverse transcriptase inhibitor is selected from the group consisting of tenofovir, tenofovir disoproxil,

tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, and tenofovir alafenamide hemifumarate.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, bictegravir (or a pharmaceutically acceptable salt thereof), or 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA).

In a particular embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**), or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with a first additional therapeutic agent selected from the group consisting of abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide fumarate and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

In a particular embodiment, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic

agents as disclosed above are administered simultaneously. Optionally, the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a patient. In other embodiments, the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with a first additional therapeutic agent selected from the group consisting of tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir alafenamide fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In a particular embodiment, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of tenofovir disoproxil fumarate, tenofovir disoproxil, and tenofovir disoproxil hemifumarate, and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine. In some embodiments, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered simultaneously. Optionally, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are combined in a unitary dosage form for simultaneous administration to a patient. In other embodiments, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and the first and second additional therapeutic agents as disclosed above are administered sequentially.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is combined with bictegravir or a pharmaceutically acceptable salt thereof.

A compound as disclosed herein (for example, any compound of Formula **(Ia)** or **(Ib)**) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula **(Ia)** or **(Ib)** (for example, from about 1 mg to about 1000 mg of compound).

In some embodiments, a compound as disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) may be combined with one or more additional therapeutic agents in any dosage amount of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof (for example, from about 1 mg to about 1000 mg of compound).

In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with about 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with about 5-10 mg, about 5-15 mg, about 5-20 mg, about 5-25 mg, about 25-30 mg, about 20-30 mg, about 15-30 mg, or about 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**), or a pharmaceutically acceptable salt thereof, is combined with about 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with about 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. A compound as disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) can be combined with the agents provided herein in any dosage amount of the compound (for example, from about 1 mg to about 1000 mg of compound), the same as if each combination of dosages were specifically and individually listed.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with about 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 5-10 mg, about 5-15 mg, about 5-20 mg, about 5-25 mg, about 25-30 mg, about 20-30 mg, about 15-30 mg, or about 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide

hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with about 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide, and about 200 mg emtricitabine. A compound as disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) can be combined with the agents provided herein in any dosage amount of the compound (for example, from about 1 mg to about 1000 mg of compound), the same as if each combination of dosages were specifically and individually listed.

In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 200-250 mg, about 200-300 mg, about 200-350 mg, about 250-350 mg, about 250-400 mg, about 350-400 mg, about 300-400 mg, or about 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. A compound as disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) can be combined with the agents provided herein in any dosage amount of the compound (for example, from about 1 mg to about 1000 mg of compound), the same as if each combination of dosages were specifically and individually listed.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 200-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), is combined with about 200-250 mg, about 200-300 mg, about 200-350 mg, about 250-350 mg, about 250-400 mg, about 350-400 mg, about 300-400 mg, or about 250-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. In certain embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a

pharmaceutically acceptable salt thereof) is combined with about 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil, and about 200 mg emtricitabine. A compound as disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) can be combined with the agents provided herein in any dosage amount of the compound (for example, from about 1 mg to about 1000 mg of compound), the same as if each combination of dosages were specifically and individually listed.

In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 20-80 mg of bictegravir or a pharmaceutically acceptable salt thereof. In some embodiments, a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) is combined with about 50 mg of bictegravir or a pharmaceutically acceptable salt thereof. A compound as disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof) can be combined with the agents provided herein in any dosage amount of the compound (for example, from about 1 mg to about 1000 mg of compound), the same as if each combination of dosages were specifically and individually listed.

In some embodiments of the methods disclosed herein, the methods further comprise administering one other therapeutic agent selected from the group consisting of tenofovir alafenamide, tenofovir alafenamide hemifumarate, and bictegravir, wherein the one other therapeutic agent is simultaneously administerd or co-administered with the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods disclosed herein further comprise administering one other therapeutic agent selected from the group consisting of tenofovir alafenamide hemifumarate and bictegravir, wherein the one other therapeutic agent is simultaneously administerd or co-administered with the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods disclosed herein further comprise simultaneously administering or co-administering tenofovir alafenamide with the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods disclosed herein further comprise simultaneously administering or co-administering tenofovir alafenamide hemifumarate with the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods disclosed herein further comprise simultaneously administering or co-administering bictegravir with the compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof.

In one embodiment, kits comprising a compound disclosed herein (for example, a compound of Formula **(Ia)** or **(Ib)**, or a pharmaceutically acceptable salt thereof) in combination with one or more (for example, one, two, three, one or two, or one to three) additional therapeutic agents are provided.

In some embodiments, kits comprising a compound disclosed herein (for example, a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof), or a pharmaceutically acceptable salt thereof, in combination with one or more (for example, one, two, three, one or two, or one to three) additional therapeutic agents are provided.

Kits and Articles of Manufacture

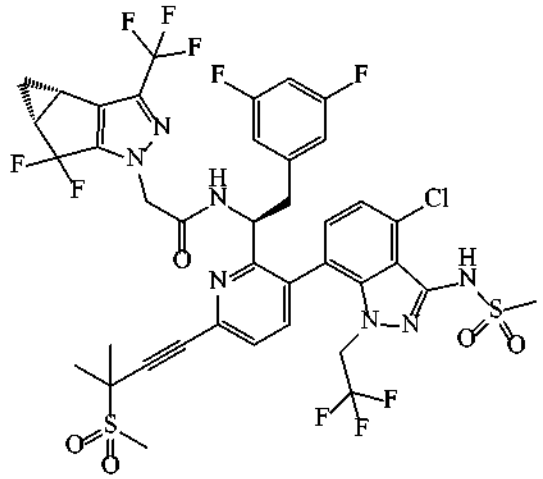
The present disclosure relates to a kit comprising a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. In one embodiment, the kit contains one or more additional therapeutic agents as described herein. The kit can further contain instructions for use, for example, instructions for use in inhibiting an HIV reverse transcriptase, such as for use in treating an HIV infection or AIDS or as a research tool. The instructions for use are generally written instructions, although electronic storage media (for example, magnetic diskette or optical disk) containing instructions are also acceptable.

The present disclosure also relates to a pharmaceutical kit containing one or more containers that contain a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals. In some embodiments, the notice reflects approval by the agency for the manufacture, use, or sale for human administration. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. The kits can be in unit dosage forms, bulk packages (for example, multi-dose packages) or sub-unit doses. Kits can also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (for example, hospital pharmacies and compounding pharmacies).

Also disclosed are articles of manufacture comprising a unit dosage of a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture can further be sterilized and/or sealed.

EXAMPLES

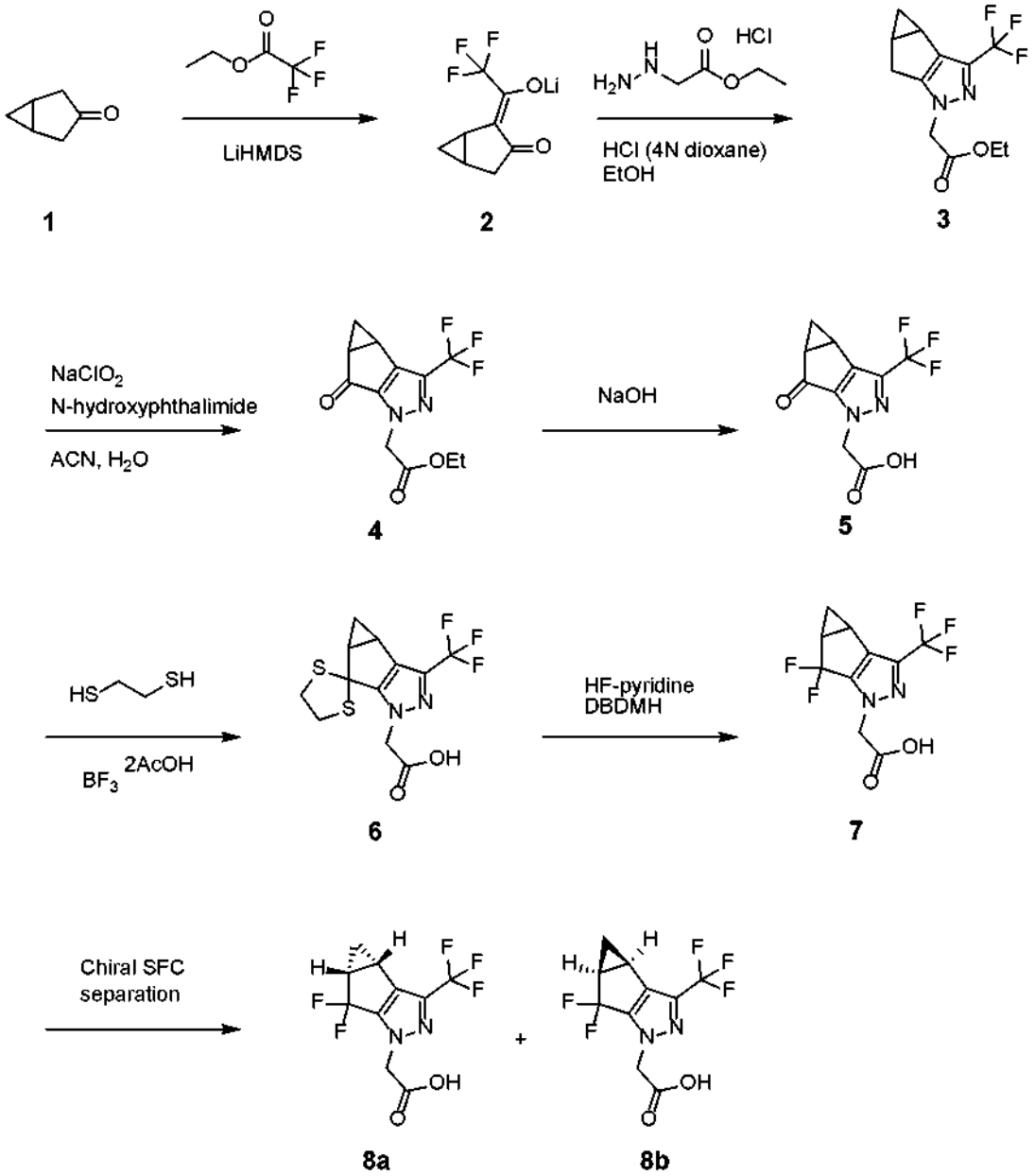
Example 1: Synthesis of the compound of Formula (Ia)



(Ia)

N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(Ia)**, was synthesized according the methods described below and is also described in WO 2018/035359, which is incorporated by reference in its entirety herein. The compound structure for the compound of Formula **(Ia)** provided above may also be named or identified as 1H-Cyclopropa[3,4]cyclopenta[1,2]pyrazole-1-acetamide, N-[(1S)-1-[3-[4-chloro-3-[(methylsulfonyl)amino]-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl]-6-[3-methyl-3-(methylsulfonyl)-1-butyn-1-yl]-2-pyridinyl]-2-(3,5-difluorophenyl)ethyl]-5,5-difluoro-3b,4,4a,5-tetrahydro-3-(trifluoromethyl)-, (3bS,4aR)- under CAS; CAS Registry Number 2189684-44-2.

A. Preparation of compounds (8a) and (8b)



Synthesis of lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate **(2)**: A reactor was charged with bicyclo[3.1.0]hexan-3-one **(1)** (95.6 g, 0.99 mol), ethyl 2,2,2-trifluoroacetate (113.2 mL, 0.95 mol), and THF (50 mL). The reaction mixture was cooled to 0 °C. LiHMDS (lithium bis(trimethylsilyl)amide) (1 L of 1.0 M solution in THF, 1 mol) was added via an addition funnel at a rate to maintain an internal temperature of ≤ 1 °C. After the addition was complete, hexanes (235 mL) was added in a steady stream via an addition funnel and stirred for 15 min. The resultant solids were collected by filtration, washed with hexanes (3 x 400 mL), and dried to provide the title compound.

Synthesis of ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(3)**: A reactor was charged with lithium 2,2,2-trifluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate **(2)** (177.2 g, 0.89 mol) and EtOH (ethanol) (779 mL). The temperature was brought to and maintained at 0 °C. HCl in dioxane (4.0 N, 443 mL) was added via an addition funnel followed by the addition of solid ethyl hydrazinoacetate HCl salt (138.4 g, 0.90 mol). The reaction temperature was adjusted to 35 °C. After 1 h, the reaction volume was reduced by ~40% by distillation at reduced pressure. Water (1.3 L) was added with vigorous agitation and the temperature was adjusted to 15 °C. The resultant solids were collected by filtration, washed with water (3 x 500 mL), then hexanes (3 x 400 mL), and dried to provide the title compound. MS (*m/z*) 275.1 $[M+H]^+$.

Synthesis of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(4)**: A reactor was charged with ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(3)** (291.2 g, 1.06 mol), acetonitrile (1.65 L) and water (825 mL) to which N-hydroxyphthalimide (17.4 g, 0.103 mol) and $NaClO_2$ (41.0 g, 0.45 mol, ~20% of total amount to be added) were added. The reaction mixture was heated to 50 °C and the remaining $NaClO_2$ (163.0 g, 1.80 mol) was added in five portions over 2 h. After consumption of starting material, the temperature was adjusted to 20 °C and aqueous sodium bisulfite (40% w/w, 350 mL) was added via an addition funnel. Ethyl acetate (1.75 L) was added and the layers were separated. The aqueous layer was back extracted with EtOAc (ethyl acetate) (500 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (500 mL) and 1:1 water/brine (500 mL). The organic layer was concentrated under reduced pressure and co-evaporated with IPAc (isopropyl acetate) (300 mL). The crude solid was crystallized from a mixture of IPAc/heptane. The resultant solids were collected by filtration, washed with heptane, and dried to provide the title compound. MS (*m/z*) 289.0 $[M+H]^+$.

Synthesis of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(5)**: To a solution of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(4)** (80.40 g, 278.95 mmol) in 2-MeTHF (2-methyltetrahydrofuran) (167 mL) was added 2M aqueous sodium hydroxide (167 mL). After 25 minutes of stirring at room temperature, the reaction mixture was diluted with 2-MeTHF and was slowly acidified by the dropwise addition of concentrated HCl. The organic layer was isolated and the aqueous layer was extracted with an additional portion of 2-MeTHF. The combined organic layers were washed with saturated

aqueous sodium chloride, then dried over sodium sulfate, filtered, and concentrated. The resulting oil was taken in ethyl acetate. Hexanes was added with vigorous stirring until solid formation was observed. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 259.00 $[M-H]^-$.

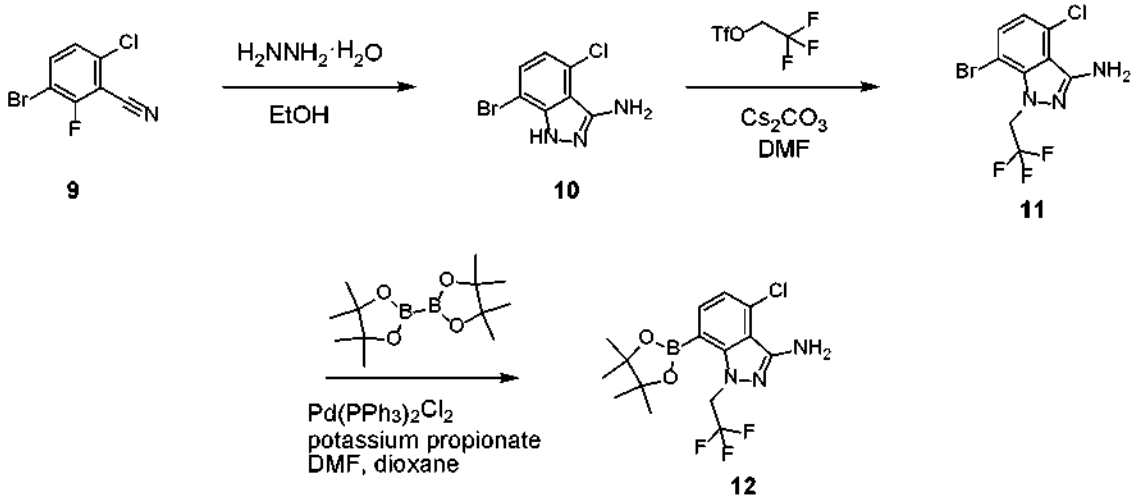
Synthesis of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid **(6)**: To a solution of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(5)** (3.0 g, 11.5 mmol) in DCM (dichloromethane) (25 mL) was added 1,2-ethanedithiol (1.07 mL, 12.68 mmol) followed by boron trifluoride-acetic acid complex (4.0 mL, 28.8 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water (60 mL) and 2-MeTHF (60 mL). The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated. The crude material was dissolved in ethyl acetate (2 mL) and the solution diluted with hexanes (12 mL) with vigorous stirring to provide a solid. The solid was isolated by filtration and dried to provide the title compound. MS (*m/z*) 337.12 $[M+H]^+$.

Synthesis of 2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(7)**: To a suspension of 1,3-dibromo-5,5-dimethylhydantoin (12.75 g, 44.6 mmol) in DCM (35 mL) was added pyridine hydrofluoride (5.0 mL) at 0 °C. The suspension was stirred at 0 °C for 10 minutes. To the suspension was added a solution of 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetic acid **(6)** (5.00 g, 14.9 mmol) dropwise. After addition was complete, the reaction mixture was stirred at 0 °C for an additional 15 minutes. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution (300 mL) with vigorous stirring. The organic layer was removed and the aqueous layer was acidified to pH ~1 with concentrated HCl. The aqueous phase was extracted with three portions of MTBE (methyl *tert*-butyl ether). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting solid was taken in MTBE (16 mL) and filtered to remove any resulting solid. The solution was then extracted with 2N NaOH (16 mL). The aqueous layer was diluted with water (16 mL) with vigorous stirring and continued stirring at room temperature for 15 minutes. The resulting solid was removed by filtration. The aqueous layer was acidified by slow, dropwise addition of concentrated HCl to pH ~1 with vigorous stirring to provide a solid precipitate. The solid was isolated by filtration to provide the title compound. MS (*m/z*) 281.12 $[M+H]^+$.

Synthesis of 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(8a)** and 2-((3bR,4aS)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(8b)**: 2-(5,5-Difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid was separated to its constituent enantiomers, the title compounds, by chiral SFC under the following conditions: Instrument: Thar 350 preparative SFC; Column: ChiralPak IC-10 u, 300×50mmI.D; Mobile phase: 35% Isopropanol (0.1% $NH_3 \cdot H_2O$) and CO_2; Flow rate: 200 mL/min; Column temperature: 38 °C; UV detection: 220 nm; Sample preparation: Compound was dissolved in isopropanol to ~ 45 mg/mL; Injection: 6.5 mL per injection. Analytical SFC [mobile phase: A for CO_2 and B for Isopropanol (0.05% DEA); Gradient: B 20%; A; Flow rate: 2.35 mL/min; Column: Chiralpak IC-3, 150×4.6 mm, 3um; Wavelength: 254 nm] **(8a)**: t= 3.39 min, **(8b)**: t= 2.17 min.

Compound **(8a)**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.93 (s, 2H), 2.52 – 2.43 (m, 2H), 1.44 – 1.38 (m, 1H), 1.15 (m, 1H).

B. Preparation of compound (12)

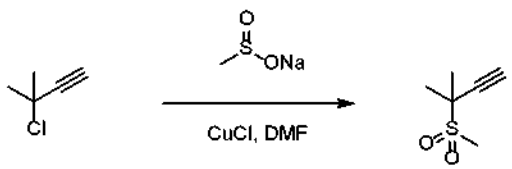


Synthesis of 7-bromo-4-chloro-1H-indazol-3-amine **(10)**: To 3-bromo-6-chloro-2-fluorobenzonitrile **(9)** (13.9 g, 59.3 mmol) in EtOH (ethanol) (60 mL) was added hydrazine monohydrate (5.77 mL). The reaction mixture was heated to 80 °C for 3 h. After cooling to ambient temperature, EtOH (20 mL) was added to allow for stirring. The solids were isolated by filtration, washed with cold EtOH, and dried to provide the title compound. MS (*m/z*) 247.9 $[M+H]^+$.

Synthesis of 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine **(11)**: A reactor was charged with 7-bromo-4-chloro-1H-indazol-3-amine **(10)** (397.2 g, 1.6 mol) and Cs_2CO_3 (1052 g, 3.2 mol) then diluted with DMF (dimethylformamide) (4000 mL). To this was slowly added 2,2,2-trifluoroethyl trifluoromethanesulfonate (463.2 g, 1.9 mol) via addition funnel. Upon completion of the addition, the reaction mixture was allowed to stir for 1 hour, at which time, H_2O (16 L) was added slowly. Upon completion of the addition, the mixture was allowed to stir for 12 hours at 15 °C. The slurry was filtered and the collected solids were suspended in DMF (800 mL). To this was added H_2O (4800 mL) and the resulting solids were collected by filtration and dried to provide the title compound. MS (*m/z*) 330.1 $[M+H]^+$.

Synthesis of 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine **(12)**: A reaction vessel was charged with 7-bromo-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine **(11)** (15.00 g, 45.66 mmol), bis(pinacolato)diboron (17.39 g, 68.49 mmol), potassium propionate (15.36 g, 136.98 mmol), dioxane (90 mL), and DMF (dimethylformamide) (30 mL). Bis(triphenylphosphine)palladium(II) dichloride (0.64 g, 0.91 mmol) was added and the reaction solution degassed by bubbling argon for 2 min. The reaction mixture was heated to 105 °C for 4 hrs. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite and silica gel while washing with EtOAc. The filtrate was washed with a 5% LiCl solution and brine. The organic layers were separated, dried, and concentrated under reduced pressure. The residue was treated with IPAc/heptane (1/10) at 60 °C then cooled to ambient temperature and stirred for 15 h. The solids were collected by filtration and dried to afford the title compound. MS (*m/z*) 376.7 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, 1H), 7.06 (d, 1H), 5.55 (s, 2H), 5.45 (q, 2H), 1.32 (s, 12H).

C. Preparation of compound (14)

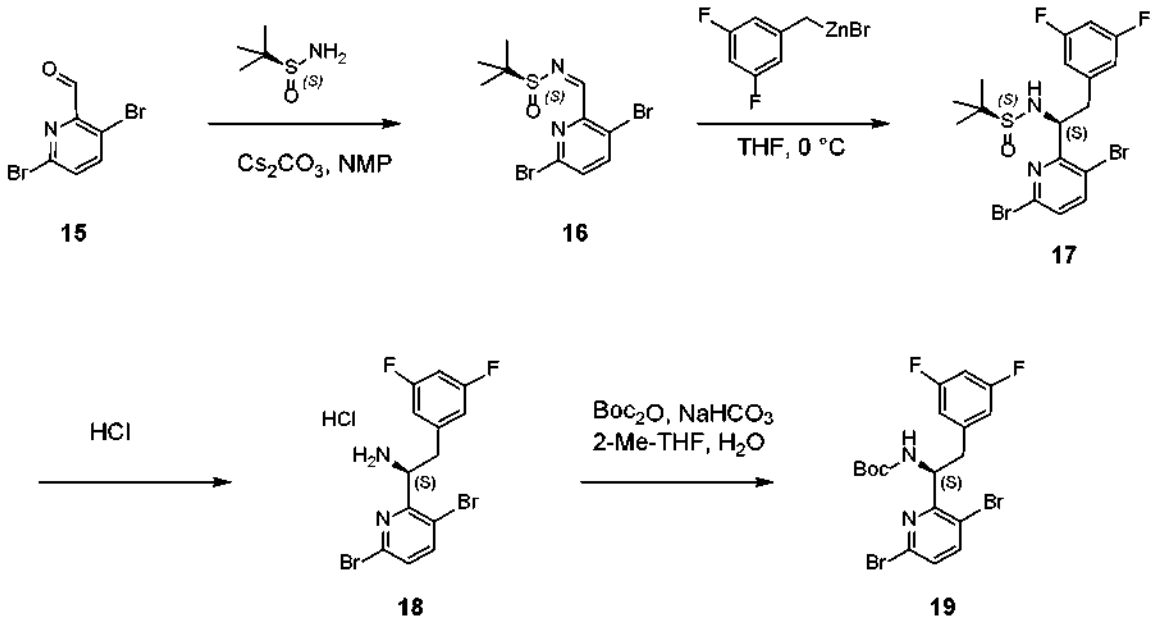


13 **14**

Synthesis of 3-methyl-3-(methylsulfonyl)but-1-yne **(14)**: To a stirred suspension of sodium methanesulfinate (18.47 g, 175.5 mmol) and copper(I) chloride (1.45 g, 14.6 mmol) in DMF (dimethylformamide) (50 mL) was added 3-chloro-3-methylbut-1-yne **(13)** (15.00 g, 146.3 mmol, 16.4 mL) dropwise. The resulting reaction mixture was heated to 40 °C and stirred for 16

h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The solution was washed with water and brine. The organic layer was collected and dried over sodium sulfate, then filtered. The solution was concentrated under vacuum and purified by silica gel chromatography to provide the title compound. Mp: 114.8–115.5 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 3.04 (s, 3H), 2.58 (s, 1H), 1.67 (s, 6H).

D. Preparation of compound (19)



15 16 17 18 19

Synthesis of (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide **(16)**: 3,6-Dibromopicolinaldehyde **(15)** (76.0 g, 0.287 mol) and (S)-2-methylpropane-2-sulfinamide (36.51 g, 0.301 mol) were combined in NMP (*N*-methyl-2-pyrrolidone) (200 mL). To the reaction mixture was added Cs_2CO_3 (41.94 g, 0.316 mol) as a solid in one portion. The reaction mixture was stirred for 2h then cooled to 5 °C. Water (1.3 L) was added to the reaction mixture. The resulting suspension was stirred for 1h, the solids were isolated by filtration, then washed with water (5 x 100 mL) and dried to provide the title compound. MS (*m/z*) 368.9 $[M+H]^+$.

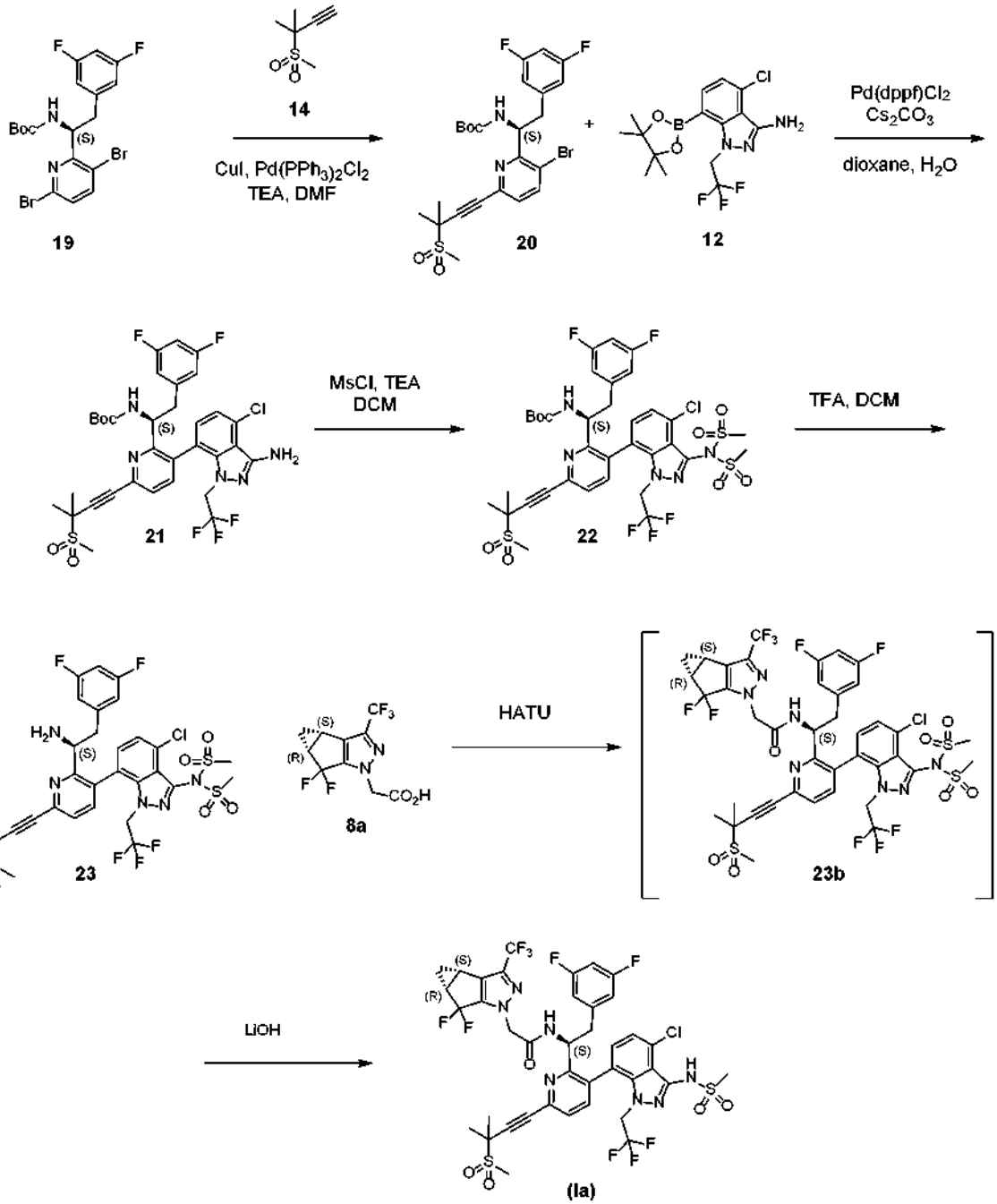
Synthesis of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide **(17)**: A reaction vessel was charged with (S)-N-((3,6-dibromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide **(16)** (65.5 g, 177.95 mmol) followed by DMF (dimethylformamide) (260 mL). The mixture was stirred for 5 min until homogeneous and the solution was cooled to 8 °C. To the reaction mixture was added (3,5-difluorobenzyl)zinc bromide (0.5 M in THF (tetrahydrofuran), 516.04 mL) dropwise over 90 mins. The mixture was stirred for an additional 2.5h. To the reaction mixture, 5% AcOH (acetic

acid) in water (640 mL) was added over 10 mins followed by CPME (cyclopentyl methyl ether) (320 mL) in one portion. The mixture was stirred for 5 mins, warmed to room temperature, and the layers were separated. The organic layer was washed with 5% AcOH (320 mL) then treated with 0.5 M NaOH (330 mL) and washed with brine. The organic layer was collected, dried with Na_2SO_4, and filtered. To the crude mixture was added MeOH (methanol) (33 mL). To the stirring mixture was added dropwise 3M HCl in CPME (128 mL) over 15 mins. After stirring for 1h, the precipitate was removed by filtration. The filtrate was diluted with hexane (300 mL) and the product was extracted with water (450 mL). The aqueous layer was basified with 8 M NaOH and extracted with CPME (375 mL). The organic layer was washed with brine, dried over Na_2SO_4, and filtered to provide the title compound in solution which was used directly in the next reaction. MS (*m/z*) 497.0 $[M+H]^+$.

Synthesis of (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine **(18)**: The resulting solution of (S)-N-((S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide **(17)** was diluted with CPME to a volume of 700 mL to which acetonitrile (350 mL) was added. To the stirring mixture, concentrated HCl (37%, 16.4 mL) was added dropwise over 10 mins at room temperature. The thick slurry was vigorously stirred for 4h. The solids were filtered and washed with 2:1 CPME:ACN to provide the title compound. MS (*m/z*) 393.3 $[M+H]^+$.

Synthesis of tert-butyl (S)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(19)**: A reaction vessel was charged with 2-MeTHF (190 mL), water (190 mL), and (S)-1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine **(18)** (46.9 g, 0.11 mol) followed by portionwise addition of $NaHCO_3$ (30.34 g, 0.36 mol). The reaction mixture was cooled to 5 °C and di-tert-butyl dicarbonate (27.47 g, 0.13 mol) was added. The reaction mixture was stirred at 0 °C for 2h and ambient temperature for 2h. The reaction mixture was diluted with water and extracted with MTBE (methyl *tert*-butyl ether). The organic layers were washed with brine, dried, and concentrated. Crude compound was purified by column chromatography on silica to provide the title compound. MS (*m/z*) 492.8 $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 7.85 (d, 1H), 7.42 (d, 1H), 6.90 – 6.72 (m, 3H), 5.33 (dd, 1H), 3.10 (dd, 1H), 2.92 (dd, 1H), 1.36 (s, 9H).

E. Preparation of the compound of Formula (Ia)



Synthesis of tert-butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(20)**: A reactor was charged with tert-butyl (*S*)-(1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(19)** (50.00 g, 101.8 mmol), 3-methyl-3-methylsulfonyl-but-1-yne **(14)** (17.86 g, 122.2 mmol), DMF (dimethylformamide) (90 mL), and Et_3N (trimethylamine) (42.5 mL, 305.4 mmol). The reaction mixture was heated to 50 °C. Bis(triphenylphosphine)palladium(II) dichloride (2.14 g, 3.1 mmol) and copper(I) iodide (0.58 g, 3.1 mmol) were added. After 30 min, the reaction mixture was diluted with MeCN (acetonitrile) (200 mL) and then 7% aq. NH_4Cl (200 mL) was added dropwise. A slurry was

formed and adjusted to ambient temperature. After 3h, the solids were collected by filtration. The cake was washed with MeCN/water twice (1:1, 75 mL) and MTBE (methyl *tert*-butyl ether) (75 mL). The solid was dried to provide the title compound. MS (*m/z*) 556 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.15 (m, 1H), 6.70 – 6.55 (m, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 5.57 – 5.45 (m, 1H), 3.21 – 3.05 (m, 4H), 2.99 – 2.88 (m, 1H), 1.80 (s, 6H), 1.40* (s, 7H), 1.30* (s, 2H). *denotes presence of atropisomers in 4.6:1 ratio.

Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(21)**: tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(20)** (1000.0 mg, 1.79 mmol), 4-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine **(12)** (808.5 mg, 2.15 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (65.6 mg, 0.09 mmol), and cesium carbonate (876.7 mg, 2.69 mmol) were charged in a round bottom flask and placed under argon. Dioxane (10 mL) and water (2 mL) were added, and the suspension was degassed by bubbling argon for 60 seconds. After degassing, the reaction flask was fitted with a reflux condenser and heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and the aqueous layer was removed. The organic layer was concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography to provide the title compound. MS (*m/z*) 726.1 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.69 – 7.55 (m), 7.55 – 7.42 (m), 7.16 – 7.06 (m), 7.07 – 6.96 (m), 6.89 (d), 6.60 (tt), 6.44 (dd), 6.20 (d), 6.16 (d), 6.08 (s), 5.69 – 5.53 (m), 5.29 (s), 5.26 (d), 4.95 – 4.85 (m), 4.64 (q), 4.59 – 4.46 (m), 4.36 – 4.19 (m), 3.94 – 3.76 (m), 3.64 – 3.54 (m), 3.18 (s), 3.17 (s), 3.01 – 2.84 (m), 2.78 – 2.68 (m), 1.86 – 1.82 (m), 1.38 (s), 1.34 (s), 1.26 (s), 1.23 (s), 1.15 (s).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(22)**: tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(21)** (37.89 g, 52.18 mmol) was dissolved in methylene chloride (380 mL) with stirring at ambient temperature. Triethylamine (21.82 mL, 156.54 mmol) was added, followed by slow addition of methanesulfonyl chloride (8.08 mL, 104.36 mmol). When the reaction was complete, water (200 mL) was added and stirred for 0.5 hours. The organic layer was separated and the aqueous layer was extracted with methylene chloride once. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and

concentrated to a small volume. Hexanes was added. The liquid suspension was decanted. The remaining solid was dried under reduced pressure to afford the title compound. MS (*m/z*): 882.69 $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 7.87 (d), 7.83 (d), 7.76 (s), 7.74 (s), 7.69 (s), 7.67 (s), 7.65 (s), 7.52 – 7.47 (m), 7.46 (s), 7.37 (d), 7.33 (d), 7.11 – 7.03 (m), 4.79 – 4.55 (m), 4.51 (t), 4.36 (dt), 4.20 – 4.05 (m), 3.64 (s), 3.62 (s), 3.60 (s), 3.59 (s), 3.23 (s), 3.04 (d), 3.01 (d), 2.95 – 2.83 (m), 1.81 (s), 1.34 (s), 1.29 (s), 0.98 (s).

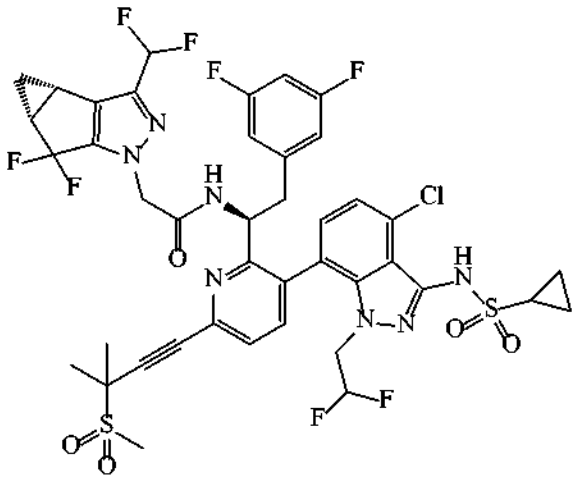
Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide **(23)**: To tert-butyl (S)-(1-(3-(4-chloro-3-(N-(methylsulfonyl)methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(22)** (39 g, 44 mmol) dissolved in methylene chloride (120 mL) was added trifluoroacetic acid (80 mL). The reaction mixture was stirred at ambient temperature for 50 minutes. The reaction mixture was diluted with methylene chloride and slowly poured into ice cold saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to dryness to afford the title compound. MS (*m/z*): 782.84 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.61 (d), 7.54 – 7.44 (m), 7.40 (d), 7.33 (d), 7.20 (d), 6.66 – 6.57 (m), 6.44 (d), 6.33 (d), 6.17 (d), 4.64 (s), 3.68 (s), 3.64 (s), 3.61 (s), 3.55 (s), 3.19 (s), 3.05 (dd), 2.85 – 2.72 (m), 1.86 (s), 1.62 (s).

Synthesis of N-((S)-1-(3-(4-chloro-3-(methylsulfonamido)-1-(2,2,2-trifluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(Ia)**: (S)-N-(7-(2-(1-Amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)-N-(methylsulfonyl)methanesulfonamide **(23)** (1757 mg, 2.25 mmol), 2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(8a)** (666 mg, 2.36 mmol), and HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (854 mg, 2.25 mmol) were charged in a round bottom flask and dissolved in DMF (dimethylformamide) (10.0 mL). To the solution was added N,N-diisopropylethylamine (0.80 mL, 4.49 mmol) at a rapid dropwise rate. After addition was complete, the reaction mixture was stirred at room temperature for 15 minutes to provide the intermediate **(23b)** which was not isolated (MS (*m/z*) 1046.65 $[M+H]^+$). To the solution was added a 2 N aq. sodium

hydroxide solution (5.0 mL). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was collected and washed with two portions of 5% lithium chloride solution followed by brine. The organic layer was isolated, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to yield the title compound **(Ia)** as an amorphous solid. MS (*m/z*) 968.24 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.87 – 7.57 (m), 7.33 – 7.09 (m), 6.80 – 6.70 (m), 6.54 (d), 6.47 (d), 6.37 – 6.19 (m), 5.02-4.94(m), 4.90 – 4.70 (m), 4.70 – 4.51 (m), 3.94 (dq), 3.32-3.28 (m), 3.23 (d), 3.07 (dd, *J* = 13.1, 7.6 Hz), 2.93 (dd), 2.68 – 2.35 (m), 1.81 (s), 1.41 (q), 1.12 – 1.00 (m). ^{19}F NMR (377 MHz, methanol-d_4) δ –63.65 , –71.78 (t), –72.35 (t), –82.75 (dd), –105.70 (ddd), –111.73 – – 113.10 (m).

Compound **(23b)** was isolated and characterized. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d), 8.99 (d), 7.96 (d), 7.83 (d), 7.80 (d), 7.76 (d), 7.45 (d), 7.41 (d), 7.31 (d), 7.02 (tt), 6.92 (m), 6.91 (d), 6.48 (m), 4.92 (m) 4.88 (d), 4.79 (d), 4.73 (d), 4.71 (m), 4.69 (m), 4.62 (m), 4.60 (m), 4.38 (dq), 4.12 (dq), 3.68 (s), 3.66 (s), 3.63 (s), 3.58 (s), 3.26 (s), 3.12 (dd), 3.05 (dd), 2.97 (dd), 2.78 (dd), 2.59 (m), 2.53 (m), 1.75 (s), 1.39 (m), 0.98 (m).

Example 2: Synthesis of the compound of Formula (Ib)

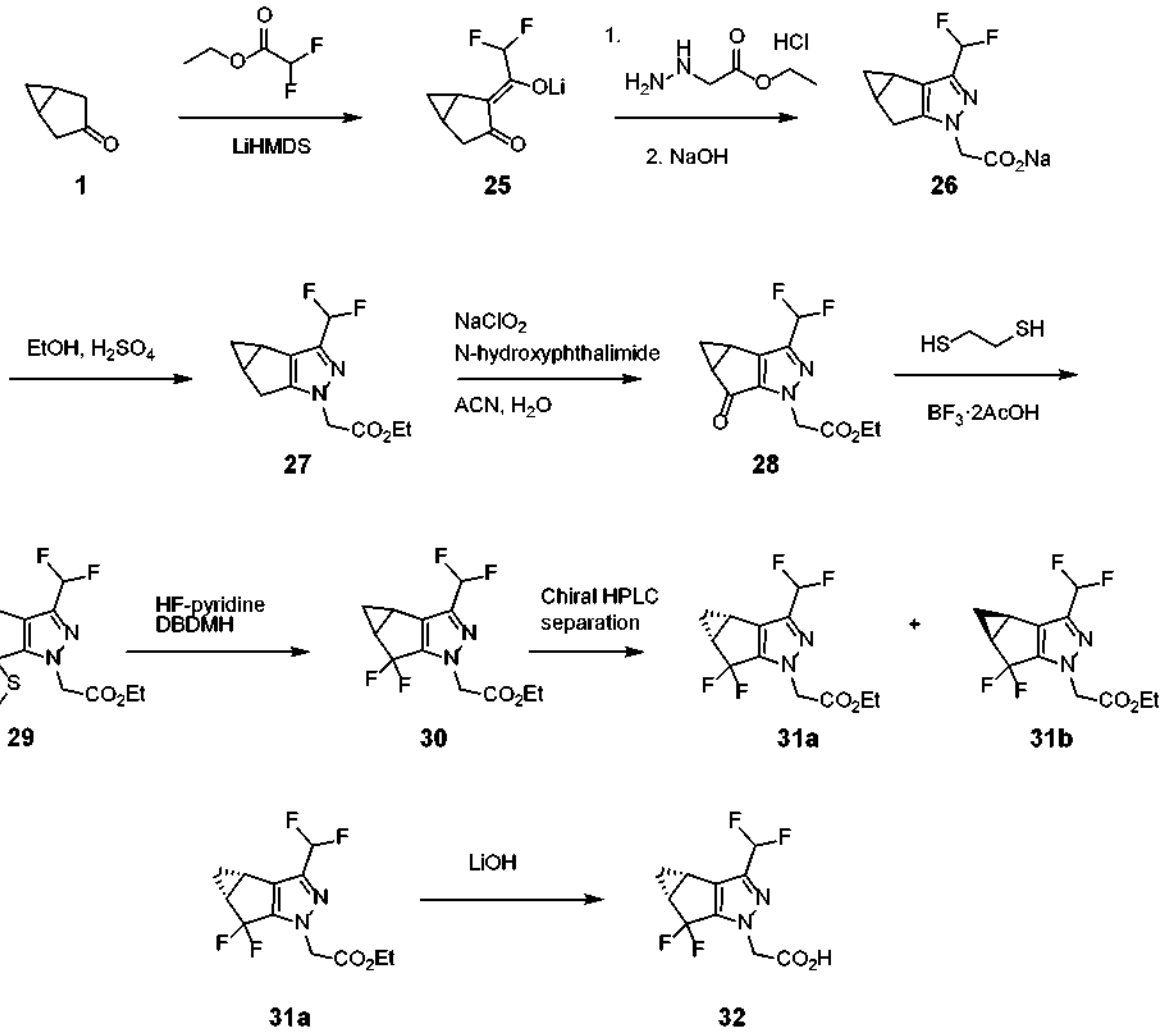


(Ib)

N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(Ib)**, was synthesized according the methods described below and is also described in WO 2018/035359, which is incorporated by reference in its entirety herein. The compound structure for the compound of Formula **(Ib)**

provided above may also be named or identified as 1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-1-acetamide, N-[(1S)-1-[3-[4-chloro-3-[(cyclopropylsulfonyl)amino]-1-(2,2-difluoroethyl)-1H-indazol-7-yl]-6-[3-methyl-3-(methylsulfonyl)-1-butyn-1-yl]-2-pyridinyl]-2-(3,5-difluorophenyl)ethyl]-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-, (3bS,4aR)-under CAS; CAS Registry Number 2189684-45-3.

A. Preparation of compound (32)



Synthesis of lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate **(25)**: The title compound **(25)** was prepared according to the method described for the synthesis of compound **(2)**, utilizing ethyl 2,2-difluoroacetate. ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.17 (t, *J* = 53.6 Hz, 1H), 2.78-2.73 (m, 1H), 2.44-2.39 (m, 1H), 2.25-2.24 (m, 1H), 1.70-1.69 (m, 1H), 1.22-1.14 (m, 1H), 0.31-0.27 (m, 1H).

Synthesis of sodium 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(26)**: Me-THF (1.32 L) was added to a 4 L

reactor, followed by lithium 2,2-difluoro-1-(3-oxobicyclo[3.1.0]hexan-2-ylidene)ethan-1-olate **(25)** (247 g, 1.32 mol). HCl (4 N in dioxane) (0.685 L, 2.74 mol) was slowly added to the mixture maintaining an internal temperature around 20 °C. Following addition of ethyl hydrazinoacetate hydrochloride (212.05 g, 1.372 mol), the resulting mixture was stirred at 20 °C for 4 hours. The reaction mixture was heated to 50 °C for overnight. 10 N aqueous NaOH (0.548 L, 5.48 mol) was slowly added to the reaction mixture and the internal temperature was maintained at 20 °C. After addition, 300 mL MeTHF was added, and the resultant suspension was stirred at 20 °C for 3 hours. The suspension was drained and filtered. The filter cake was washed with hexane (1 L) and dried in a vacuum oven at 56 °C to obtain the title compound which was used directly in the next step. MS (m/z) 229.1 $[M–Na+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(27)**: Ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(26)** from the previous step was charged in a 4 L reactor, followed by the addition of EtOH (3.5 L) and concentrated H_2SO_4 (152 mL, 2.74 mol). The resulting mixture was stirred under reflux for 2 hours. The EtOH was reduced under vacuo to 150 mL. H_2O (500 mL) was then added slowly. Solids were collected and washed with H_2O and $NaHCO_3$, followed by hexane (500 mL). The solid was dried in the oven at 45 °C to obtain the title compound. MS (m/z) 257.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(28)**: The title compound **(28)** was prepared according to the method presented for the synthesis of compound **(4)** utilizing ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(27)**. MS (m/z) 271.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate **(29)**: To ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(28)** (148.5 g, 0.55 mol) in DCM (2.0 L) was added ethane-1,2-dithiol (88.0 g, 0.94 mol) in one portion followed by BF_3•2AcOH (175.8 g, 0.94 mol). The reaction was stirred at room temperature for 12 h. The system was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (1000 mL). The organic layer was separated, washed with brine (500 mL), and dried over Na_2SO_4. Solvents

were removed in vacuo and the residue was purified by silica gel column chromatography to provide the title compound. MS (m/z): 347.1 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(30)**: A solution of DBDMH (99 g, 0.35 mol) in DCM (120 mL) was cooled to –8 °C in a teflon bottle. HF/Py (120 mL) was added drop-wise over a period of 30 min. The reaction was stirred at –78 °C for 30 min. A solution of ethyl 2-(3-(difluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate **(29)** (40 g, 0.12 mol) in DCM (80 mL) was added drop-wise over a period of 15 min at –78 °C. The resulting mixture was stirred for 30 min, then slowly warmed to –30 °C and stirred for 1.5 h. The reaction mixture was slowly poured into aq. $NaHCO_3$ (500 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic layer was washed with 10% aq. $Na_2S_2O_3$ (500 mL), brine (500 mL), and dried over Na_2SO_4. Solvents were removed in vacuo to afford the crude product, which was further purified by column chromatography to provide the title compound. MS (m/z): 293.2 $[M+H]^+$.

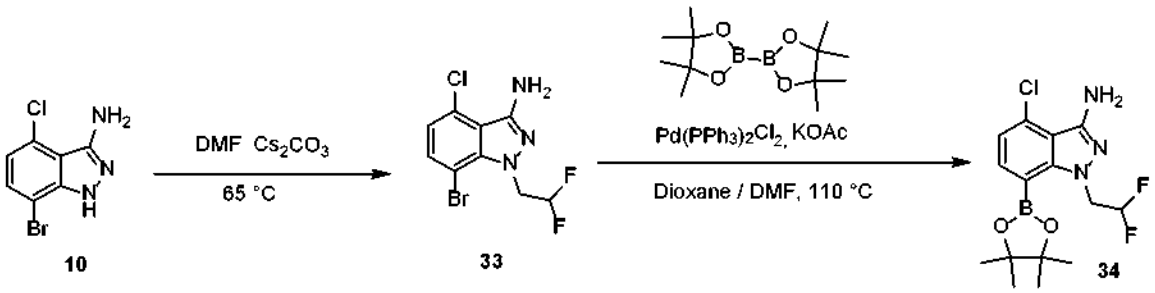
Separation of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(31a)** and ethyl 2-((3bR,4aS)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(31b)**: Ethyl 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate was separated to its constituent enantiomers, the title compounds **(31a)** and **(31b)**, by chiral HPLC under the following conditions: Column: ChiralPak AD; Mobile phase: Hex/3C EtOH = 95/5; Room temperature; UV detection: 250 nm. Analytical HPLC [mobile phase: Hex/3C EtOH = 95/5; Flow rate: 0.75 mL/min; Column: Chiralpak AD-H, 150×4.6 mm, 5um; Wavelength: 220 nm] **(31a)**: t= 5.30 min, **(31b)**: t= 7.00 min.

Compound **(31a)**: ^1H NMR (400 MHz, chloroform-*d*) δ 6.63 (t, J = 54.8 Hz, 1H), 4.83 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.48-2.45 (m, 2H), 1.38-1.36 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.13-1.12 (m, 1H).

Synthesis of 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(32)**: To a solution of ethyl 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate **(31a)** (26 g, 89.0 mmol) in THF (180

mL), MeOH (90 mL), and water (90 mL) was added LiOH (5.13 g, 213.5 mmol). The mixture was stirred for 4 h. The mixture was concentrated to remove most of the THF and MeOH, and the aqueous layer was acidified by 1N HCl to adjust the pH to 2-3, then extracted with ethyl acetate (2 x 600 mL). The organic phase was separated and combined, dried over Na_2SO_4, filtered, and concentrated in vacuum to provide the title compound. MS (m/z) 265.0 $[M+H]^+$.

B. Preparation of compound (34)

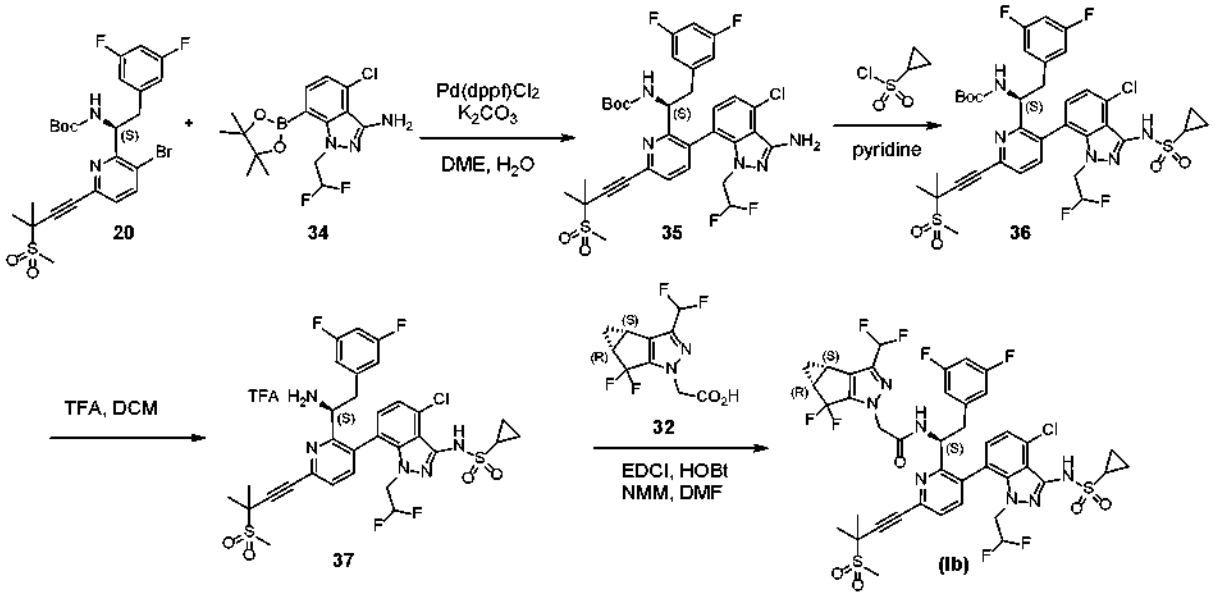


Synthesis of 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine **(33)**: To a 2000 mL 4-necked round-bottom flask was placed 7-bromo-4-chloro-1H-indazol-3-amine **(10)** (130 g, 527.40 mmol, 1.00 equiv), N,N-dimethylformamide (1300 mL), and Cs_2CO_3 (260 g, 797.99 mmol, 1.50 equiv) with stirring for 20 min, followed by the addition of 1,1-difluoro-2-iodoethane (122 g, 635.59 mmol, 1.20 equiv). The resulting mixture was stirred overnight at 65 °C, then cooled to room temperature, quenched by the addition of 3 L of water/ice, and extracted with 3 x 1.5 L of ethyl acetate. The combined organic layer was washed with 1 x 1.5 L of H_2O, 1 x 1.5 L of brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and recrystallized from ethanol to afford the title compound. MS (m/z) 312.1 $[M+H]^+$.

Synthesis of 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine **(34)**: To a 3000-mL 4-necked round-bottom flask that was purged and maintained with an inert atmosphere of nitrogen was placed 7-bromo-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-amine **(33)** (80 g, 257.63 mmol, 1.00 equiv), 1,4-dioxane (800 mL), N,N-dimethylformamide (800 mL), KOAc (76 g, 774.40 mmol, 3.00 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (197 g, 775.78 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8 g, 11.40 mmol, 0.04 equiv). The mixture was stirred for 4 h at 110 °C, then cooled to room temperature, quenched by the addition of 5 L of water/ice, and extracted with 2 x 2 L of ethyl acetate. The combined organic layer was washed with 1 x 1 L of H_2O, 1 x 1 L of brine, dried over anhydrous sodium sulfate, and concentrated under vacuum.

The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10) to afford the title compound. MS (*m/z*): 358 $[M+H]^+$. ^{1}H-NMR: (DMSO-d_6, 300MHz, ppm): δ7.63-7.66 (1H, d), 7.00-7.03 (1H, d), 6.06-6.43 (1H, t), 5.46 (2H, s), 4.90-5.01 (2H, t), 1.34 (12H, s).

C. Preparation of the compound of Formula (Ib)



Synthesis of tert-butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate

(35): tert-Butyl (S)-(1-(3-bromo-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(20)** (300 mg, 0.53 mmol), 4-chloro-1-(2,2-difluoroethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-amine **(34)** (250 mg, 0.7 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14 mg, 0.016 mmol), and potassium carbonate (186 mg, 1.35 mmol) were charged in a microwave tube and placed under argon. Dimethoxyethane (2.5 mL) and water (0.3 mL) were added, and the reaction mixture was heated to 130 °C in a microwave reactor (Biotage® Initiator+) for 7 minutes. The reaction mixture was cooled to room temperature, and partitioned between EtOAc and 0.1 N HCl. The aqueous layer was removed and the organic layer was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography to provide the title compound. MS (m/z) 708.20 $[M+H]^+$). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.91 – 7.50 (m), 7.28 – 6.89 (m), 6.88 – 6.65 (m), 6.56 (dd), 6.46 – 6.17 (m), 6.08 – 5.60 (m), 4.76 – 4.47 (m), 4.04 – 3.73 (m), 3.73 – 3.41 (m), 3.22 (s), 3.17 – 2.69 (m), 1.80 (s), 1.29 (d), 0.98 (d).

Synthesis of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(36)**: tert-Butyl (S)-(1-(3-(3-amino-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(35)** (700 mg, 0.99 mmol) and 4-dimethylaminopyridine (24 mg, 0.2 mmol) were dissolved in pyridine (2 mL) with stirring at ambient temperature. Cyclopropane-1-sulfonyl chloride (222 μL, 2.2 mmol) was then added. The reaction mixture was stirred at 70 °C until the reaction was complete. Water was added and stirred for 1 hour, and the resulting precipitate was collected by vacuum filtration and then dissolved in methylene chloride, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica chromatography to afford the title compound. MS (m/z): 812.44 $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 7.93 – 7.58 (m), 7.50 – 7.15 (m), 7.00 (dd), 6.82 – 6.51 (m), 6.47 – 6.29 (m), 6.18 – 5.65 (m), 4.77 – 4.43 (m), 4.31 – 4.08 (m), 3.99 – 3.63 (m), 3.22 (s), 3.18 – 2.71 (m), 1.80 (s), 1.28 (s), 1.20 – 0.76 (m).

Synthesis of (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide **(37)**: To a solution of tert-butyl (S)-(1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamate **(36)** (705 mg, 0.87 mmol) in methylene chloride (5 mL) was added trifluoroacetic acid (3 mL). The reaction mixture was stirred for 1 hour, then slowly poured into a saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford the title compound. MS (m/z): 712.34 [M+H]+. ^1H NMR (400 MHz, methanol-d_4) δ 7.93 - 7.58 (m), 7.50 - 7.15 (m), 7.00 (dd), 6.82 - 6.51 (m), 6.47 - 6.29 (m), 6.18 - 5.65 (m), 4.77 - 4.43 (m), 4.31 - 4.08 (m), 3.99 - 3.63 (m), 3.22 (d), 3.18 - 2.71 (m), 1.80 (d), 1.28 (s), 1.20 - 0.76 (m).

Synthesis of N-((S)-1-(3-(4-chloro-3-(cyclopropanesulfonamido)-1-(2,2-difluoroethyl)-1H-indazol-7-yl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide **(Ib)**: (S)-N-(7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-4-chloro-1-(2,2-difluoroethyl)-1H-indazol-3-yl)cyclopropanesulfonamide **(37)** (514 mg, 0.72 mmol), 2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-

cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid **(32)** (191 mg, 0.72 mmol), 1-hydroxybenzotriazole (49 mg, 0.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (180 mg, 0.94 mmol) were charged in a round bottom flask and dissolved in DMF (10 mL). n-Methylmorpholine (0.20 mL, 1.8 mmol) was then added. The reaction mixture was stirred at ambient temperature for 30 minutes. Water was added and stirred for 1 hour. The resulting precipitate was collected by vacuum filtration, then dissolved in methylene chloride, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by RP-HPLC to yield the title compound **(Ib)** as a TFA salt. MS (m/z) 958.88 $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 7.90 – 7.56 (m), 7.30 – 7.07 (m), 6.91 – 6.54 (m), 6.54 – 6.39 (m), 6.37 – 6.21 (m), 6.16 – 5.70 (m), 4.85 – 4.57 (m), 4.34 – 4.12 (m), 3.87 – 3.41 (m), 3.23 (s), 3.17 – 3.02 (m), 3.00 – 2.77 (m), 2.57 – 2.37 (m), 1.81 (s), 1.50 – 0.84 (m).

Example 3: Formulations

Formulations containing the compound of Formula **(Ia)** were prepared as aqueous solutions or oral formulations and administered subcutaneously to rats, dogs, cynomolgus monkey, and/or rhesus monkey.

A. 10% ethanol/13% water/77% PEG 200 solution (400 mg/mL Formula (Ia))

A solution of the compound of Formula **(Ia)** in 10% ethanol, 13% water, and 77% PEG 200 (400 mg/mL) was prepared. The solution was administered subcutaneously to dogs at a dose of 12 mg/kg and rats at a dose of 50 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 3 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. In both species, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM (corresponding to an IQ of 5) for at least 84 days (12 weeks). The results are summarized in Table 1 below.

Table 1. PK parameters of the compound of Formula (Ia) following SC administration in solution

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}84d}$ (μM•h)	$AUC_{0\text{-}140d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C84d (μM)
Wistar Han Rat	50	400	0.125	404 ± 139	569 ± 157	0.283 ± 0.119	840 ± 291	0.162 ± 0.030
Beagle Dog	12	400	0.030	89.6 ± 10.1	111 ± 14	0.107 ± 0.013	336 ± 0	0.0234 ± 0.0057

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day
Values are the mean ± SD from 3 animals

B. 15% water/85% PEG 300 solution (300 mg/mL Formula (Ia))

A solution of the free acid of the compound of Formula **(Ia)** in 15% water and 85% PEG 300 (300 mg/mL) was prepared. The solution was administered subcutaneously to male Wistar Han rats at a dose level of 50 mg/kg and dose volume of 0.167 mL/kg and the pharmacokinetic (PK) profile was determined. FIG. 4 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. The results are summarized in Tables 2 and 3 below.

Table 2. PK parameters of the compound of Formula (Ia) following single SC dose in rats (mean ± SD, n=3)

Dosing Concentration (mg/mL)	300
Dosing Volume (mL/kg)	0.167
Dose (mg/kg)	50
Formulation	85:15 w/w PEG 300:water
$AUC_{0\text{-}168h}$ (μM•h)	13.3 ± 0.3
$AUC_{0\text{-}336h}$ (μM•h)	47.6 ± 1.2
$AUC_{0\text{-}672h}$ (μM•h)	146 ± 6
$AUC_{0\text{-}1344h}$ (μM•h)	338 ± 15
$AUC_{0\text{-}1680h}$ (μM•h)	412 ± 21
AUC_{inf} (μM•h)	NA
$t_{1/2}$ (days)	NA
C_{max} (μM)	NA
T_{max} (h)	NA

Table 3. Plasma concentration-time data of the compound of Formula (Ia) in rats after subcutaneous administration (mean ± SD, n=3)

Time (h)	**Plasma concentration (nM)**			**Mean**	**SD**
	#1	**#2**	**#3**		
0	BLQ	BLQ	BLQ	NC	NC
1	8.9	11.4	5.6	8.6	2.9
3	27.0	17.3	20.1	21.5	5.0
8	37.0	32.8	26.8	32.2	5.1
24	52.6	49.2	42.8	48.2	5.0
48	69.8	71.1	70.8	70.6	0.7
72	65.6	66.9	70.1	67.5	2.3
96	65.5	76.8	85.2	75.8	9.9
168	143	132	137	137	5.5
336	258	273	284	272	13.1
504	327	267	281	292	31.4
672	333	299	304	312	18.4
840	322	316	302	313	10.3
1008	300	258	289	282	21.8

1344	251	229	278	253	24.5
1680	202	166	200	189	20.2

C. 15% water/85% PEG 300 solution (400 mg/mL Formula (Ia))

A solution of the compound of Formula **(Ia)** in 15% water and 85% PEG 300 (400 mg/mL) was prepared. The solution was administered subcutaneously to male beagle dogs at a dose level of 12 mg/kg and dose volume of 0.04 mL/kg and the pharmacokinetic (PK) profile was determined. FIG. 5 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. The results are summarized in Tables 4 and 5 below.

Table 4. PK parameters of the compound of Formula (Ia) following single SC dose in male beagle dogs (mean ± SD, n=3)

Dosing Concentration (mg/mL)	400
Dosing Volume (mL/kg)	0.03
Dose (mg/kg)	12
Formulation	85% PEG300 and 15% water
$AUC_{0\text{-}24h}$ (µM•h)	0.304 ± 0.082
$AUC_{0\text{-}48h}$ (µM•h)	1.08 ± 0.44
$AUC_{0\text{-}72h}$ (µM•h)	2.04 ± 0.98
$AUC_{0\text{-}168h}$ (µM•h)	5.82 ± 3.04
$AUC_{0\text{-}672h}$ (µM•h)	51.2 ± 21.0
$AUC_{0\text{-}1344h}$ (µM•h)	102 ± 30
$AUC_{0\text{-}1680h}$ (µM•h)	116 ± 35
$t_{1/2}$ (days)	NA
C_{max} (µM)	NA
T_{max} (h)	NA

Table 5. Plasma concentration-time data of the compound of Formula (Ia) in beagle dogs after subcutaneous administration (mean ± SD, n=3)

Time (h)	**Plasma concentration (nM)**			**Mean**	**SD**
	#1	**#2**	**#3**		
0	BLQ	BLQ	BLQ	NC	NC
1.0	BLQ	1.2	1.2	1.2	NC
3.0	1.2	2.6	2.3	2.0	0.8
8.0	10.6	15.5	9.2	11.8	3.3
24.0	19.8	27.8	16.8	21.5	5.7
48.0	54.6	60.6	13.2	42.8	25.8
72.0	62.8	37.8	13.2	37.9	24.8
96.0	58.9	28.8	10.4	32.7	24.5
168	71.9	43.1	30.8	48.6	21.1
336	135	64.7	53.0	84.2	44.4

504	172	114	82.9	123	45.2
672	93.1	81.5	56.9	77.2	18.5
840	150	110	107	122.3	24.0
1008	80.2	70.7	54.1	68.3	13.2
1344	42.7	41.2	30.2	38.0	6.8
1680	69.5	42.2	28.5	46.7	20.9

D. 22.6% water/50% PEG 300/1.1%NaOH/26.3% Formula (Ia) solution

A solution of the compound of Formula **(Ia)** sodium salt in water and 300 (300 mg/mL) was prepared that contained 22.6% water/50% PEG 300/1.1%NaOH/26.3% Formula **(Ia)**. The solution was administered subcutaneously to male beagle dogs at a dose level of 12 mg/kg and dose volume of 0.04 mL/kg and the pharmacokinetic (PK) profile was determined. FIG. 6 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. The results are summarized in Tables 6 and 7 below. The results for the male beagle dogs is also shown in Table 6a.

Table 6. PK parameters of the compound of Formula (Ia) sodium salt following single SC dose in male beagle dogs (mean ± SD, n=3)

Dosing Concentration (mg/mL)	300
Dosing Volume (mL/kg)	0.04
Dose (mg/kg)	12
Formulation	50, 22.6, 1.1, 26.3/PEG300:Water:NaOH:GS-6207 w/w/w/w%
$AUC_{0\text{-}24h}$ (µM•h)	0.85 ± 0.31
$AUC_{0\text{-}48h}$ (µM•h)	2.03 ± 0.76
$AUC_{0\text{-}72h}$ (µM•h)	3.16 ± 1.27
$AUC_{0\text{-}168h}$ (µM•h)	6.83 ± 3.24
$t_{1/2}$ (days)	NA
C_{max} (µM)	NA
T_{max} (h)	NA

Table 6a. PK parameters of the compound of Formula (Ia) sodium salt following single SC dose in male beagle dogs (mean ± SD, n=3)

Dosing Concentration (mg/mL)	300
Dosing Volume (mL/kg)	0.04
Dose (mg/kg)	12
Formulation	50, 22.6, 1.1, 26.3/PEG300:Water:NaOH:compound of Formula **(Ia)** w/w/w/w%
$AUC_{0\text{-}24h}$ (µM•h)	0.85 ± 0.31
$AUC_{0\text{-}48h}$ (µM•h)	2.03 ± 0.76

AUC_{0-72h} (μM•h)	3.16 ± 1.27
AUC_{0-168h} (μM•h)	6.83 ± 3.24
$t_{1/2}$ (days)	NA
C_{max} (μM)	NA
T_{max} (h)	NA

Table 7. Plasma concentration-time data of the compound of Formula (Ia) sodium salt in beagle dogs after subcutaneous administration (mean ± SD, n=3)

Time (h)	Plasma concentration (nM)			Mean	SD
	#1	#2	#3		
0	BLQ	BLQ	BLQ	NC	NC
1.0	14.0	7.2	8.6	10.0	3.6
3.0	26.0	17.0	16.8	19.9	5.3
8.0	56.3	25.8	32.1	38.1	16.1
24	57.1	25.4	54.5	45.7	17.6
48	71.1	29.0	57.8	52.6	21.5
72	51.5	16.2	58.0	41.9	22.5
96	46.4	14.0	59.2	39.9	23.3
168	47.7	13.6	43.1	34.8	18.5

E. 5% ethanol/20% propylene glycol/45% PEG 300/30% 0.01 N HCl oral formulation

An oral formulation containing a compound of Formula **(Ia)** in 5% ethanol, 20% propylene glycol, 45% PEG 300, and 30% 0.01 N HCl was prepared. The formulation was orally administered to male rat, dog, cynomolgus monkey, and rhesus monkey according to the doses shown in Table 8 below. The plasma PK parameters are also summarized in Table 8. The compound of Formula **(Ia)** demonstrated moderate F% (bioavailability) in rats and dogs and low F% in cynomolgus monkey and rhesus monkey. The compound of Formula **(Ia)** was slowly absorbed with an average T_{max} range from 8.7 to 18.7 hours.

Table 8. Plasma PK parameters following a single oral administration of the compound of Formula (Ia) in solution to rat, dog, cynomolgus monkey, and rhesus monkey

Species	Dose (mg/kg)	AUC_{0-24h} (nM•h)	AUC_{0-72h} (nM•h)	AUC_{inf} (nM•h)	C_{max} (nM)	T_{max} (h)	F (%)
Sprague-Dawley Rat	5.0	ND	13467 ± 3927	25200 ± 10221	336 ± 116	10.0 ± 3.5	21.7 ± 8.9[a]
Beagle Dog	4.0	ND	11410 ± 4324	16533 ± 10366	471 ± 203	10.7 ± 11.5	22.1 ± 8.4[a]
Cynomolgus Monkey	4.0	298 ± 85	ND	ND	17.7 ± 5.6	8.7 ± 3.1	2.2 ± 0.6[b]
Rhesus	4.0	ND	972 ± 367	1133 ±	29.4 ±	18.7 ±	4.4 ± 1.7[a]

Monkey				446	7.5	9.2	

AUC_{0-24h} = area under the plasma concentration-time curve from 0 to 24 h; AUC_{0-72h} = area under the plasma concentration-time curve from 0 to 72 h; AUC_{inf} = area under the plasma concentration-time curve extrapolated to time infinity; C_{max} = maximum plasma concentration; F = oral bioavailability; ND = not determined; T_{max} = time to reach the maximum plasma concentration

[a] Calculated based on AUC_{0-72h}

[b] Calculated based on AUC_{0-24h}

Values are the mean ± standard deviation from 3 animals

F. Liquid-filled capsules

A single dose of the compound of Formula **(Ia)**, formulated as liquid-filled capsules (LFC) containing either 100% glycerol monocaprylocaprate or 20% caprylocaproyl polyoxyl-8 glycerides and 80% glycerol monocaprylocaprate was administered orally at 7.5 mg fixed dose to 6 male beagle dogs (Table 9). At 100 mg/mL of the compound of Formula **(Ia)**, the AUC_{inf} increased with increasing glycerol monocaprylocaprate content. For the formulation with 100% glycerol monocaprylocaprate, the AUC_{inf} at 50 mg/mL was higher than that at 100 mg/mL.

Table 9. Pharmacokinetics of the compound of Formula (Ia) following oral administration in liquid-filled capsules at 7.5 mg fixed dose to fasted male beagle dogs pretreated with pentagastrin[a,b]

Formulation	(Ia) Dose Concentration (mg/mL)	AUC_{0-72h} (nM•h)	AUC_{inf} (nM•h)	C_{max} (nM)	T_{max} (h)	F%[c]
20% caprylocaproyl polyoxyl-8 glycerides and 80% glycerol monocaprylocaprate	100	1181 ± 575	1303 ± 634	53.2 ± 16.7	7.7 ± 8.0	11 ± 4
100% glycerol monocaprylocaprate	100	1667 ± 1045	1867 ± 1188	71.2 ± 25.8	5.0 ± 1.1	16 ± 9
	50	2178 ± 1243	2329 ± 1348	82.7 ± 32.1	4.0 ± 0.0	22 ± 10

[a] Animals were fasted at least 12 hours prior to dosing and fed 4 hours post dose

[b] Pentagastrin (6 µg/kg) was administered intramuscularly ~30 minutes prior to dosing to ensure an acidic pH in the gastrointestinal tract

[c] %F calculated based on AUC_{0-72h} with average IV AUC_{0-72h} = 13,467 nM•h at 1 mg/kg

Values are the mean ± standard deviation from 6 animals

G. 9.8 w/w% water, 65.0 w/w% PEG 300, and 25.2 w/w% of a compound of Formula (Ia) solution (300 mg/mL of compound of Formula (Ia))

A 300 mg/ml solution of a compound of Formula **(Ia)** having 9.8 w/w% water, 65.0 w/w% PEG 300, and 25.2 w/w% of the compound of Formula **(Ia)** was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 12 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 7A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 7B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 168 days (24 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 84 days (12 weeks). The results are summarized in Tables A and B below.

Table A. PK parameters of the compound of Formula (Ia) following subcutaneous (SC) administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-98d} (µM•h)	AUC_{0-168d} (µM•h)	C_{max} (µM)	T_{max} (h)	C_{d168} (µM)
Wistar Han Rat	50	300	0.167	531 ± 30	730 ± 55	0.318 ± 0.146	728 ± 97	0.0784 ± 0.0138

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table B. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-98d} (µM•h)	AUC_{0-126d} (µM•h)	C_{max} (µM)	T_{max} (h)	C_{84d} (µM)
Beagle Dog	12	300	0.04	130.0 ± 9.1	139 ± 8	0.133 ± 0.010	336 ± 0	0.0217 ± 0.0065

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

H. 27.92 w/w% water, 58.04 w/w% PEG 300, 13.47 w/w% of a compound of Formula (Ia), and 1.1 w/w% NaOH solution (150 mg/mL of compound of Formula (Ia))

A 150 mg/ml solution of a compound of Formula **(Ia)** having 27.92 w/w% water, 58.04 w/w% PEG 300, 13.47 w/w% of a compound of Formula **(Ia)**, and 1.1 w/w% NaOH was

prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 12 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 8A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 8B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 126 days (18 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 56 days (8 weeks). The results are summarized in Tables C and D below.

Table C. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}98d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{d98} (µM)
Wistar Han Rat	50	150	0.333	801 ± 119	0.809 ± 0.021	448 ± 97	0.0370 ± 0.0107

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table D. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}28d}$ (µM•h)	$AUC_{0\text{-}126d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{56d} (µM)
Beagle Dog	12	150	0.08	137.0 ± 38	196 ± 31	0.312 ± 0.093	392 ± 97	0.0229 ± 0.0056

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

I. 23.2 w/w% water, 50.0 w/w% PEG 300, 25.7 w/w% of a compound of Formula (Ia), and 1.1 w/w% NaOH solution (300 mg/mL of compound of Formula (Ia))

A 300 mg/ml solution of a compound of Formula **(Ia)** having 23.2 w/w% water, 50.0 w/w% PEG 300, 25.7 w/w% of a compound of Formula **(Ia)**, and 1.1 w/w% NaOH was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 12 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 9A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 9B shows a plot of the plasma concentration of the compound of Formula

(Ia) as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 126 days (18 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 56 days (8 weeks). The results are summarized in Tables E and F below.

Table E. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}126d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{d168} (µM)
Wistar Han Rat	50	300	0.167	698 ± 13	0.355 ± 0.036	616 ± 96	0.0128 ± 0.0035

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table F. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}56d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{56d} (µM)
Beagle Dog	12	300	0.04	166 ± 110	0.267 ± 0.176	296 ± 231	0.0296 ± 0.0308

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

J. 30.07 w/w% water, 64.40 w/w% PEG 300, 4.68 w/w% of a sodium salt of the compound of Formula (Ia), and 0.85 w/w% poloxamer 188 solution (50 mg/mL of compound of Formula (Ia))

A 50 mg/ml solution of a compound of Formula **(Ia)** having 30.07 w/w% water, 64.40 w/w% PEG 300, 4.68 w/w% of a sodium salt of the compound of Formula **(Ia)**, and 0.85 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 10A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 10B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 28 days (4 weeks). In the dog, plasma concentrations of the compound of Formula

(Ia) were maintained above the target trough concentration of 20 nM for at least 14 days (2 weeks). The results are summarized in Tables G and H below.

Table G. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}7d}$ (μM•h)	$AUC_{0\text{-}28d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{d28} (μM)
Wistar Han Rat	50	50	1.0	156 ± 48	643 ± 75	N/A	N/A	0.082 ± 0.035

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table H. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}24h}$ (μM•h)	$AUC_{0\text{-}14d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{14d} (μM)
Beagle Dog	6	50	0.12	14.7 ± 4.4	108 ± 16	N/A	N/A	0.0372 ± 0.0139

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

K. 29.21 w/w% water, 62.55 w/w% PEG 300, 6.97 w/w% of a sodium salt of the compound of Formula (Ia), and 1.68 w/w% poloxamer 188 solution (75 mg/mL of compound of Formula (Ia))

A 75 mg/ml solution of a compound of Formula **(Ia)** having 29.21 w/w% water, 62.55 w/w% PEG 300, 6.97 w/w% of a sodium salt of the compound of Formula **(Ia)**, and 1.68 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 11A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 11B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 42 days (6 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 21 days (3 weeks). The results are summarized in Tables I and J below.

Table I. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-7d} (µM•h)	AUC_{0-28d} (µM•h)	C_{max} (µM)	T_{max} (h)	C_{d28} (µM)
Wistar Han Rat	50	75	0.667	241 ± 22	690 ± 32	N/A	N/A	0.0325 ± 0.0185

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table J. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-24h} (µM•h)	AUC_{0-28d} (µM•h)	C_{max} (µM)	T_{max} (h)	C_{21d} (µM)
Beagle Dog	6	75	0.06	5.88 ± 1.95	101 ± 11	N/A	N/A	0.040 ± 0.024

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

L. 28.36 w/w% water, 60.73 w/w% PEG 300, 9.23 w/w% of a sodium salt of a compound of Formula (Ia), and 1.68 w/w% poloxamer 188 solution (100 mg/mL of compound of Formula (Ia))

A 100 mg/ml solution of a compound of Formula **(Ia)** having 28.36 w/w% water, 60.73 w/w% PEG 300, 9.23 w/w% of a sodium salt of a compound of Formula **(Ia)**, and 1.68 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 12A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 28 days (4 weeks). The results are summarized in Table K below.

Table K. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}7d}$ (μM•h)	$AUC_{0\text{-}28d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{d28} (μM)
Wistar Han Rat	50	100	0.5	202 ± 27	716 ± 62	N/A	N/A	0.415 ± 0.098

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

M. 28.36 w/w% water, 60.73 w/w% PEG 300, 9.23 w/w% of a sodium salt of a compound of Formula (Ia), and 1.68 w/w% poloxamer 188 solution (100 mg/mL of compound of Formula (Ia))

A 100 mg/ml solution of a compound of Formula **(Ia)** having 28.36 w/w% water, 60.73 w/w% PEG 300, 9.23 w/w% of a sodium salt of a compound of Formula **(Ia)**, and 1.68 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 12B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 14 days (2 weeks). The results are summarized in Table L below.

Table L. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}24h}$ (μM•h)	$AUC_{0\text{-}14d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{14d} (μM)
Beagle Dog	6	100	0.06	6.05 ± 3.43	104 ± 26	N/A	N/A	219 ± 70

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

N. 27.51 w/w% water, 58.92 w/w% PEG 300, 11.48 w/w% of a sodium salt of the compound of Formula (Ia), and 2.09 w/w% poloxamer 188 solution (125 mg/mL of compound of Formula (Ia))

A 125 mg/ml solution of a compound of Formula **(Ia)** having 27.51 w/w% water, 58.92 w/w% PEG 300, 11.48 w/w% of a sodium salt of the compound of Formula **(Ia)**, and 2.09 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a

dose of 50 mg/kg and to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 13A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 13B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 28 days (4 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 14 days (2 weeks). The results are summarized in Tables M and N below.

Table M. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-7d} (μM•h)	AUC_{0-28d} (μM•h)	C_{max} (μM)	T_{max} (h)	C_{d28} (μM)
Wistar Han Rat	50	125	0.4	153 ± 38	673 ± 67	N/A	N/A	0.0279 ± 0.0262

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table N. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-24h} (μM•h)	AUC_{0-14d} (μM•h)	C_{max} (μM)	T_{max} (h)	C_{14d} (μM)
Beagle Dog	6	125	0.048	4.71 ± 1.51	90.3 ± 3.5	N/A	N/A	173 ± 70

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

O. 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula (Ia), 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 solution (150 mg/mL of compound of Formula (Ia))

A 150 mg/ml solution of a compound of Formula **(Ia)** having 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula **(Ia)**, 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 14A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough

concentration of 20 nM for at least 98 days (14 weeks). The results are summarized in Table O below.

Table O. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}98d}$ (μM•h)	$AUC_{0\text{-}112d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{d84} (μM)
Wistar Han Rat	50	150	0.330	949 ± 114	963 ± 102	N/A	N/A	0.0533 ± 0.0457

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

P. 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula (Ia), 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 solution (150 mg/mL of compound of Formula (Ia))

A 150 mg/ml solution of a compound of Formula **(Ia)** having 26.6 w/w% water, 56.97 w/w% PEG 300, 13.39 w/w% of a compound of Formula **(Ia)**, 0.57 w/w% NaOH, and 2.49 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 14B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 56 days (8 weeks). The results are summarized in Table P below.

Table P. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}56d}$ (μM•h)	$AUC_{0\text{-}84d}$ (μM•h)	C_{max} (μM)	T_{max} (h)	C_{56d} (μM)
Beagle Dog	6	150	0.04	69.0 ± 13.9	76.6 ± 8.5	0.101 ± 0.044	240 ± 374	0.0249 ± 0

Formula (Ia): 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Q. 21.97 w/w% water, 47.05 w/w% PEG 300, 25.21 w/w% of a compound of Formula (Ia), 1.08 w/w% of NaOH, and 4.69 w/w% poloxamer 188 solution (300 mg/mL of compound of Formula (Ia))

A 300 mg/ml solution of a compound of Formula **(Ia)** having 21.97 w/w% water, 47.05 w/w% PEG 300, 25.21 w/w% of a compound of Formula **(Ia)**, 1.08 w/w% of NaOH, and 4.69 w/w% poloxamer 188 was prepared. The solution was administered subcutaneously to rats at a dose of 50 mg/kg and to dogs at a dose of 6 mg/kg and the pharmacokinetic (PK) profile was determined. FIG. 15A shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the rat and FIG. 15B shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time in the dog. In the rat, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 98 days (14 weeks). In the dog, plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 56 days (8 weeks). The results are summarized in Tables Q and R below.

Table Q. PK parameters of the compound of Formula (Ia) following SC administration in solution in rats

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}98d}$ (µM•h)	$AUC_{0\text{-}140d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{d98} (µM)
Wistar Han Rat	50	300	0.170	928 ± 175	948 ± 169	0.915 ± 0.248	504 ± 0	0.0513 ± 0.0365

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

Table R. PK parameters of the compound of Formula (Ia) following SC administration in solution in dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	$AUC_{0\text{-}56d}$ (µM•h)	$AUC_{0\text{-}84d}$ (µM•h)	C_{max} (µM)	T_{max} (h)	C_{56d} (µM)
Beagle Dog	6	300	0.02	55.4 ± 20.8	65.4 ± 21.5	0.069 ± 0.022	840 ± 0	0.0304 ± 0.0072

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 3 animals

R. Liquid-filled Capsules

A single dose of the compound of Formula **(Ia)**, formulated as liquid-filled capsules (LFC) containing 100% glycerol monocaprylocaprate, was administered orally at 7.5 mg fixed dose to 6 beagle dogs (Table S) and the pharmacokinetic (PK) profile was determined. FIG. 16 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 72 hours (3 days).

Table S. PK parameters of the compound of Formula (Ia) following oral administration in liquid-filled capsules at 7.5 mg fixed dose to dogs

Species	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC_{0-72h} (μM•h)	AUC_{0-14d} (μM•h)	C_{max} (μM)	T_{max} (h)	C_{72h} (μM)
Beagle Dog	6	50	0.12	5,070 ± 4,649	108 ± 16	201 ± 129	11.0 ± 10.1	0.0201 ± 0.0244

Formula **(Ia)**: 1 nM = 0.968 ng/mL; d = day; h = hour
Values are the mean ± SD from 6 animals

S. Spray-Dried Dispersion (SDD) Tablets

A tablet, prepared from a spray-dried disperstion of a sodium salt of the compound of Formula **(Ia)**, was prepared in a composition shown in Table T below (with an outer film coating made of Opadry® II White 85F18422, wherein the outer film coating provides a 3% weight gain based on the uncoated tablet) and was administered orally at 300 mg fixed dose to 6 beagle dogs (Table U) and the pharmacokinetic (PK) profile was determined. FIG. 17 shows a plot of the plasma concentration of the compound of Formula **(Ia)** as a function of time. Plasma concentrations of the compound of Formula **(Ia)** were maintained above the target trough concentration of 20 nM for at least 14 days (2 weeks).

Table T. Composition of SDD tablets at 300 mg fixed dose

Ingredient	Amount (w/w%)
Sodium salt of compound of Formula **(Ia)**	20.46
Copovidone	4.88
Poloxamer 407	1.33
Microcrystalline Cellulose	21.28
Mannitol	42.55
Croscarmellose Sodium	8.00
Magnesium Stearate	1.50

Table U. PK parameters of the compound of Formula (Ia) following oral administration in SDD tablets at 300 mg fixed dose to dogs

Species	Dose	AUC_{0-72h} (μM•h)	AUC_{inf} (μM•h)	C_{max} (μM)	T_{max} (h)	C_{72h} (μM)
Beagle Dog	300 mg fixed	15.8 ± 10.0	18.5 ± 11.1	0.718 ± 0.409	5.3 ± 3.3	0.0614 ± 0.0300

Formula **(Ia)**: 1 nM = 0.968 ng/mL; h = hour
Values are the mean ± SD from 6 animals

Example 4: Pharmacology

A. Activity against HIV clinical isolates

The antiretroviral activity of the compound of Formula **(Ia)** was tested against a panel of 22 HIV-1 clinical isolates of HIV-1 and two HIV-2 isolates in freshly isolated, PHA-stimulated human peripheral blood mononuclear cells (PBMCs). The HIV-1 isolates included representative strains from subtypes A, B, C, D, E, F, G, N, O, AE, and AG. Following a 7-day infection, virus production was determined by measuring reverse transcriptase activity in cell-free culture supernatants. The compound of Formula **(Ia)** displayed potent antiviral activity against all HIV-1 clinical isolates tested, with a mean EC_{50} value of 0.05 ± 0.03 nM (range of 0.02 to 0.16 nM) (Table 4). When tested in parallel against the same panel of viruses, DTG and AZT exhibited mean EC_{50} values of 0.70 ± 0.26 nM and 19.0 ± 13.5 nM, respectively. The compound of Formula **(Ia)** was 11- to 20-fold less active against HIV-2 relative to HIV-1 as evidenced by its higher EC_{50} value of 0.57 nM and 1.02 nM against HIV-2 strains CBL-20 and CDC310319, respectively (Table 10). Both of these HIV-2 isolates were susceptible to dolutegravir (DTG) and atazanavir (AZT).

Table 10. Antiviral activity against HIV clinical isolates

			EC_{50} in human PBMCs (nM)[a]		
Subtype	**HIV Isolate**	**Genbank Accession #**	**(Ia)**	**DTG**	**AZT**
A	92UG031	L34667	0.04	0.63	51.6
A	92UG037	AB253428	0.07	0.47	21.7
B	89BZ_167	AY173956	0.08	1.18	10.1
B	90US_873	AY713412	0.04	0.82	13.2
B	91US001	AY173952	0.03	0.53	20.3
B	91US004	AY173955	0.04	0.40	19.7
B	96TH_NP1538	AY713408	0.05	0.40	4.10
B	Ba-L	AY713409	0.04	0.40	43.2

B	JR-CSF	M38429	0.04	0.41	4.53
C	92BR025	U52953	0.05	0.91	16.9
C	98US_MSC5016	AY444801	0.10	0.77	37.8
D	92UG001	AJ320484	0.02	1.09	7.29
D	98UG_57128	AF484502	0.03	0.70	6.61
E	CMU02	AY494967	0.05	0.81	8.13
E	CMU08	U48268	0.05	0.96	34.1
F	93BR020	AF005494	0.05	0.38	25.1
G	JV1083	U88826	0.16	0.93	20.5
Group N	YBF30	AJ006022	0.02	0.54	8.96
Group O	BCF01	AF458283	0.04	0.64	10.5
CRF01_AE	90TH_CM235	AF259954	0.04	1.02	10.7
CRF02_AG	01CM0008BBY	AY371124	0.05	1.04	8.21
CRF02_AG	91DJ263	AF063223	0.04	0.45	34.9
	HIV-1 EC_{50} (nM)	**Mean ± s.d.**	**0.05 ± 0.03**	**0.70 ± 0.26**	**19.0 ± 13.5**
		Median	**0.04**	**0.67**	**15.1**
		Range	**0.02 – 0.16**	**0.38 – 1.18**	**4.1 – 51.6**
HIV-2	CBL-20	AY965906	0.57	0.36	14.3
HIV-2	CDC310319	AT965902	1.02	1.81	28.8

[a] EC_{50} values represented the mean of triplicate measurements in human PBMCs

B. Activity against viruses resistant to other antiretroviral classes

The antiviral activity of the compound of Formula **(Ia)** was tested against a panel of known HIV-1 mutants resistant to HIV PIs (ATV and DRV), NRTIs (TFV and FTC), NNRTIs (RPV and EFV) or INSTIs (RAL, EVG and DTG) using a cytopathic antiviral assay in MT-2 cells. The compound of Formula **(Ia)** was fully active against all tested mutants resistant to PIs (Table 11), NRTIs (Table 12), NNRTIs (Table 13) or INSTIs (Table 14). These results support the use of the compound of Formula **(Ia)** in the treatment of infection with HIV-1 variants resistant to these four approved classes of antiretrovirals.

Table 11. Activity of the compound of Formula (Ia) against PI-resistant viruses

Compound[a]	**WT HXB2D EC_{50} (nM)[b]**	**EC_{50} Fold-Change[b,c]**			
		I50V	**I84V/L90M**	**G48V/V82A/L90M**	**G48V/V82S**
(Ia)	0.24 ± 0.14	0.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.2	0.4 ± 0.1
ATV	4.18 ± 0.46	3.5 ± 0.4	33.1 ± 7.8	32.5 ± 11.9	15.4 ± 3.1
DRV	2.82 ± 0.47	31.6 ± 22.8	1.9 ± 0.9	0.5 ± 0.2	0.3 ± 0.1
EFV	1.64 ± 0.55	3.0 ± 0.9	0.4 ± 0.1	0.9 ± 0.4	0.7 ± 0.1
EVG	2.02 ± 0.88	1.7 ± 1.0	1.0 ± 0.7	0.8 ± 0.4	0.7 ± 0.3

[a] ATV = atazanavir (PI); DRV = darunavir (DRV); EFV = efavirenz (NNRTI); EVG = elvitegravir (INSTI)

[b] The data represent the mean (± s.d.) of three independent experiments performed in triplicate
[c] Mutant/WT EC_{50} ratio

Table 12. Activity of the compound of Formula (Ia) against NRTI-resistant viruses

Compound[a]	WT LAI EC_{50} (nM)[b]	EC_{50} Fold-Change[b,c]		
		K65R	M184V	6TAMs
(Ia)	0.14 ± 0.03	0.7 ± 0.2	0.5 ± 0.3	0.4 ± 0.2
TFV	4.458 ± 1.872	2.4 ± 1.0	0.9 ± 1.0	3.0 ± 1.1
FTC	2.406 ± 1.156	12.8 ± 2.4	> 20.8	4.1 ± 2.5
EVG	2.64 ± 0.90	0.8 ± 0.2	1.1 ± 0.7	0.6 ± 0.4
ATV	4.78 ± 1.26	0.9 ± 0.3	0.6 ± 0.2	0.5 ± 0.2

[a] TFV = tenofovir (NRTI); FTC = emtracitabine (NRTI); EVG = elvitegravir (INSTI); ATV = atazanavir (PI)
[b] The data represent the mean (± s.d.) of three independent experiments performed in triplicate
[c] Mutant/WT EC_{50} ratio

Table 13. Activity of the compound of Formula (Ia) against NNRTI-resistant viruses

Compound[a]	WT HXB2D EC_{50} (nM)[b]	EC_{50} Fold-Change[b,c]				
		K103N	Y181C	Y188L	L100I / K103N	K103N / Y181C
(Ia)	0.18 ± 0.02	0.3 ± 0.1	1.6 ± 1.0	0.5 ± 0.1	0.5 ± 0.2	0.5 ± 0.2
RPV	0.93 ± 0.23	0.7 ± 0.3	5.9 ± 4.3	6.9 ± 1.3	7.8 ± 2.6	3.2 ± 1.4
EFV	2.23 ± 0.18	14.2 ± 2.7	3.3 ± 2.5	> 22.4	> 22.4	> 22.4
ATV	4.60 ± 1.48	0.6 ± 0.3	1.8 ± 1.0	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3

[a] RPV = rilpivirine (NNRTI); EFV = efavirenz (NNRTI); ATV = atazanavir (PI)
[b] The data represent the mean (± s.d.) of three independent experiments performed in triplicate
[c] Mutant/WT EC_{50} ratio

Table 14. Activity of the compound of Formula (Ia) against INSTI-resistant viruses

Compound[a]	WT HXB2D EC_{50} (nM)[b]	EC_{50} Fold-Change[b,c]					
		Y143R	E138K / Q148K	G140S / Q148R	E92Q / N155H	N155H / Q148R	R263K / M50I
(Ia)	0.13 ± 0.03	0.5 ± 0.1	0.7 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	1.3 ± 0.7	0.9 ± 0.5
RAL	6.41 ± 2.15	10.1 ± 1.2	> 15.6	> 15.6	> 15.6	13.9 ± 2.2	1.6 ± 1.2
EVG	1.87 ± 0.19	2.1 ± 0.2	> 53.5	> 53.5	> 53.5	51.0 ± 2.5	5.1 ± 3.7
DTG	2.24 ± 0.46	0.8 ± 0.3	7.3 ± 4.1	6.9 ± 3.1	3.0 ± 1.1	1.5 ± 0.6	2.8 ± 2.1
EFV	1.37 ± 0.51	0.9 ± 0.6	0.7 ± 0.3	1.0 ± 0.3	1.2 ± 0.6	1.1 ± 0.5	1.3 ± 0.9
ATV	3.7 ± 1.07	0.8 ± 0.2	0.8 ± 0.3	1.1 ± 0.5	1.0 ± 0.4	0.9 ± 0.4	1.1 ± 0.6

[a] RAL = raltegravir (INSTI); EVG = elvitegravir (INSTI); DTG = dolutegravir (INSTI); EFV = efavirenz (NNRTI); ATV = atazanavir (PI)
[b] The data represent the mean (± s.d.) of three independent experiments performed in triplicate
[c] Mutant/WT EC_{50} ratio

C. Activity in combination with other antiretrovirals

The antiviral activity of the compound of Formula **(Ia)** was evaluated in MT-2 cells infected with HIV-1 IIIb in combination with selected approved anti-HIV drugs: tenofovir alafenamide (TAF), efavirenz (EFV), dolutegravir (DTG), and darunavir (DRV). The combinatorial effects of the compound of Formula **(Ia)** were analyzed by the Prichard and Shipman method using MacSynergy II software. The results of the combination assays were expressed as the mean combination volumes ($\mu M^2\%$) that were calculated at the 95% confidence level from three independent experiments performed in triplicate (Table 15). The combination effects were defined as:

- Highly synergistic: > 100 μM2%
- Moderate synergy: > 50 and < 100 μM2%
- Additive: < 50 and > -50 μM2%
- Moderate antagonism: < -50 and > -100 μM2%
- Highly antagonistic: < -100 μM2%

Combinations of the compound of Formula **(Ia)** with EFV, DTG or DRV showed highly synergistic anti-HIV activity. The compound of Formula **(Ia)** was slightly synergistic when combined with TAF. The compound of Formula **(Ia)**, combined with itself, TAF combined with EVG, and ribavirin combined with d4T were used as additivity, synergy and antagonism controls, respectively.

Table 15. Antiviral activity of the compound of Formula (Ia) in combination with other antiretrovirals

Drug Combination[a]	Combination Volume ($\mu M^2\%$)[b]		Combination Effect
	Type	Mean	
(Ia) + TAF	Synergy Antagonism	87 ± 32 -8 ± 7	Moderate Synergy
(Ia) + EFV	Synergy Antagonism	101 ± 40 -8 ± 8	Highly Synergistic
(Ia) + DTG	Synergy Antagonism	116 ± 13 -8 ± 7	Highly Synergistic
(Ia) + DRV	Synergy Antagonism	119 ± 39 -3 ± 3	Highly Synergistic
(Ia) + (Ia)	Synergy Antagonism	18 ± 8 -16 ± 6	Additive
TAF + EVG	Synergy Antagonism	164 ± 24 -3 ± 3	Highly Synergistic
RBV + d4T	Synergy Antagonism	0 ± 0 -398 ± 23	Highly Antagonistic

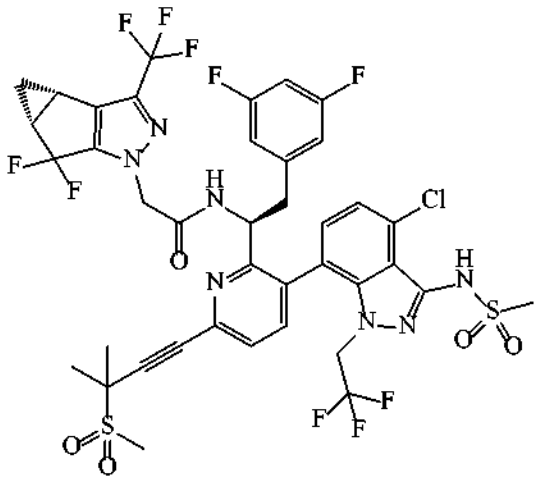
[a] TAF = tenofovir alafenamide (NRTI); EFV = efavirenz (NNRTI); DTG = dolutegravir (INSTI); DRV = darunavir (PI); EVG = elvitegravir (INSTI); RBV = ribavirine; d4T = stavudine

[b] The synergy/antagonism volumes represent the mean (± s.d.) of three independent experiments performed in triplicate

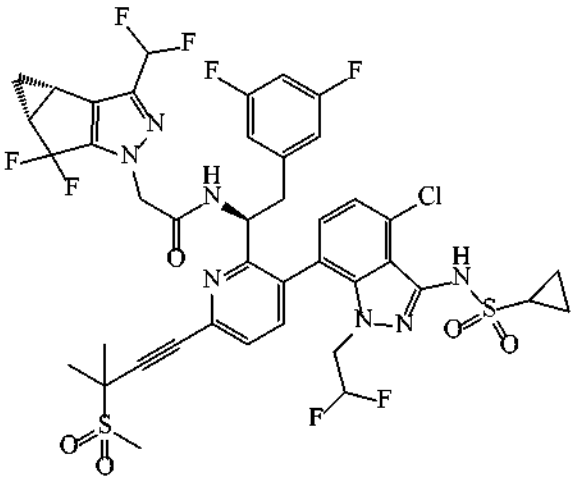
CLAIMS

What is claimed is:

1. A method of treating human immunodeficiency virus (HIV) infection in a heavily treatment-experienced patient, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to one or more antiretroviral medications.

3. The method of claim 1, wherein the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to two or more antiretroviral medications.

4. The method of claim 1, wherein the HIV infection is an HIV-1 infection characterized by HIV-1 mutant resistance to three or more antiretroviral medications.

5. The method of any one of claims 1-4, wherein the HIV-1 mutant is resistant to a protease inhibitor (PI), a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI).

6. The method of claim 5, wherein the HIV-1 mutant resistant to a protease inhibitor is selected from I50V, I84V/L90M, G48V/V82A/L90M, and G48V/V82S.

7. The method of claim 5, wherein the HIV-1 mutant resistant to a nucleoside or nucleotide reverse transcriptase inhibitor is selected from K65R, M184V, and 6TAMs.

8. The method of claim 5, wherein the HIV-1 mutant resistant to a non-nucleoside or non-nucleotide reverse transcriptase inhibitor is selected from K103N, Y181C, Y188L, L100I/K103N, and K103N/Y181C.

9. The method of claim 5, wherein the HIV-1 mutant resistant to a integrase strand transfer inhibitor is selected from Y143R, E138K/Q148K, G140S/Q148R, E92Q/N155H, N155H/Q148R, and R263K/M50I.

10. The method of any one of claims 1-9, wherein the patient is infected with HIV-1 resistant to at least one antiretroviral medication.

11. The method of any one of claims 1-10, wherein the patient is infected with multidrug resistant HIV-1 which is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

12. The method of any one of claims 1-10, wherein the patient is infected with multidrug resistant HIV-1 which is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

13. The method of claim 11 or claim 12, wherein the different classes of antiretroviral medications are selected from a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), a non-nucleoside or non-nucleotide reverse transcriptase inhibitor (NNRTI), and a protease inhibitor (PI).

14. The method of any one of claims 11-13, wherein the NRTI is selected from emtricitabine, lamivudine (3TC), zidovudine (azidothymidine (AZT)), didanosine (ddI),

dideoxyinosine, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, stavudine (d4T), zalcitabine (dideoxycytidine, ddC), and abacavir.

15. The method of any one of claims 11-13, wherein the NNRTI is selected from efavirenz, etravirine, rilpivirine, nevirapine, and delavirdine.

16. The method of any one of claims 11-13, wherein the PI is selected from amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

17. The method of any one of claims 11-13, wherein the INSTI is selected from raltegravir, elvitegravir, dolutegravir, cabotegravir, and bictegravir.

18. The method of any one of claims 10-17, wherein the patient had been previously treated with at least one antiretroviral medication for at least 3 months.

19. The method of any one of claims 10-17, wherein the patient had been previously treated with at least one antiretroviral medication for at least 6 months.

20. The method of any one of claims 10-17, wherein the patient had been previously treated with at least one antiretroviral medication for at least 9 months.

21. The method of any one of claims 10-17, wherein the patient had been previously treated with at least one antiretroviral medication for at least 12 months.

22. The method of any one of claims 10-21, wherein the patient failed a prior HIV treatment regimen comprising administration of at least one antiretroviral medication.

23. The method of claim 22, wherein the prior treatment regimen comprised administration of at least one antiretroviral medication from each of two different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

24. The method of claim 22, wherein the prior treatment regimen comprised administration of at least one antiretroviral medication from each of three different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

25. The method of claim 23 or claim 24, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and a protease inhibitor (PI).

26. The method of any one of claims 1-25, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally, subcutaneously, intramuscularly, or intravenously.

27. The method of claim 26, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally.

28. The method of claim 27, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally at a concentration of about 20 mg/mL to about 100 mg/mL.

29. The method of claim 28, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally at a concentration of about 30 mg/mL.

30. The method of claim 28, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered orally at a concentration of about 50 mg/mL.

31. The method of any one of claims 27-30, wherein the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a hard gelatin capsule.

32. The method of any one of claims 27-30, wherein the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a soft gelatin capsule.

33. The method of any one of claims 27, wherein the compound of Formula **(Ia)** or Formula **(Ib)** is formulated as a tablet.

34. The method of claim 26, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously.

35. The method of claim 34, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously at a concentration of about 50 mg/mL to about 500 mg/mL.

36. The method of claim 35, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously at a concentration of about 100 mg/mL.

37. The method of claim 35, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously at a concentration of about 150 mg/mL.

38. The method of claim 35, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered subcutaneously at a concentration of about 300 mg/mL.

39. The method of any one of claims 34-38, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as a solution formulation.

40. The method of any one of claims 34-38, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is formulated as an aqueous suspension.

41. The method of claim 39 or claim 40, wherein the compound of Formula **(Ia)** is a sodium salt.

42. The method of claim 39 or claim 40, wherein the compound of Formula **(Ib)** is a trifluoroacetic acid salt.

43. The method of any one of claims 26-42, wherein the compound of Formula **(Ia)** or Formula **(Ib)** is formulated with one or more other compounds selected from HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV nucleoside reverse transcriptase translocation inhibitors, and pharmacokinetic enhancers.

44. The method of claim 43, wherein the compound of Formula **(Ia)** or Formula **(Ib)** is formulated with an HIV nucleoside reverse transcriptase translocation inhibitor.

45. The method of claim 44, wherein the HIV nucleoside reverse transcriptase translocation inhibitor is 4'-ethynyl-2-fluoro-2'-deoxyadenosine triphosphate (MK-8591).

46. The method of any one of claims 1-45, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once daily.

47. The method of any one of claims 1-45, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, or 48 weeks.

48. The method of claim 47, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 4 weeks.

49. The method of claim 47, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 8 weeks.

50. The method of claim 47, wherein the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is administered once every 12 weeks.

51. The method of any one of claims 1-50, wherein the patient has a viral load of greater than about 200 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

52. The method of any one of claims 1-50, wherein the patient has a viral load of greater than about 500 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

53. The method of any one of claims 1-50, wherein the patient has a viral load of greater than about 750 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

54. The method of any one of claims 1-50, wherein the patient has a viral load of greater than about 1000 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

55. The method of any one of claims 1-50, wherein the patient has a viral load of greater than about 2000 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

56. The method of any one of claims 1-50, wherein the patient is failing an HIV treatment regimen comprising administration of at least one antiretroviral medication at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

57. The method of any one of claims 51-56, wherein administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, results in a decrease in the viral load in the patient.

58. The method of claim 57, wherein the viral load is decreased by about 0.5 $\log_{10}$ to about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

59. The method of claim 57, wherein the viral load is decreased by about 0.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning

administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

60. The method of claim 57, wherein the viral load is decreased by about 1 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

61. The method of claim 57, wherein the viral load is decreased by about 1.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

62. The method of claim 57, wherein the viral load is decreased by about 2 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

63. The method of claim 57, wherein the viral load is decreased by about 2.5 $\log_{10}$ after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks as compared to the viral load at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof.

64. The method of claim 57, wherein the viral load in the patient is about 200 copies of HIV-1 RNA/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks.

65. The method of claim 57, wherein the viral load in the patient is about 50 copies of HIV-1 RNA/mL or less after administration of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, for about 24 weeks.

66. The method of any one of claims 1-65, wherein the patient is concurrently treated with at least one additional antiretroviral medication.

67. The method of claim 66, wherein the additional antiretroviral medication is selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), an integrase strand transfer inhibitor (INSTI), a gp41 fusion inhibitor, a CCR5 co-receptor antagonist, and combinations thereof.

68. The method of claim 67, wherein the NRTI is selected from emtricitabine, lamivudine (3TC), zidovudine (azidothymidine (AZT)), didanosine (ddI), dideoxyinosine, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, stavudine (d4T), zalcitabine (dideoxycytidine, ddC), and abacavir.

69. The method of claim 67, wherein the NNRTI is selected from efavirenz, etravirine, rilpivirine, nevirapine, and delavirdine.

70. The method of claim 67, wherein the PI is selected from amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

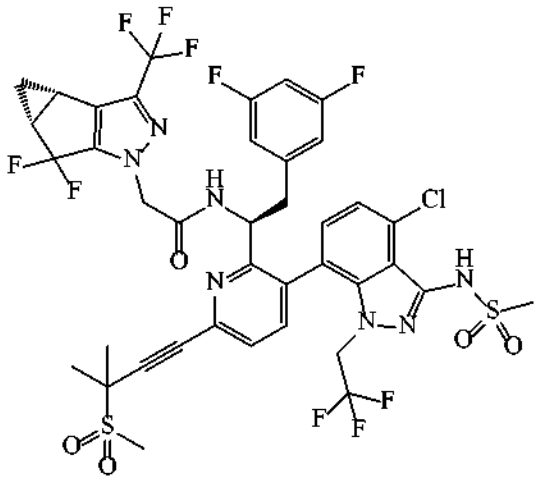
71. The method of claim 67, wherein the INSTI is selected from raltegravir, elvitegravir, dolutegravir, and bictegravir.

72. The method of claim 67, wherein the gp41 fusion inhibitor is selected from albuvirtide, enfuvirtide, BMS-986197, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors (P26-Bapc), ITV-1, ITV-2, ITV-3, ITV-4, PIE-12 trimer, and sifuvirtide.

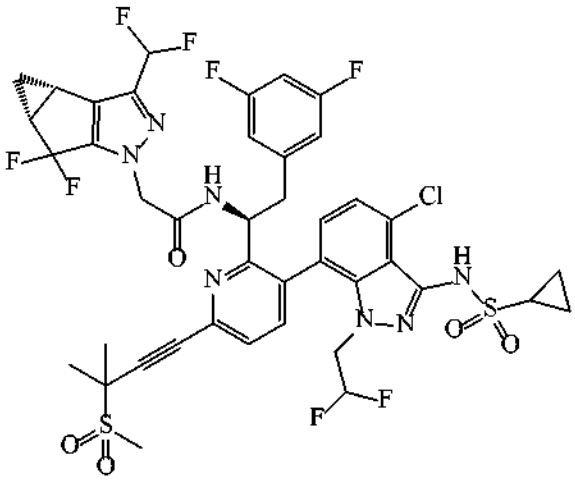
73. The method of claim 67, wherein the CCR5 co-receptor antagonist is selected from aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc (TD-0232), anti-GP120/CD4 or CCR5 bispecific antibodies, B-07, MB-66, polypeptide C25P, TD-0680, and vMIP (Haimipu).

74. A method of treating human immunodeficiency virus-1 (HIV-1) infection in a heavily treatment-experienced patient with multidrug resistant HIV-1, the method comprising

administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

the patient had been previously treated with an HIV treatment regimen comprising administration of at least one antiretroviral medication and failed the treatment regimen; and

administration of the compound results in a reduction in HIV viral load in the patient.

75. The method of claim 74, wherein the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

76. The method of claim 74, wherein the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of three different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

77. The method of claim 75 or claim 76, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and a protease inhibitor (PI).

78. The method of claim 77, wherein the NRTI is selected from emtricitabine, lamivudine (3TC), zidovudine (azidothymidine (AZT)), didanosine (ddI), dideoxyinosine, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, stavudine (d4T), zalcitabine (dideoxycytidine, ddC), and abacavir.

79. The method of claim 77, wherein the NNRTI is selected from efavirenz, etravirine, rilpivirine, nevirapine, and delavirdine.

80. The method of claim 77, wherein the PI is selected from amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

81. The method of claim 77, wherein the INSTI is selected from raltegravir, elvitegravir, dolutegravir, cabotegravir, and bictegravir.

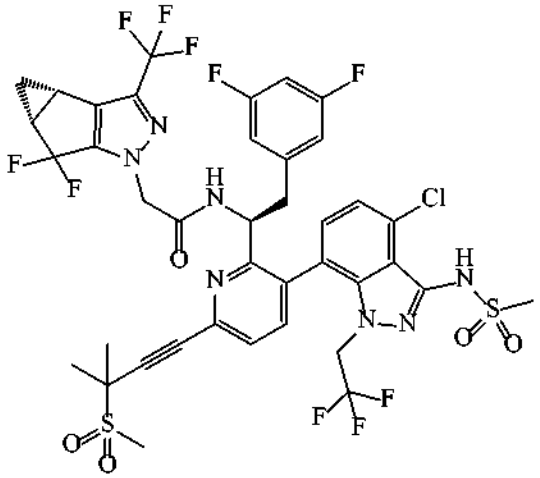
82. The method of any one of claims 74-81, wherein the patient had been previously treated with at least one antiretroviral medication for at least 3 months, at least 6 months, at least 9 months, or at least 12 months.

83. The method of any one of claims 74-82, wherein the prior treatment regimen comprised administration of at least one antiretroviral medication from each of two different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

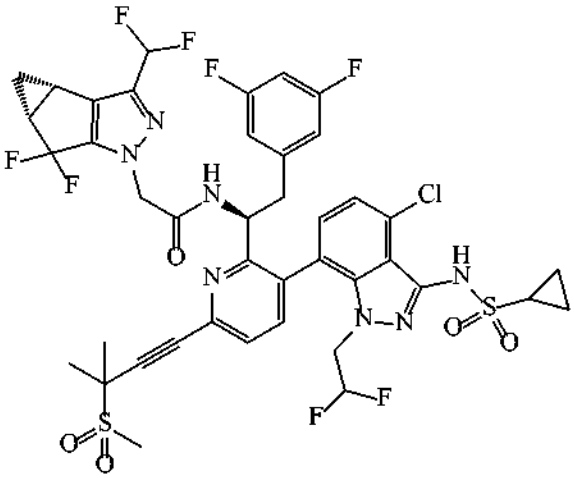
84. The method of any one of claims 74-82, wherein the prior treatment regimen comprised administration of at least one antiretroviral medication from each of three different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI).

85. The method of claim 83 or claim 84, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and a protease inhibitor (PI).

86. A method of treating human immunodeficiency virus-1 (HIV-1) infection in a heavily treatment-experienced patient with multidrug resistant HIV-1, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

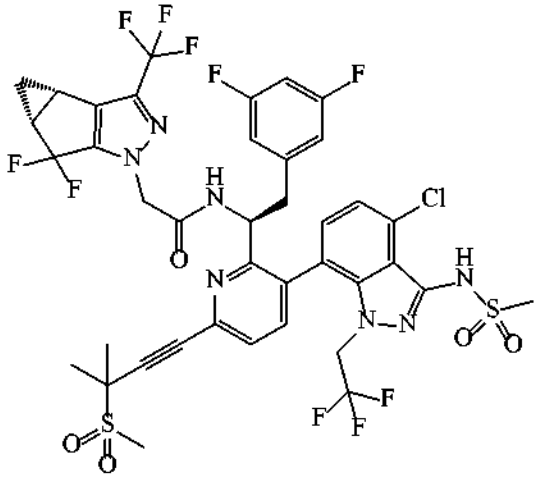
the multidrug resistant HIV-1 is resistant to at least one antiretroviral medication from each of two different classes of antiretroviral medications, wherein the different classes of antiretroviral medications are selected from a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), and an integrase strand transfer inhibitor (INSTI);

the patient had been previously treated with an HIV treatment regimen comprising administration of at least one antiretroviral medication and failed the treatment regimen;

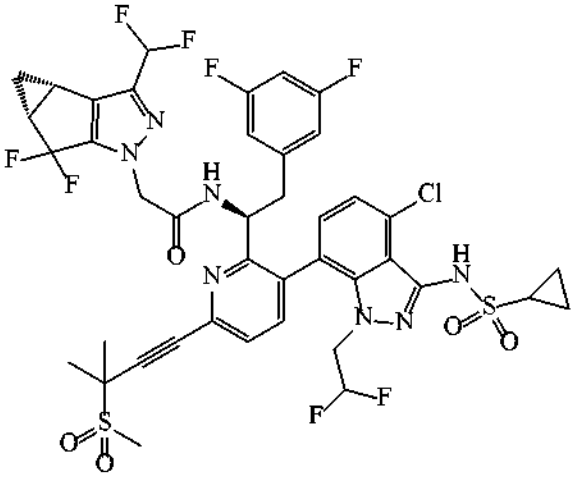
the patient has a viral load of greater than about 200 copies of HIV-1 RNA/mL at the time of beginning administration of the compound of Formula **(Ia)** or Formula **(Ib)**; and

administration of the compound results in a reduction in HIV viral load in the patient.

87. A method of reducing the viral load associated with an HIV infection in a heavily treatment-experienced patient with multidrug resistant HIV, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula **(Ia)** or Formula **(Ib)**:



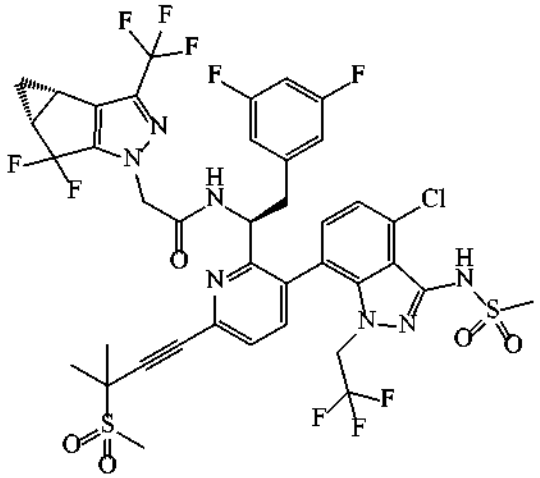
(Ia)



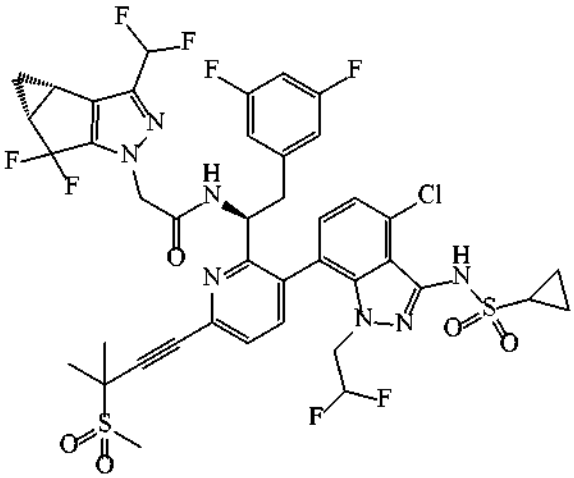
(Ib)

or a pharmaceutically acceptable salt thereof.

88. A pharmaceutical composition comprising a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is in the form of a solution and the solution comprises PEG 300 and water.

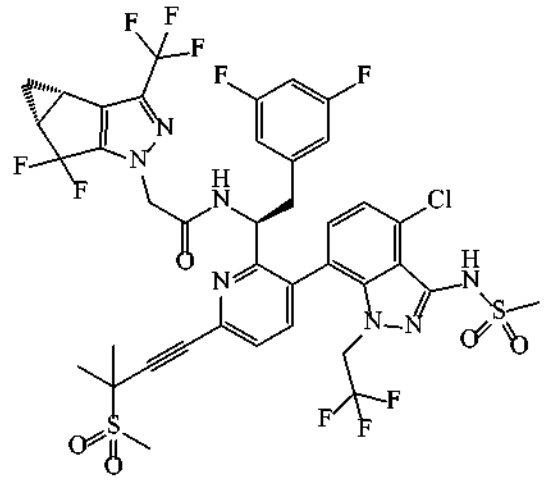
89. The pharmaceutical composition of claim 88, wherein the solution comprises about 5 w/w% to about 15 w/w% water, about 50 w/w% to about 85 w/w% PEG 300, and about 15 w/w% to about 35 w/w% of a compound of Formula **(Ia)**.

90. The pharmaceutical composition of claim 88, wherein the solution comprises about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, and about 5 w/w% to about 35 w/w% of a sodium salt of a compound of Formula **(Ia)**.

91. The pharmaceutical composition of claim 88, wherein the solution further comprises sodium hydroxide.

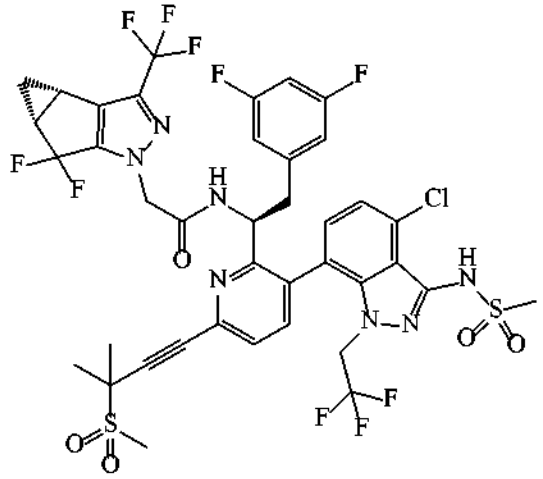
92. The pharmaceutical composition of claim 91, wherein the solution comprises about 10 w/w% to about 40 w/w% water, about 35 w/w% to about 75 w/w% PEG 300, about 5 w/w% to about 35 w/w% of a compound of Formula **(Ia)**, and about 0.05 w/w% to about 2 w/w% of sodium hydroxide.

93. A pharmaceutical composition in the form of a solution, wherein the solution comprises about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about 0.5 w/w% to about 40 w/w% of a sodium salt of a compound of Formula **(Ia)**, and about 0.1 w/w% to about 10 w/w% of poloxamer 188, wherein the compound of Formula **(Ia)** has the structure:



(Ia).

94. A pharmaceutical composition in the form of a solution, wherein the solution comprises about 10 w/w% to about 45 w/w% water, about 30 w/w% to about 85 w/w% PEG 300, about 0.5 w/w% to about 40 w/w% of a compound of Formula **(Ia)**, about 0.01 w/w% to about 3.0 w/w% of sodium hydroxide, and about 0.1 w/w% to about 10 w/w% of poloxamer 188, wherein the compound of Formula **(Ia)** has the structure:



(Ia).

95. An oral formulation comprising a compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, and glycerol monocaprylocaprate.

96. The oral formulation of claim 95, wherein the oral formulation is prepared in a hard gelatin or soft gelatin capsule.

97. The hard gelatin or soft gelatin capsule of claim 96, wherein the hard gelatin or soft gelatin capsule comprises about 30 w/w% to about 85 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 40 w/w% of a compound of Formula **(Ia)**.

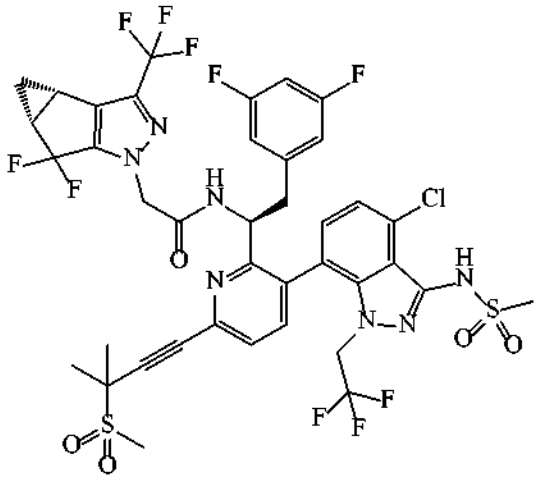
98. The hard gelatin or soft gelatin capsule of claim 96, wherein the hard gelatin or soft gelatin capsule comprises about 30 w/w% to about 99 w/w% of glycerol monocaprylocaprate and about 1 w/w% to about 40 w/w% of a sodium salt of the compound of Formula **(Ia)**.

99. The hard gelatin or soft gelatin capsule of any one of claims 96-98, wherein the concentration of the compound of Formula **(Ia)** is about 10 mg/ml to about 500 mg/ml.

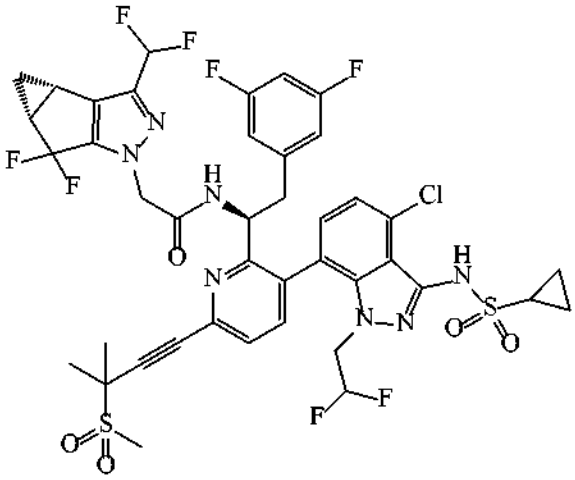
100. The hard gelatin or soft gelatin capsule of claim 96-99, further comprising an outer capsule shell.

101. The hard gelatin or soft gelatin capsule of claim 100, wherein the outer shell comprises gelatin, glycerin, titanium dioxide, and iron oxide.

102. A tablet comprising a compound of Formula **(Ia)** or Formula **(Ib)**:



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein the tablet is prepared from a spray-dried dispersion technology.

103. The tablet of claim 102, wherein the amount of the compound of Formula **(Ia)** or Formula **(Ib)**, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 500 mg.

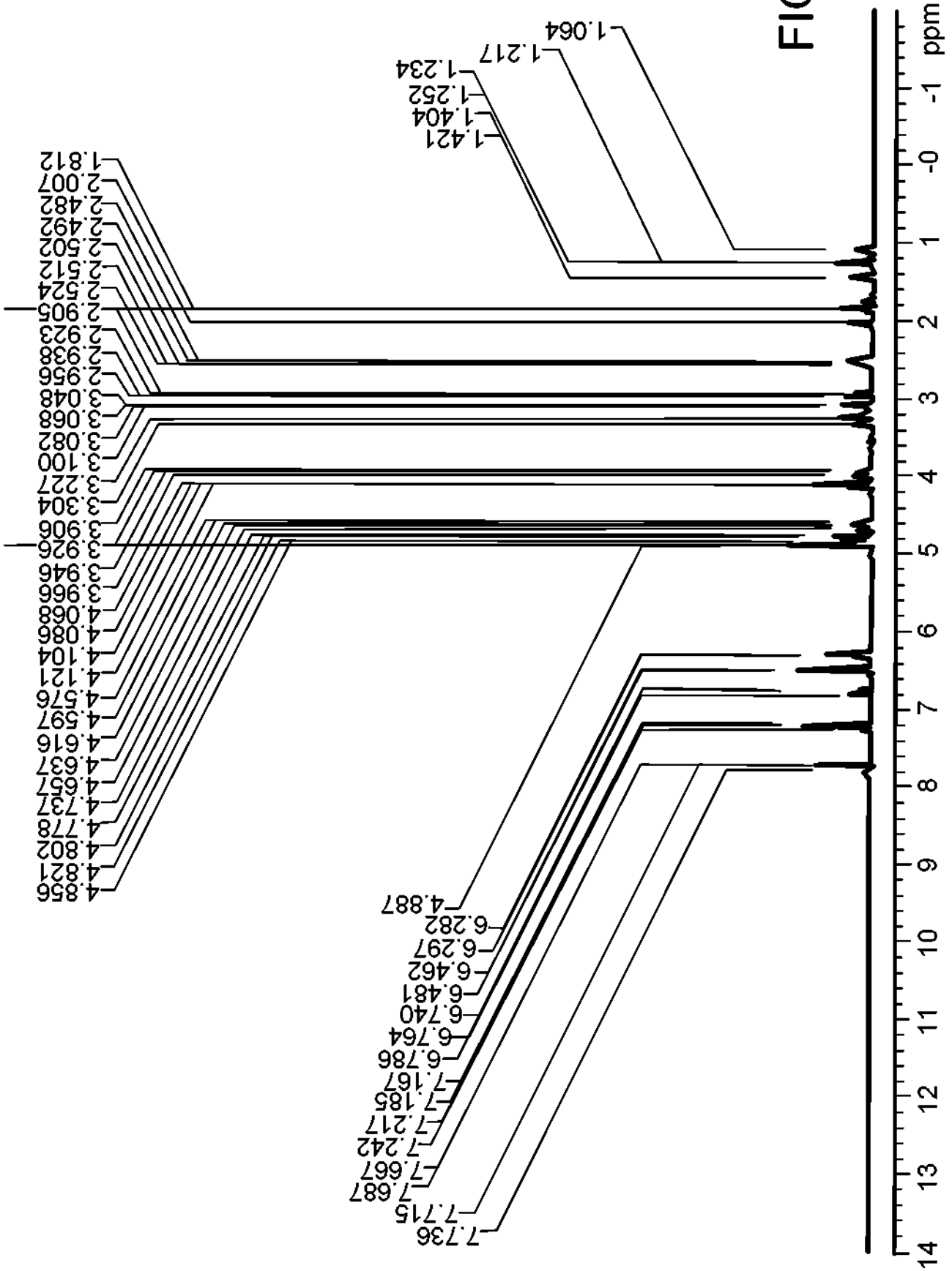
104. The tablet of any one of claims 102-103, wherein the tablet comprises a sodium salt of the compound of Formula **(Ia)**.

105. The tablet of any one of claims 102-104, wherein the tablet comprises about 5 w/w% to about 45 w/w% of the sodium salt of the compound of Formula **(Ia)**, about 1 w/w% to about 10 w/w% of copovidone, about 0.01 w/w% to about 10 w/w% of poloxamer 407, about 5 w/w% to about 45 w/w% of microcrystalline cellulose, about 15 w/w% to about 70 w/w% of mannitol, about 1 w/w% to about 30 w/w% of croscarmellose sodium, and about 0.01 w/w% to about 10 w/w% of magnesium stearate.

106. The tablet of any one of claims 102-105, wherein the tablet further comprises an outer film coat.

107. The tablet of claim 106, wherein the outer film coat provides from about 1% to about 8% weight gain based on the uncoated tablet.

FIG. 1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2.923
2.938
2.956
3.048
3.068
3.082
3.100
3.227
3.304
3.906
3.926
3.946
3.966
4.068
4.086
4.104
4.121
4.576
4.597
4.616
4.637
4.657
4.737
4.778
4.802
4.821
4.856
4.887
6.282
6.297
6.462
6.481
6.740
6.764
6.786
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7.185
7.217
7.242
7.667
7.687
7.715
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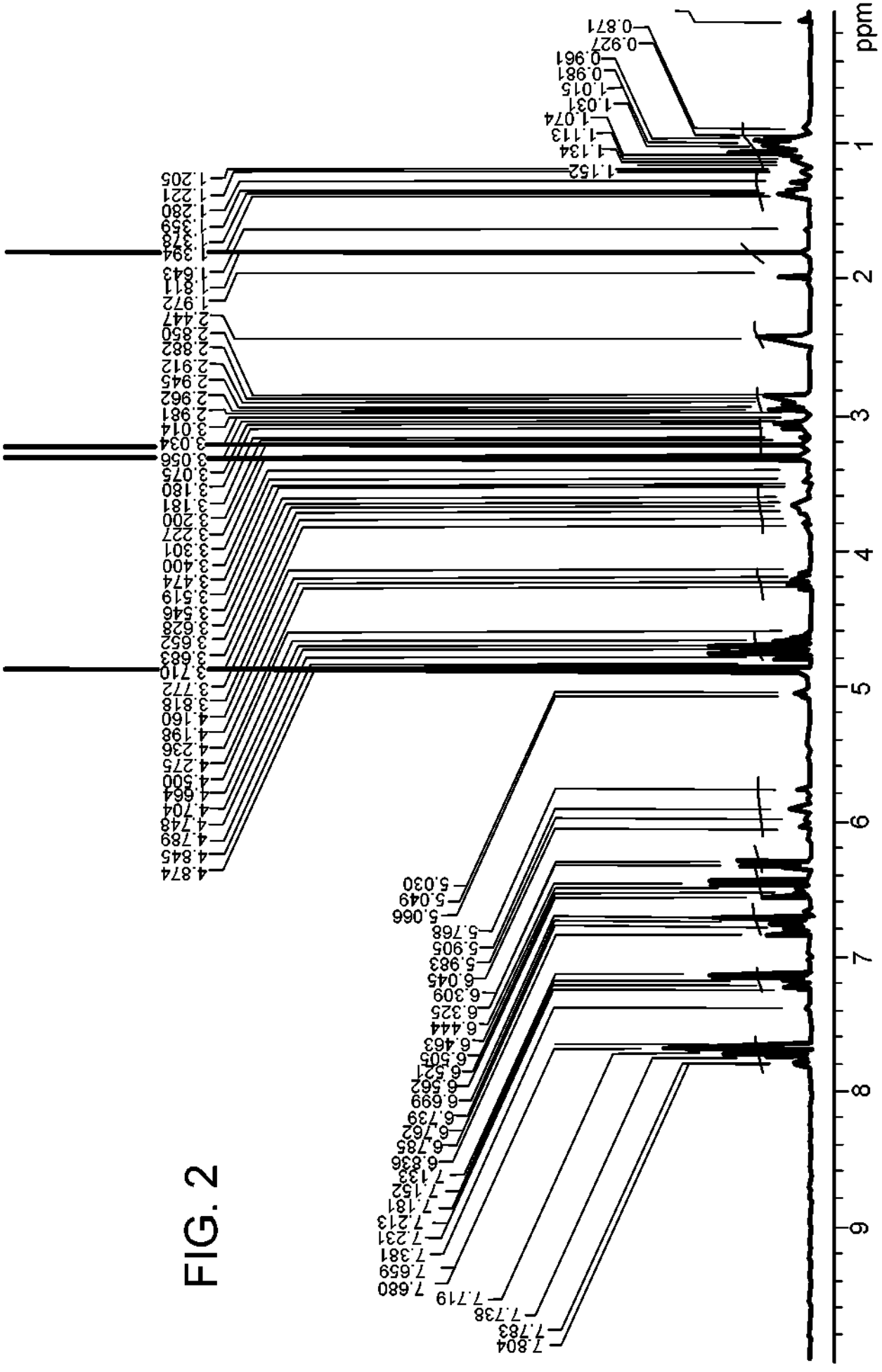
10
11
12
13
14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1.134
1.152
1.205
1.221
1.280
1.359
1.378
1.394
1.643
1.811
1.972
2.447
2.850
2.882
2.912
2.945
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2.981
3.014
3.034
3.056
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3.180
3.181
3.200
3.227
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3.400
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3.519
3.546
3.628
3.652
3.683
3.710
3.772
3.818
4.160
4.198
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4.874
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7.804

FIG. 2

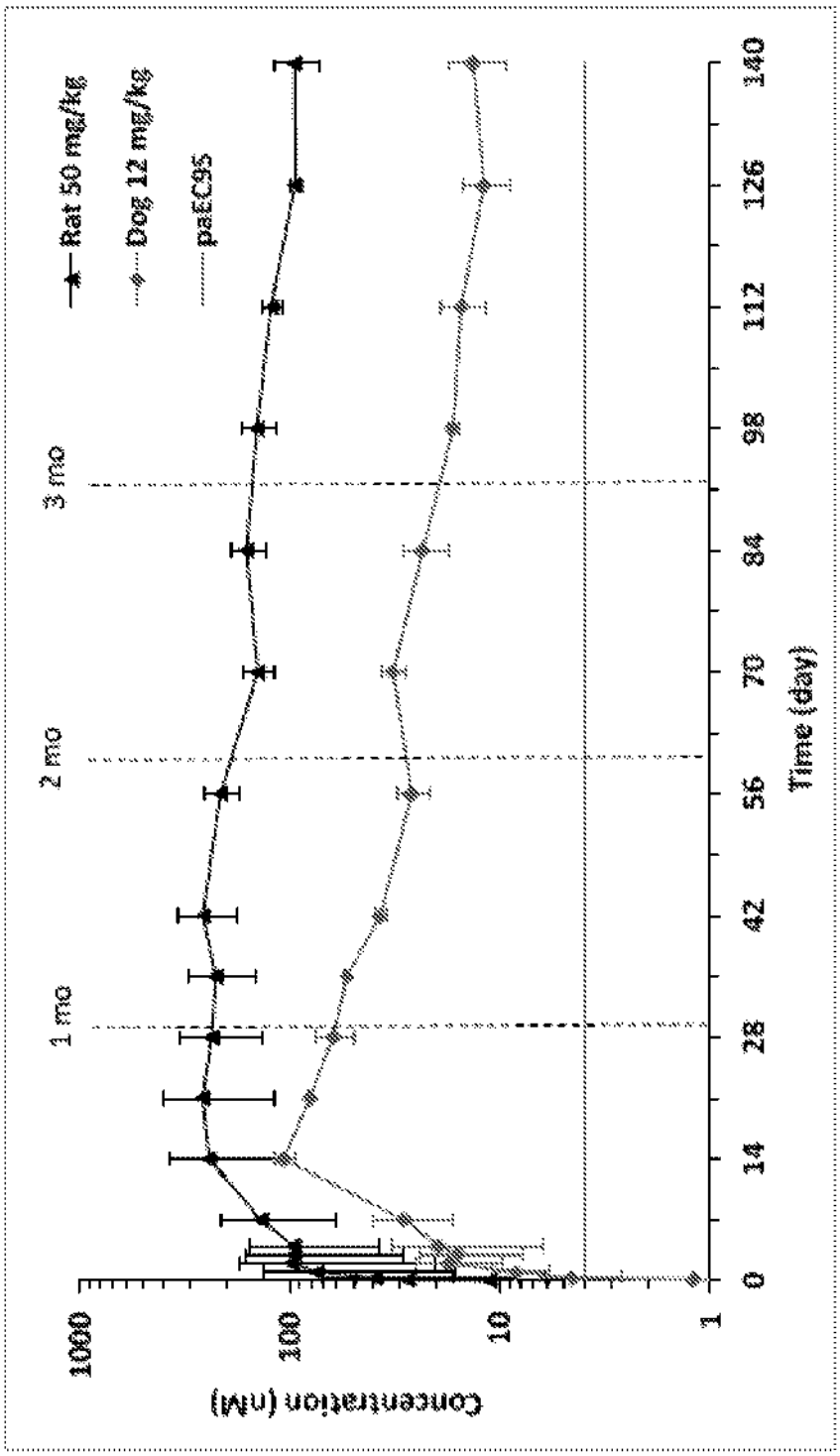
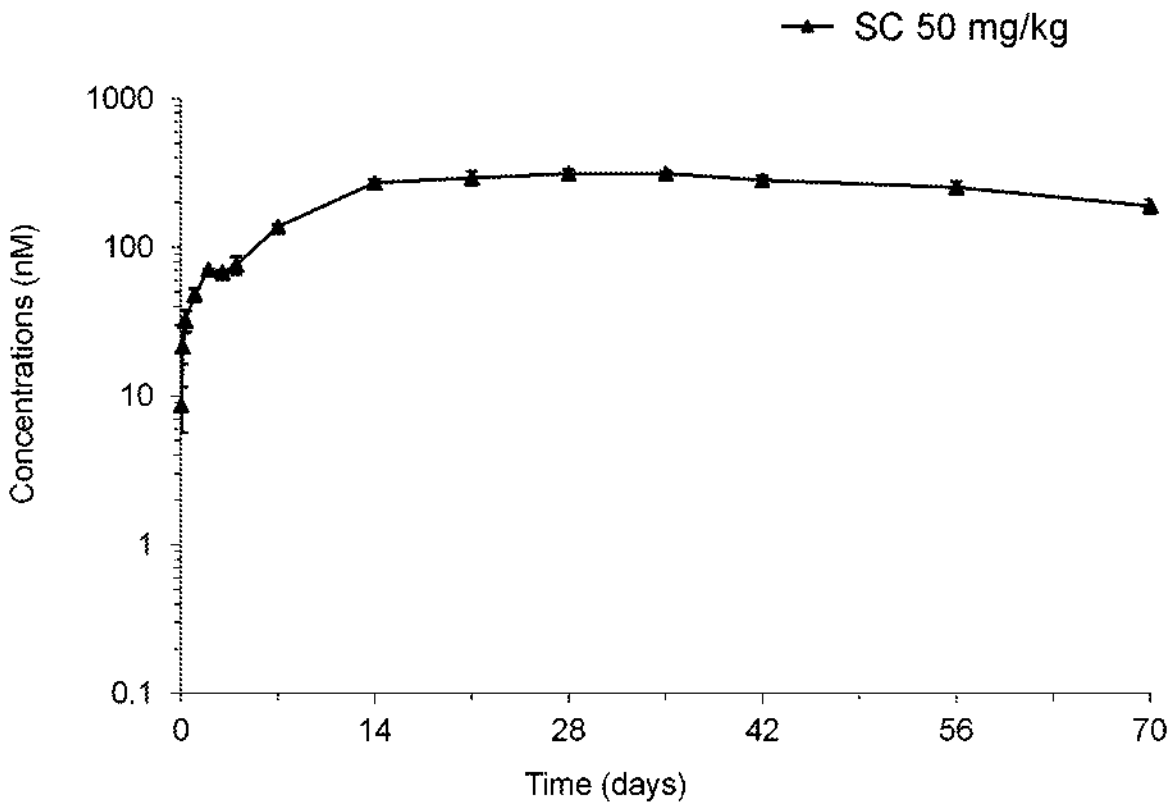

Rat 50 mg/kg
Dog 12 mg/kg
paEC95
1 mo
2 mo
3 mo
Concentration (nM)
1000
100
10
1
0
14
28
42
56
70
84
98
112
126
140
Time (day)

FIG. 3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100
10
1
0.1
Concentrations (nM)
0
14
28
42
56
70
Time (days)

FIG. 4

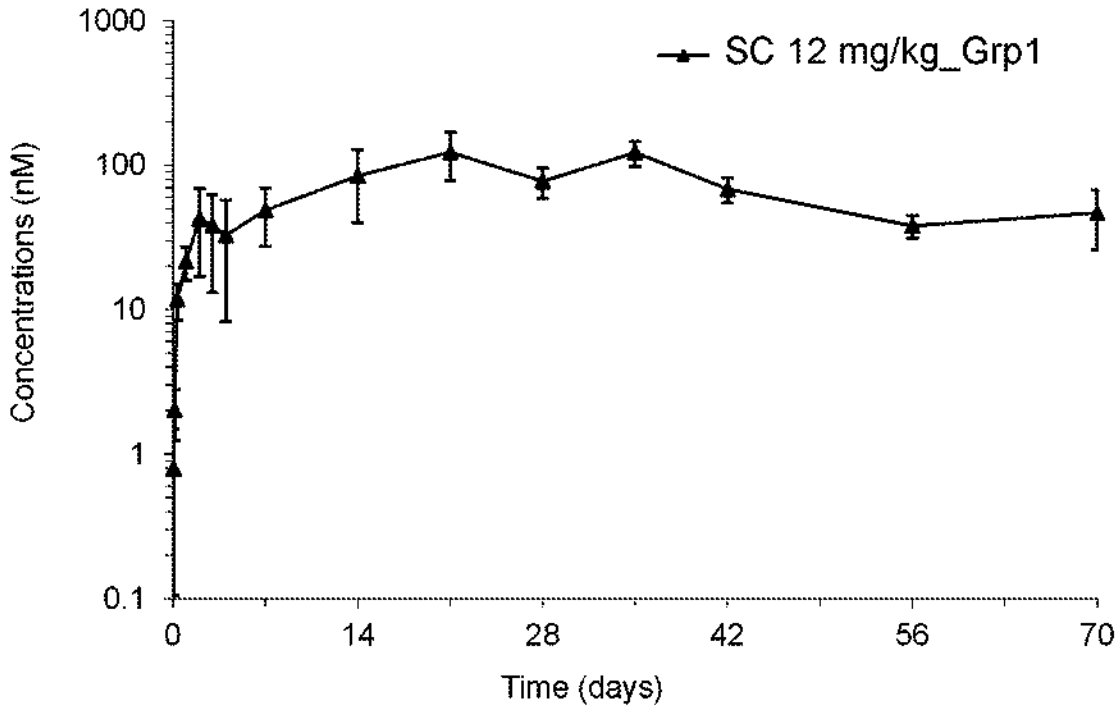
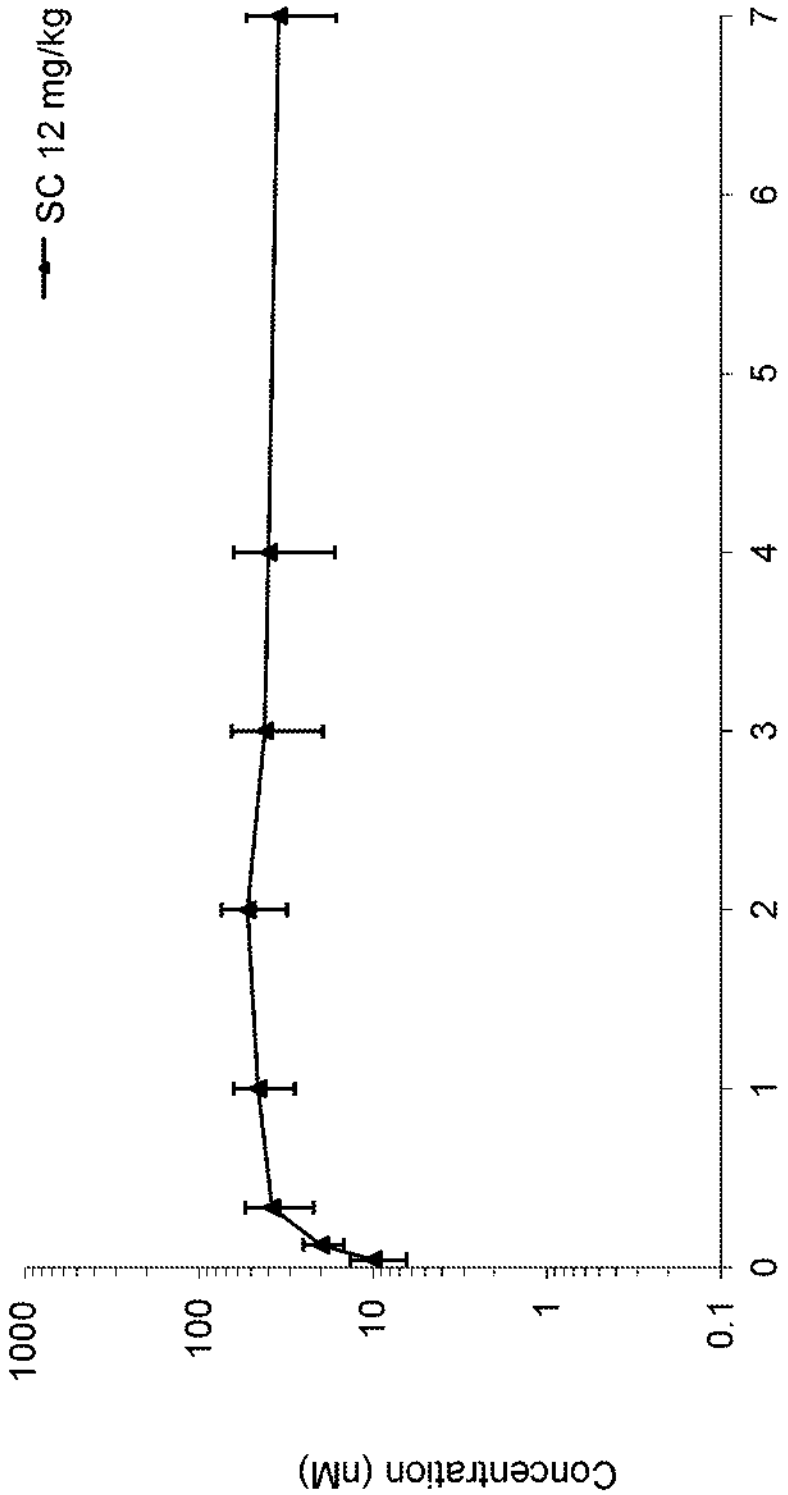

1000
100
10
1
0.1
Concentrations (nM)
SC 12 mg/kg_Grp1
0
14
28
42
56
70
Time (days)

FIG. 5


SC 12 mg/kg
Concentration (nM)
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100
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0.1
0
1
2
3
4
5
6
7
Time (day)

FIG. 6

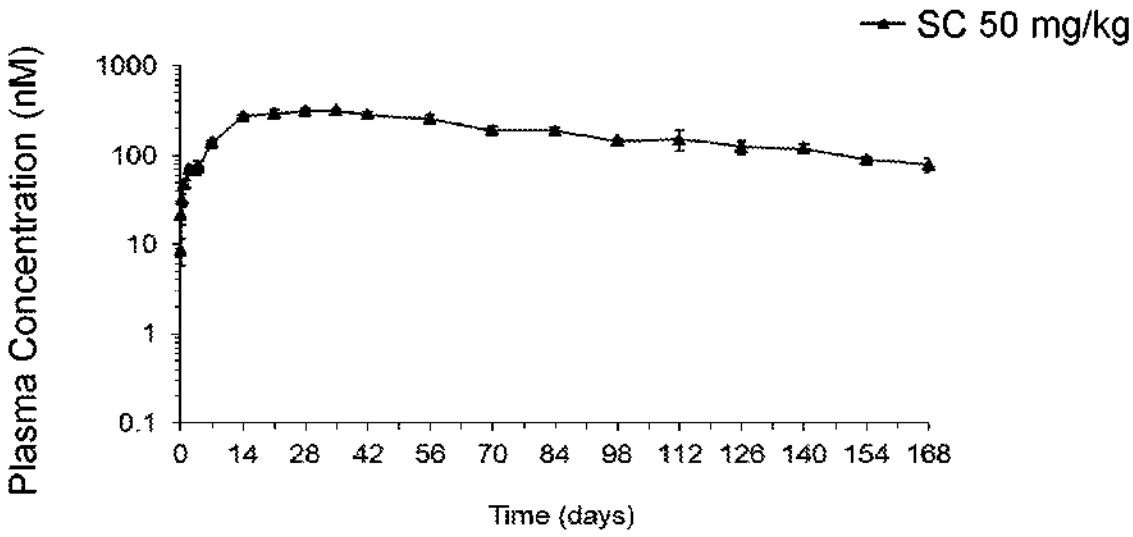
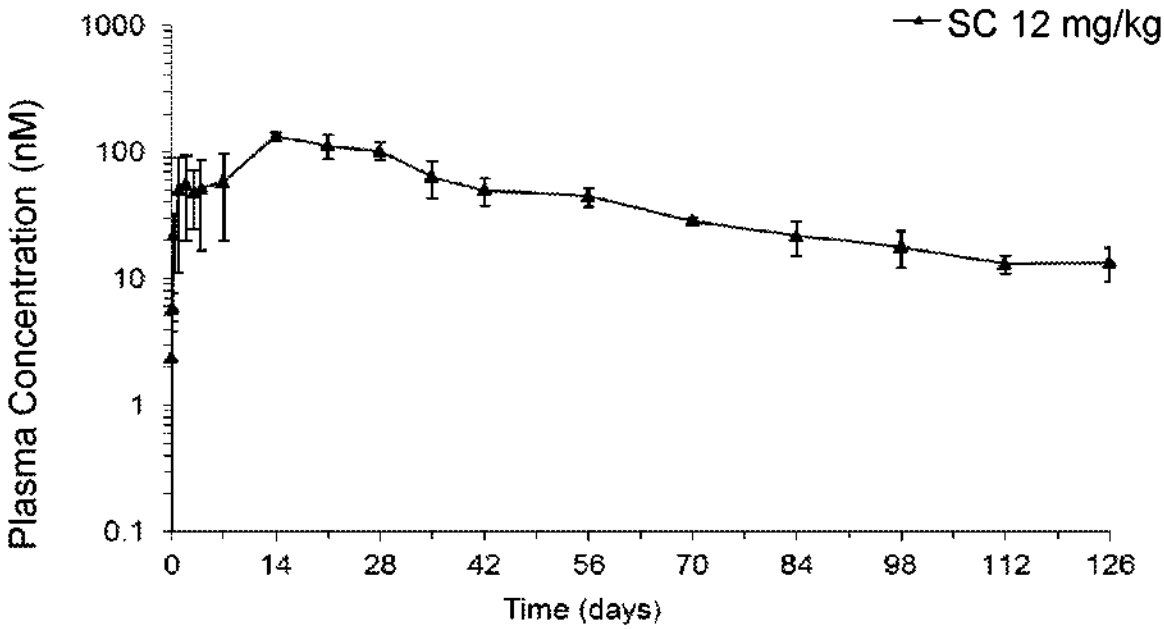

SC 50 mg/kg
Plasma Concentration (nM)
1000
100
10
1
0.1
0
14
28
42
56
70
84
98
112
126
140
154
168
Time (days)

FIG. 7A


SC 12 mg/kg
Plasma Concentration (nM)
1000
100
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1
0.1
0
14
28
42
56
70
84
98
112
126
Time (days)

FIG. 7B

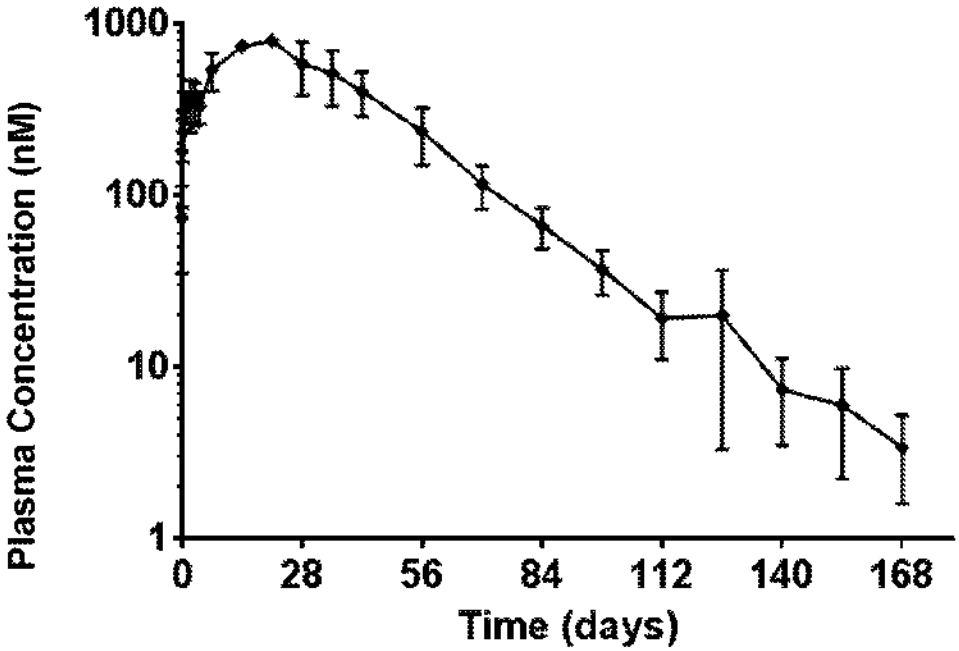

Plasma Concentration (nM)
1000
100
10
1
0
28
56
84
112
140
168
Time (days)

FIG. 8A

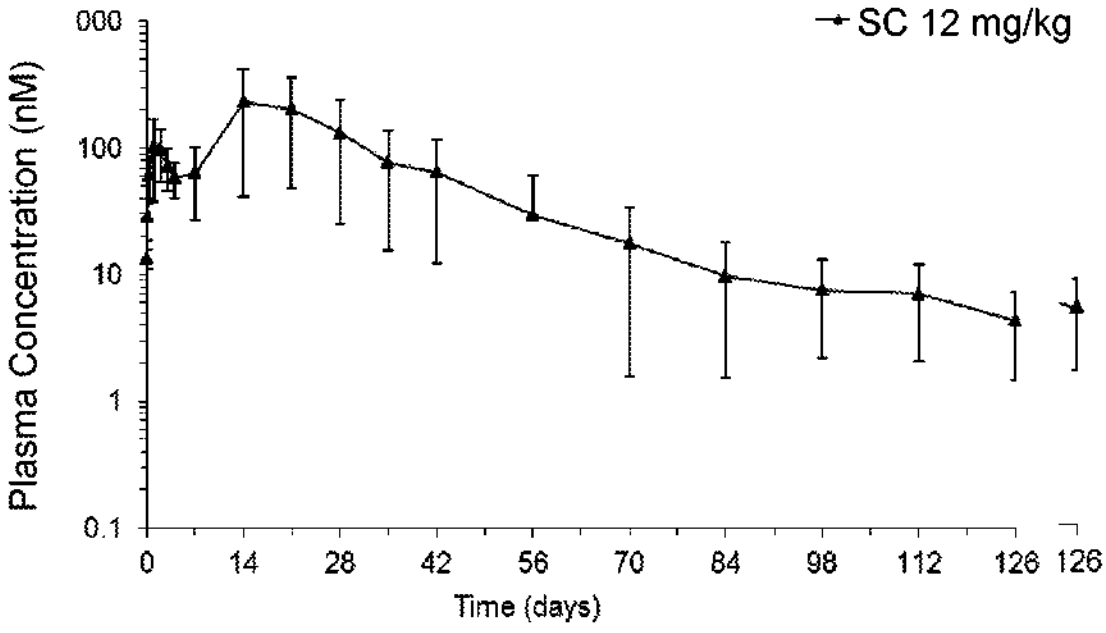
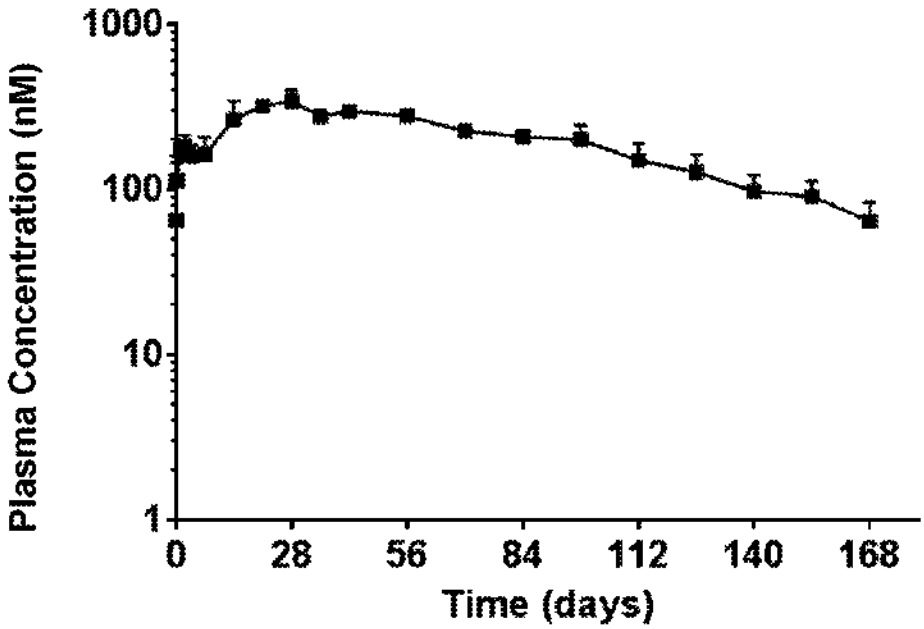

SC 12 mg/kg
Plasma Concentration (nM)
000
100
10
1
0.1
0
14
28
42
56
70
84
98
112
126
126
Time (days)

FIG. 8B


Plasma Concentration (nM)
1000
100
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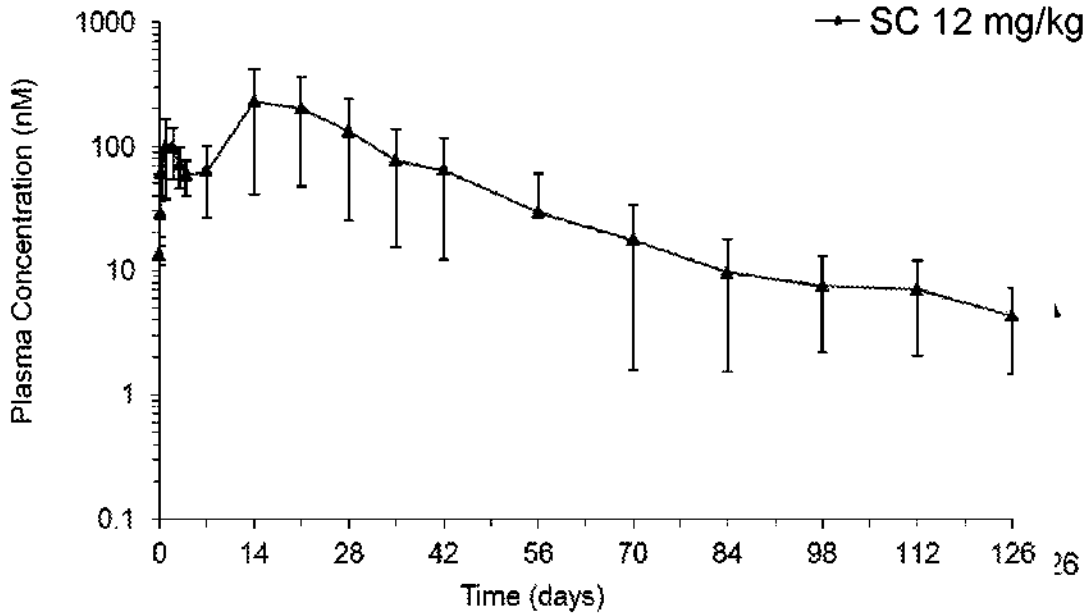
1
0
28
56
84
112
140
168
Time (days)

FIG. 9A


SC 12 mg/kg
Plasma Concentration (nM)
1000
100
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1
0.1
0
14
28
42
56
70
84
98
112
126
Time (days)

FIG. 9B

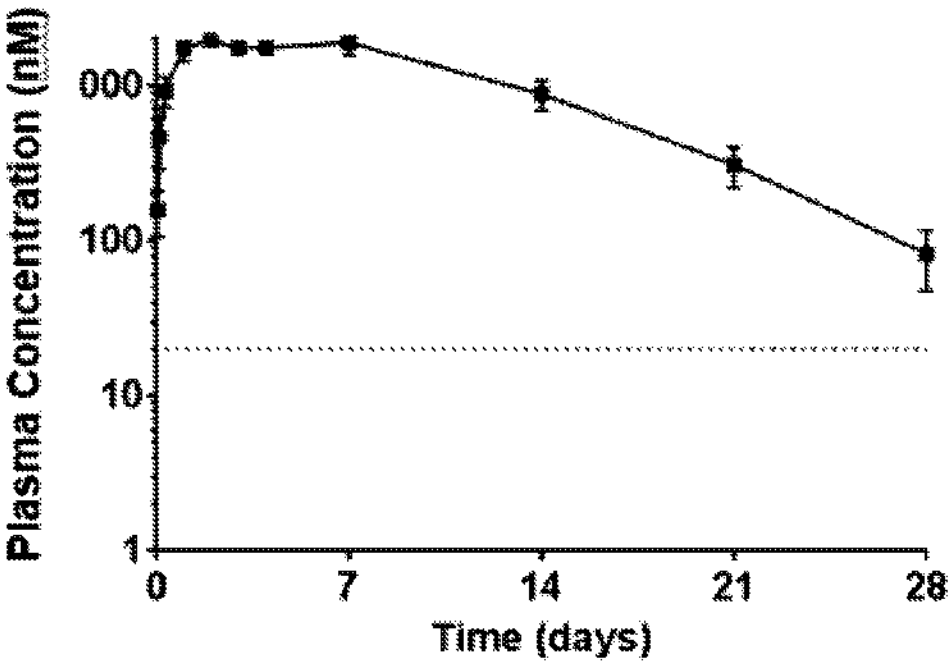

FIG. 10A

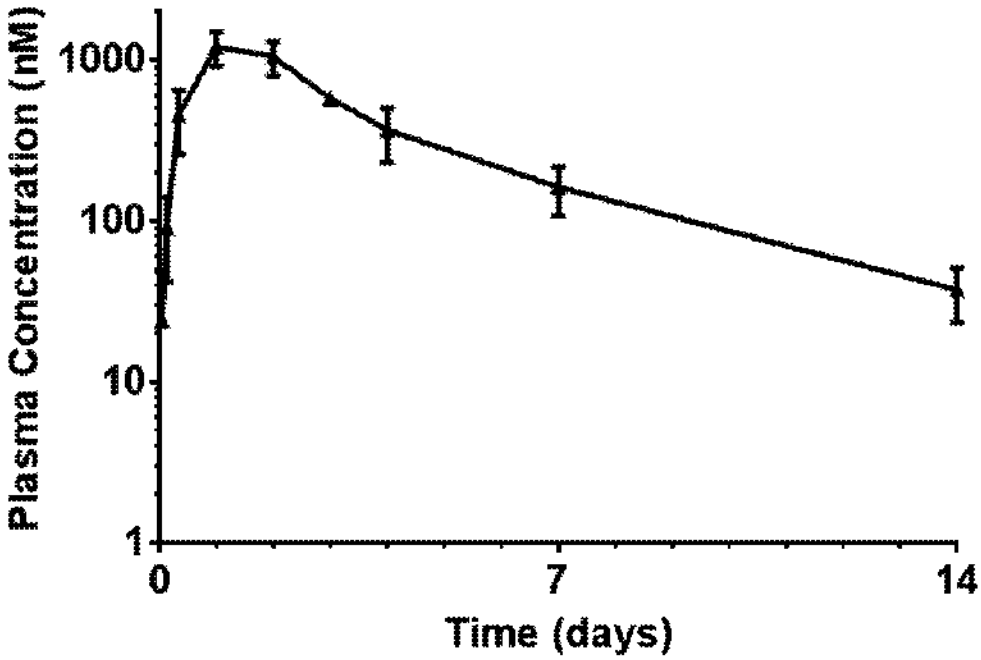

FIG. 10B

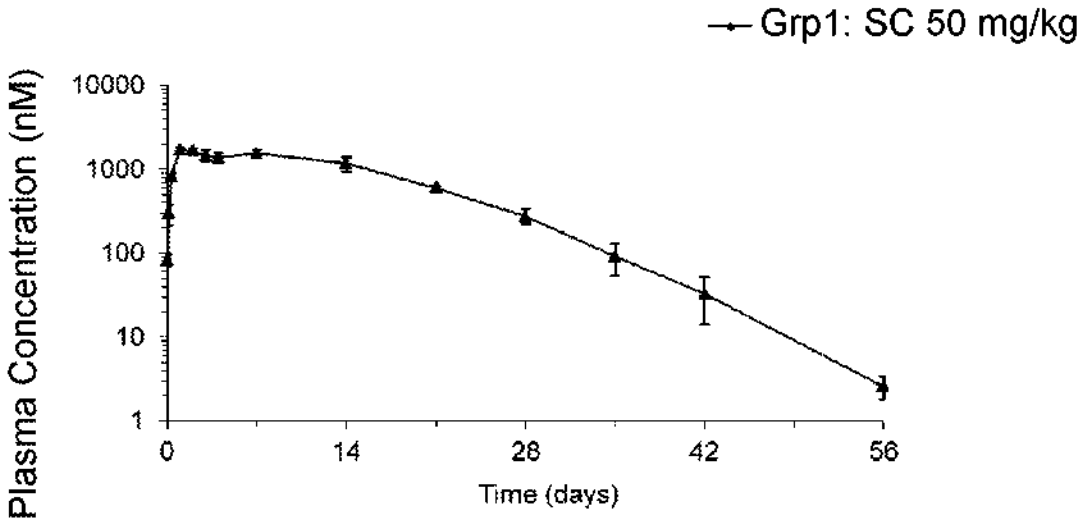

FIG. 11A

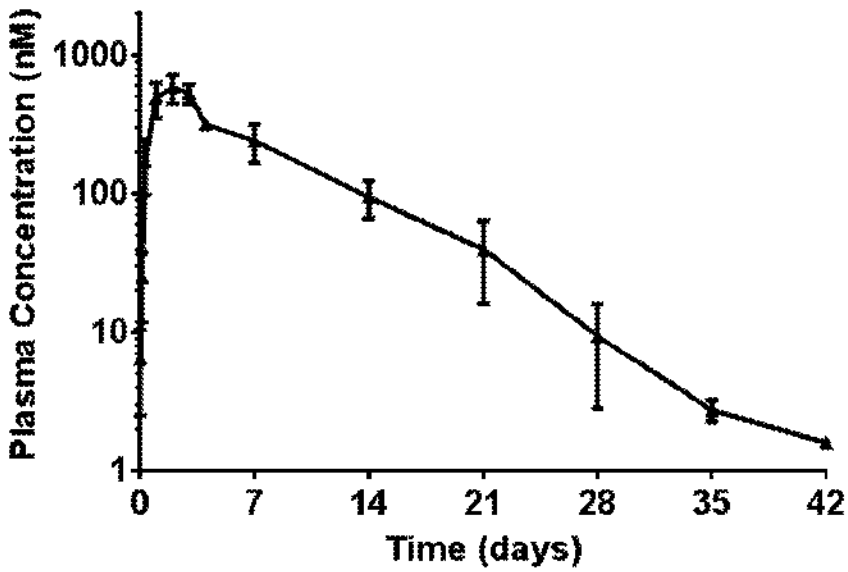

FIG. 11B

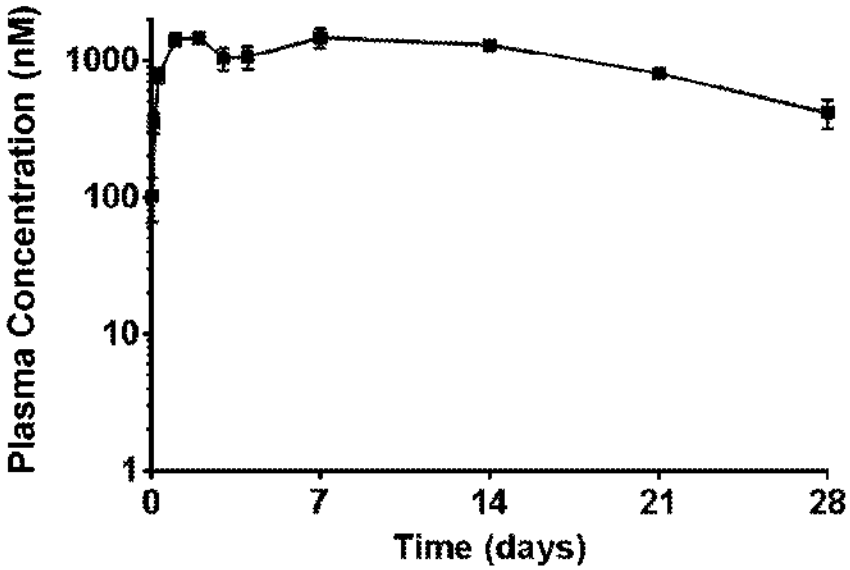

FIG. 12A

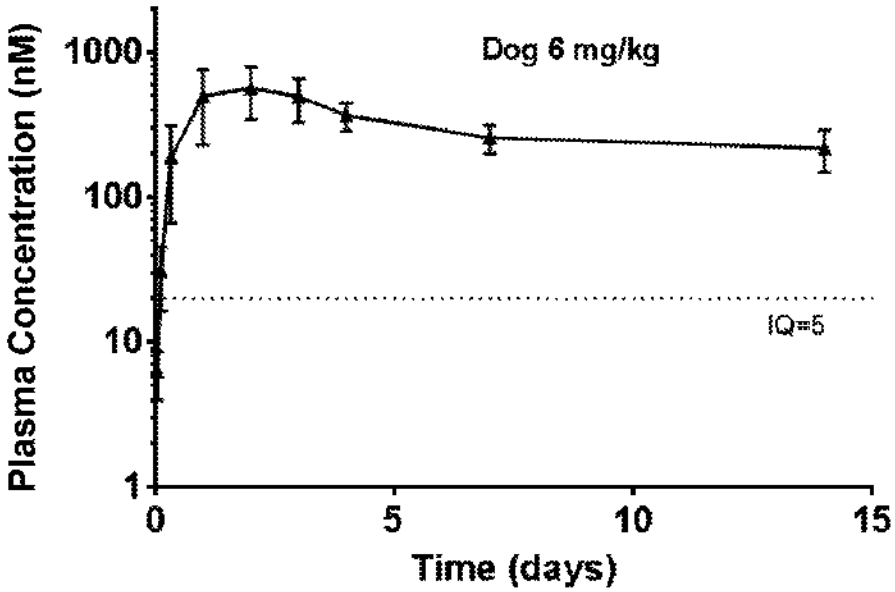

FIG. 12B

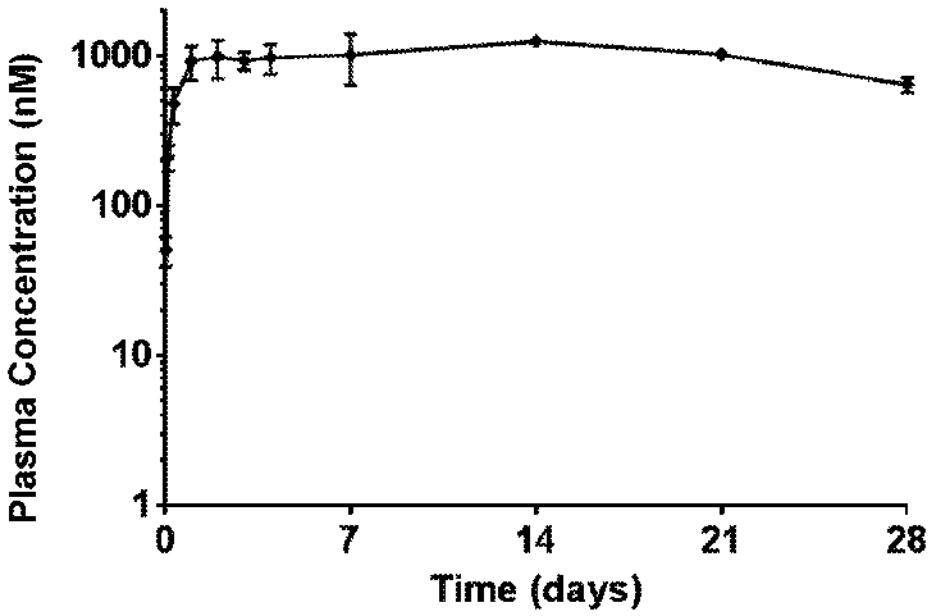

FIG. 13A

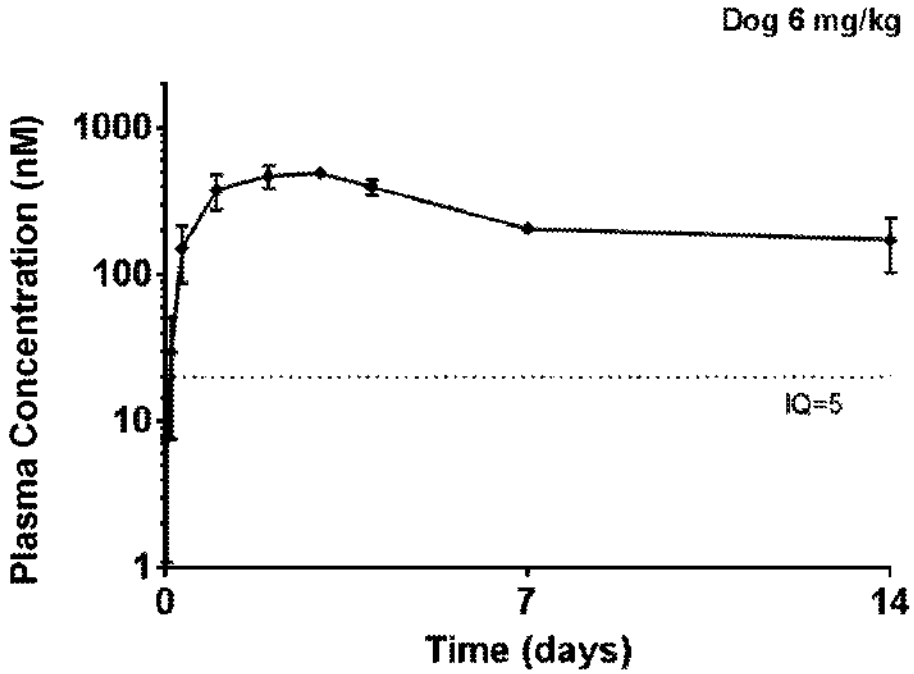

FIG. 13B

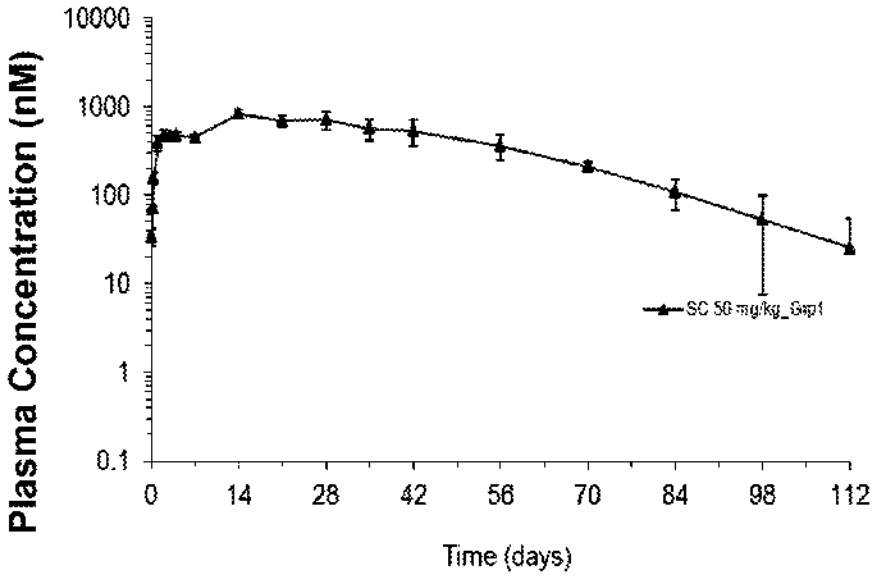

FIG. 14A

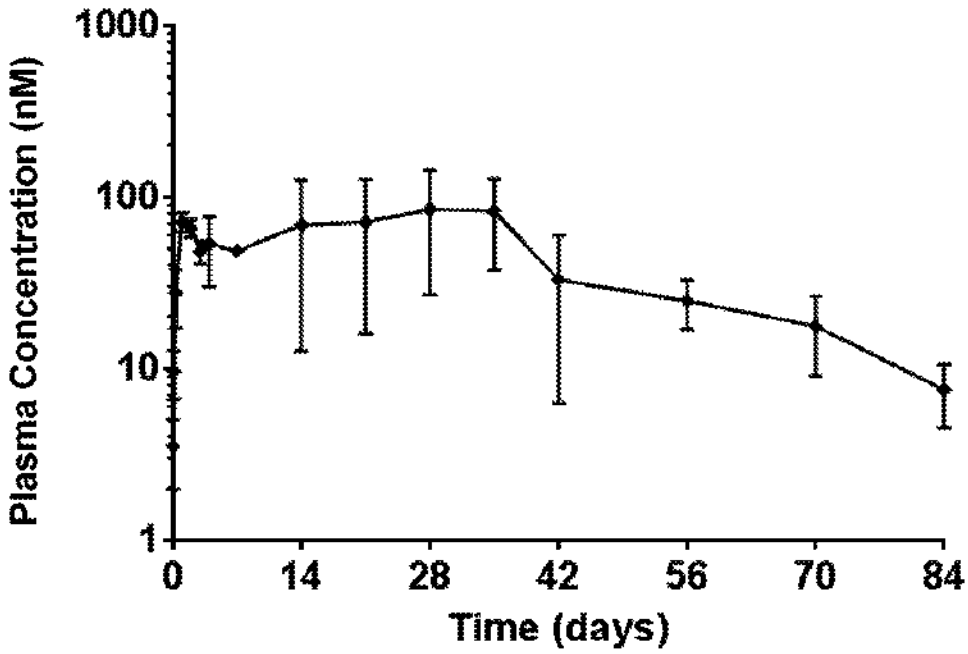

FIG. 14B

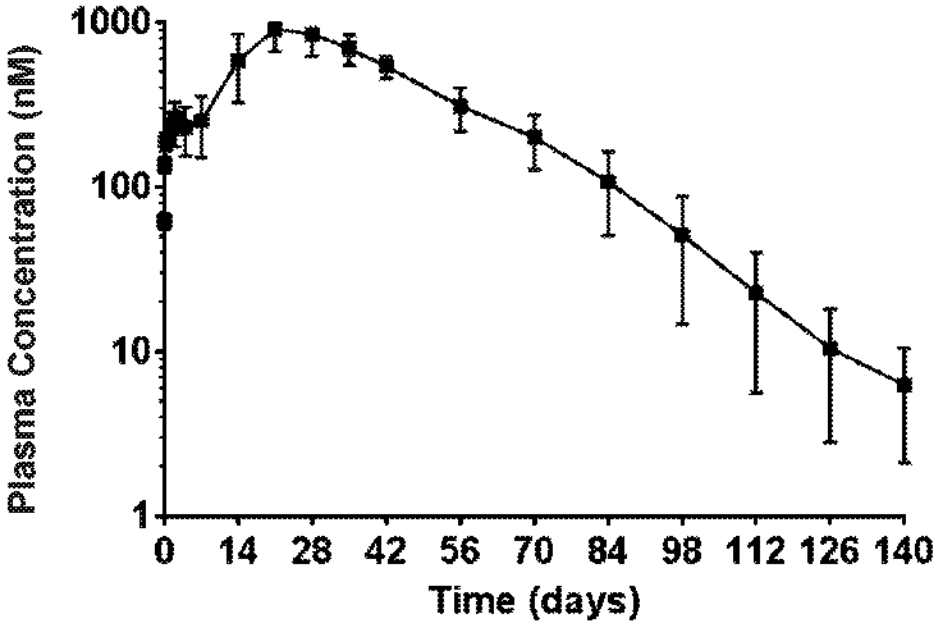

FIG. 15A

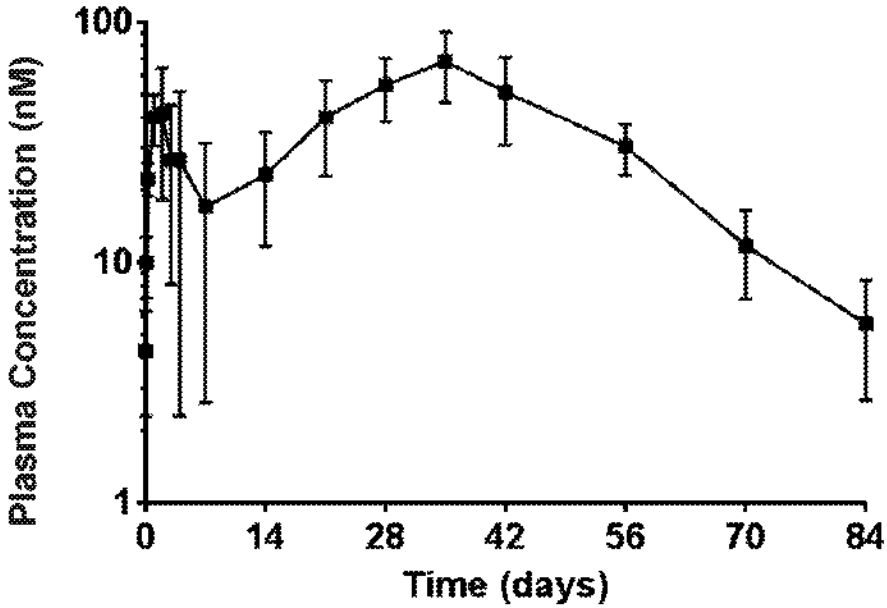

FIG. 15B

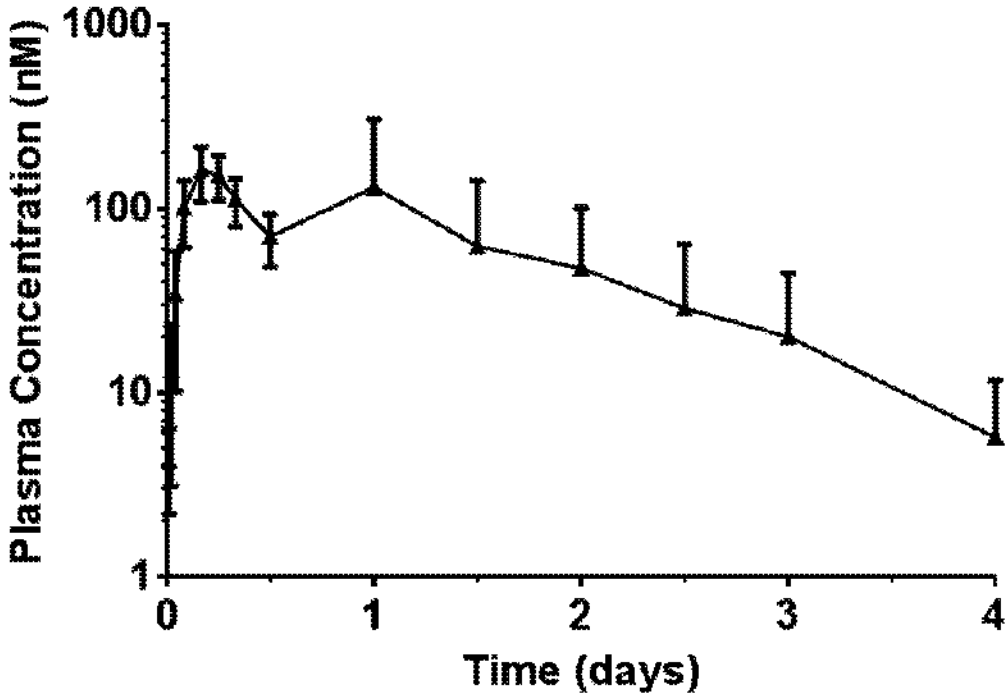
Plasma Concentration (nM)
1000
100
10
1
0
1
2
3
4
Time (days)

FIG. 16

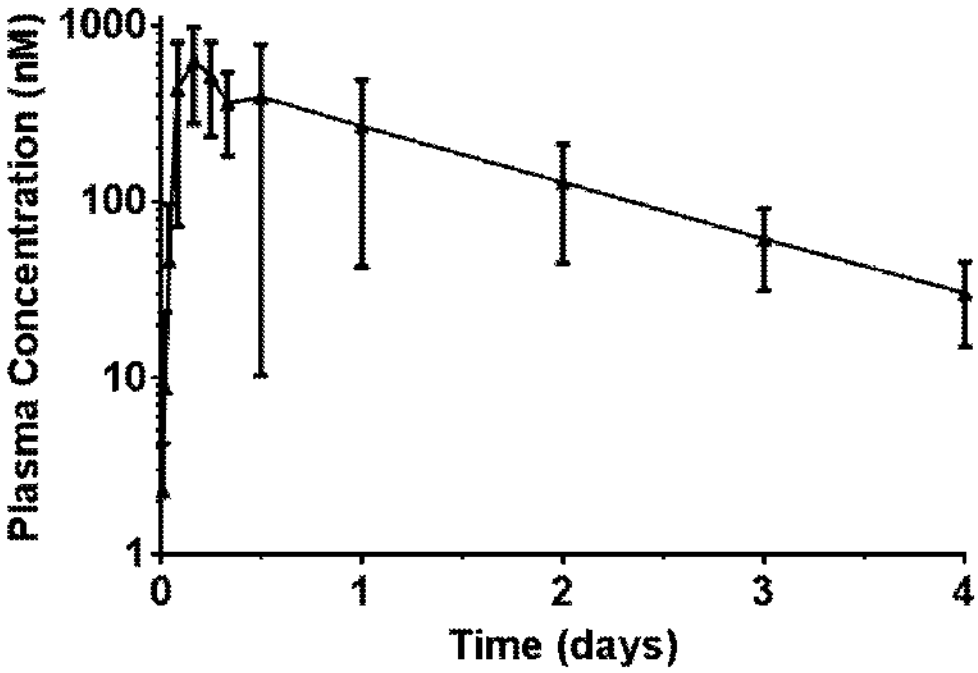
Plasma Concentration (nM)
1000
100
10
1
0
1
2
3
4
Time (days)

FIG. 17

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/041880

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4427 A61K31/4439 A61K45/06 A61K9/00 A61K9/08
A61K9/20 A61K9/48 A61P31/18
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Winston C. Tse: "Discovery of Novel Potent HIV Capsid Inhibitors with Long-Acting Potential", , 14 February 2017 (2017-02-14), XP055632979, Retrieved from the Internet: URL:http://www.natap.org/2017/CROI/croi_17.htm [retrieved on 2019-10-16]	1-17, 22-26, 34,56, 57, 74-81, 83-85,87
Y	the whole document	1-107

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2019	25/10/2019

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Lisa M. Jarvis ET AL: "Conquering HIV's capsid", , 31 July 2017 (2017-07-31), XP055632804, Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/cen-09531-bus2 [retrieved on 2019-10-16] the whole document	1-107
X	WO 2018/035359 A1 (GILEAD SCIENCES INC [US]) 22 February 2018 (2018-02-22) cited in the application	1,26,27, 31-34, 39-41, 43-50, 66-73,88
Y	the whole document	1-107

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/041880

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The Use of Phospholipids to Make Pharmaceutical Form Line Extensions

Peter van Hoogevest, Harry Tiemessen, Josbert M. Metselaar, Simon Drescher, and Alfred Fahr*

This review describes the use of phospholipid excipients to make Pharmaceutical Form (Dosage Form) Line Extensions of existing drugs as part of a Product Life Cycle Management. Product examples and development candidates, which show the versatility of phospholipids as key excipients in formulations to develop line extension drug products for any administration route by reformulating existing products, are provided. The resulting patented products enable the application of a drug substance for another administration route or show an increased efficacy and/or reduced toxicity of the formulated drug substances, or enable a more convenient use, through reduction of dosing frequency, or adapt a product for regulatory requirements for specific patient populations. Parenteral line extensions for lipophilic drugs using non-toxic phospholipid-based solubilising formulations are clearly an alternative to products with solubilising synthetic detergents with the risk for allergic and anaphylactic reactions. This review draws the attention to academic and industrial formulation scientist to consider using phospholipid excipients to reformulate existing products to improve the product properties by an active product life cycle management. Phospholipids are suitable for this purpose because they are biocompatible, biodegradable, non-toxic, and available at large scale and of pharmaceutical grade. Besides, they are well known to regulatory authorities.

1. Introduction

1.1. General aspects

In search of the best possible therapies for the treatment of diseases, the pharmaceutical industry has two main ways to generate new products. Considering that such products comprise the drug substance and the dosage form, the first obvious option is to look for new drug substances, which are more efficacious in certain diseases and/or are less toxic. The development of such New Chemical Entities (NCEs) does require extensive preclinical resources, safety testing, and extensive clinical testing to prove its safe and superior efficacious use. The costs of such developments are immense and can only be carried by major pharmaceutical companies. In addition, the failure rates of such developments are high, but in case of success, such products may generate sales. Another challenge of such an approach is that the development stage may be so long that a considerable part of the life span of the protective patents, which secures the sales of such new products, is consumed. A second option is to employ new formulations of the NCE, which make, e.g., the NCE suitable for another administration route, enable less frequent administration or lower doses, and suppress side effects or increase the efficacy.

Generic drug substances may be reformulated to generate innovative, patentable, drug products serving patients' needs.[1] In this review, these (re)formulations related line extensions for NCEs as well as generic drug substances are called "Pharmaceutical Form Line Extensions."

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In the European Union (EU), extensions of indications are subject to a line extension procedure when changes to strength, pharmaceutical form, and route of administration apply.[2] Such a procedure is necessary because, as compared to the original product, the new product may entail one or more of the following changes of product characteristics, caused by the new dosage form[3]

- "change of bioavailability,"
- "change of pharmacokinetics (PK), e.g., changes in the rate of release,"
- "change or addition of a new strength/potency,"
- "change or addition of a new route of administration."

Line extensions require less research and development (R&D) as the initial discovery, and early-stage clinical research of a new molecular entity is not needed.[4] Further, the supply-side incentives that encourage innovation via patent exclusivity periods can often be applied to line extensions. Thus, line extensions are not subject to generic competition at the same time as the original product, but they are improved substitutes for the original products.[5]

In the seventies of the previous century, reformulation development strategies, resulting in mostly intellectual property (IP)-protected product line extensions, were successfully explored and applied by companies like ALZA Corporation (Palo Alto, USA) and Ciba-Geigy Ltd. (Basel, Switzerland). These companies developed dosage form line extensions based on combining generic drugs and oral slow-release technologies (e.g., osmotic release oral system, OROS) and transdermal delivery systems (e.g., Nitroderm TTS, Estraderm TTS, Nicotinell TTS), respectively, both with impressive sales potentials. Also, the oral product Voltaren with diclofenac sodium was successfully reformulated in a topical dosage form line extension (Voltaren Emulgel) for local pain treatment of, e.g., arthrosis-related complications. More examples of such successful product line extensions can be found in the literature.[6]

Needless to say, that successful reformulations require suitable excipients, which preferably have a broad scope of use, enabling the introduction of one or more of many new features that characterise the line extension for an established drug product. This review illustrates the many options, which exist to make Pharmaceutical Form Line Extensions with phospholipids as key excipients (as part of product life cycle management) and underscores these options by providing examples of these line extensions and patents which cover these products. The cited patents serve as examples to underscore the commercial impact of the developed line extension but do not represent the complete IP protection of these products. The review draws the attention to academic and industrial formulation scientists to consider using phospholipid excipients to reformulate existing products to yield innovative products with improves product properties compared to the original product as part of an active product life cycle management.

1.2. Phospholipids

The molecular structure of phospholipids comprises a glycerol backbone which is esterified in positions 1 and 2 with fatty acids and position 3 with phosphate. The systematic designation of, for example, phosphatidic acid (PA) is 1,2-diacyl-*sn*-glycero-3-phosphate, where "*sn*" means stereospecific numbering or stereo-specifically numbered, i.e., the carbon atom that appears on top in the Fischer projection showing a vertical carbon chain with the hydroxyl group at carbon-2 to the left is designated as C-1.[7] The specific and non-random distribution of substituents over the positions 1, 2, and 3 of the glycerol introduces chirality. In typical membrane phospholipids, the phosphate group is further esterified with an additional alcohol, for instance in phosphatidylcholine (PC) with choline, in phosphatidylethanolamine (PE) with ethanolamine, and in phosphatidylglycerol (PG) with glycerol (**Figure 1**).

Depending upon the structure of the polar region and pH of the medium, PE and PC are zwitterionic and have a neutral charge at pH values of about 7. The phospholipid may have two esterified fatty acids and are called "diacyl-phospholipids," whereas phospholipids with one fatty acid are called "monoacyl-phospholipids" or "lyso-phospholipids." In scientific literature, synthetic phospholipids are named in an abbreviated way according to "number of the position of fatty acids"—"type of fatty acid"—"phosphatidyl"—"alcohol." The number of fatty acids could be "mono" or "di," the fatty acids are described as, e.g., oleoyl or palmitoyl (coming from oleic acid and palmitic acid, respectively), "phosphatidyl" describes the backbone of the phospholipid molecule which encompasses glycerol, further esterified with one or two fatty acid and a phosphate group, and finally the alcohol is mentioned as described above. The International Union of Pure and Applied Chemistry (IUPAC)[8] instead uses "glycero"—"phospho"—"alcohol." Examples are POPC, 1-palmitoyl-2-oleoylphosphatidylcholine (IUPAC: 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) or DOPE, 1,2-dioleoylphosphatidylethanolamine (IUPAC: 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine). The nomenclature of natural phospholipids is described in the Discussion section below.

Technologically, phospholipids can be used as emulsifier, wetting agent, solubiliser, and liposome- and mixed micelle-former. From a pharmaceutical perspective, they are, for instance, used as excipients for solubilising hydrophobic drugs in mixed micelles, liposomes, and emulsions, where phospholipids act as emulsifier. Further on, controlled release or targeted delivery, increasing the therapeutic index of the formulated drug, can be achieved with the aid of phospholipids.[9]

Phospholipids are present in a range of pharmaceutical products and are for these reasons well-known to regulatory authorities. A broad variety of natural as well as synthetic phospholipids with pharmaceutical quality is available, which further increases the possibilities to generate improved (re)formulations of existing drugs.[9]

In the following, product and development examples of phospholipid-based Pharmaceutical Form Line Extensions are provided. The line extensions are systematically discussed in relation to their administration routes.

In all cases, illustrative examples, wherein the phospholipids play a crucial role in improving the pharmaceutical performance of the original products, are shown and commented on. The review does not intend to provide a complete and exhaustive list of all products containing phospholipid excipients. The description of the phospholipids in the corresponding products is taken

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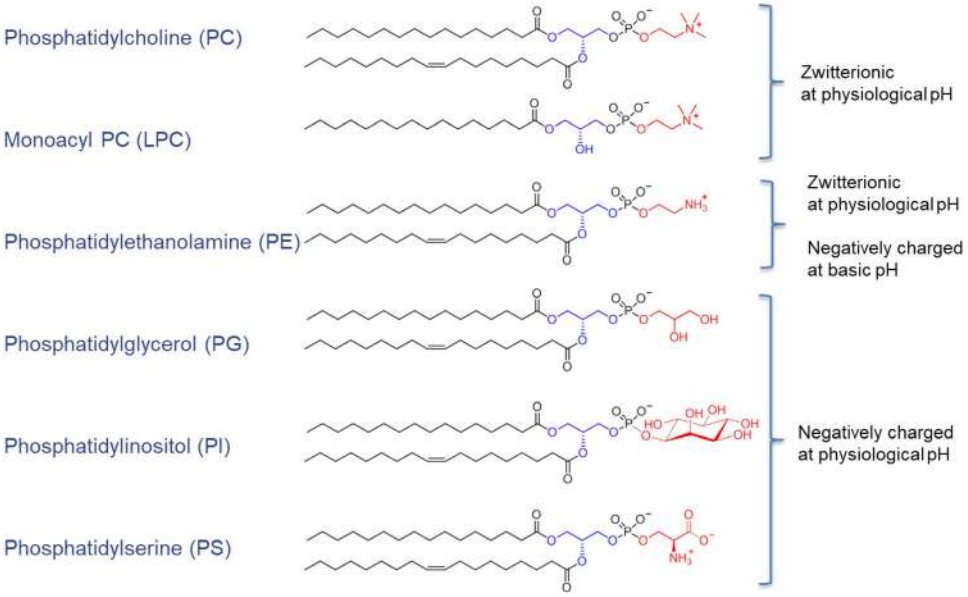

Figure 1. Chemical structure of phospholipids.

Table 1. Examples of Pharmaceutical Form Line Extensions using phospholipids as key excipients to convert an oral dosage form into a parenteral dosage form.

API (Class)	Originator oral product dosage form and (product example)	Parenteral line extension product dosage form and (product)	Advantage of Line extension
Aprepitant (Anti emetic)	Tablet (EMEND)	o/w emulsions with egg lecithin (Cinvanti)	Adequate solubilisation, without organic solvents / synthetic detergents
Carprofen (NSAID)	Tablet (Canidryl)	Mixed micelles with lecithin (Rimadyl)	
Dexamethasone palmitate (Corticosteroid)	Tablet (Dexamethasone USP)	o/w emulsions with egg yolk phospholipids (Limethason)	
Diazepam (Tranquilliser)	Tablet (Valium)	Mixed micelles with soybean lecithin (Valium MM) o/w emulsions with egg lecithin (Diazepam-Lipuro)	
Flurbiprofen axetil (NSAID)	Tablet (Ansaid, Flurbiprofen)	o/w emulsions with egg lecithin (Kaifen)	
Vitamin A, D, and E (Vitamin supplement)	Tablet (various)	Mixed micelles with soybean phospholipids (Cernevit)	
Estradiol (estrogen steroid hormone)	Tablet (Estradiol USP) (Estrace)	Skin flux enhancing component in adhesive layer with lecithin (Vivelle TTS)	Increasing skin penetration, general advantages of TTS versus oral treatment

from the references, which mention the composition of the products.

2. Parenteral Pharmaceutical Form Line Extensions

2.1. Converting from the Oral to the Parenteral Administration Route

In **Table 1**, the possibilities to use phospholipids to convert an oral drug product into a parenteral product are demonstrated with a few notable examples.

The list of parenteral Pharmaceutical Form Line Extension in Table 1 shows that phospholipid-based solubilization technologies play an essential role in reformulation of particularly oral compounds with low water solubility for intravenous administration. The motivation to create parenteral line extensions may be of general reasons (e.g., when patients are unable to take oral medication or to have a fast onset of action) and/or it may be a drug substance-specific issue, as described below.

2.1.1. Aprepitant

The lipophilic antiemetic aprepitant is a substance P/neurokinin-1 (NK_1) receptor antagonist used for chemotherapy-induced nausea and vomiting (CINV) prevention, which is an oral product on the market (EMEND, 40–125 mg tablets).[10] The company Heron Therapeutics (San Diego, USA) found that aprepitant could be successfully reformulated in an oil-in-water (o/w) emulsion using egg lecithin as the main emulsifier to enable solubilization of the drug[11] and the intravenous administration of the original drug. The egg lecithin is used in this product (Cinvanti) as an emulsifier and is an essential component of this type of

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formulation. The same product is discussed in more detail in Section 2.3 as a parenteral Pharmaceutical Form Line Extension where polysorbate as a potentially toxic excipient is replaced from the original product.

2.1.2. Carprofen

Carprofen is a non-steroidal anti-inflammatory drug (NSAID) with low water solubility[12] used in veterinarian medicine for pain treatment as a result of arthrosis. Oral therapy (Canidryl tablets) may give rise to gastric irritation typical for NSAIDs.[13] For these reasons, a parenteral Pharmaceutical Form Line Extension was developed to permit parenteral administration. The resulting product Rimadyl comprises mixed micelles of lecithin and glycolic acid to solubilise the drug substance and to enable subcutaneous injection to dogs.[14] Lecithin is an essential component in the mixed micelles with non-allergenic properties and eliminating the haemolytic activity of the used bile salt.[9]

2.1.3. Dexamethasone

Dexamethasone is administered orally as a tablet.[15] To enable parenteral administration, the company Mitsubishi Tanabe Pharma (Osaka, Japan) followed a coordinated double line extension strategy: A prodrug of dexamethasone, a palmitate ester of dexamethasone, with high oil solubility was developed and formulated in the o/w emulsion product Limethason, suitable for parenteral administration, using egg yolk phospholipids (bearing 79% PC, 17% PE, and 4% other phospholipids by weight) as an emulsifier.[16] This emulsion product is also on the market in Germany (Lipotalon of Recordati Pharma, Ulm, Germany). The alternative approach to make dexamethasone suitable for parenteral administration using the water-soluble dexamethasone sodium phosphate—an inorganic ester of dexamethasone—is inferior, because Lipotalon has a more substantial inhibiting effect on the production of proinflammatory cytokines in peritoneal macrophages than dexamethasone sodium phosphate.[17] Lipotalon appears to be clinically, histologically more efficacious regarding T-cell reactions. In addition, dexamethasone palmitate formulated in an emulsion showed a 5.6-time higher efficacy in inflamed tissue compared to dexamethasone sodium phosphate.[18]

2.1.4. Diazepam

Diazepam was patented in 1959 by Hoffmann-La Roche AG (Basel, Switzerland).[19] It has been one of the most frequently prescribed medications in the world since its launch in 1963.[19b] Injectable diazepam is a valuable adjunct in status epilepticus and severe recurrent convulsive seizures. Diazepam is a useful premedication in patients undergoing surgery. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.[20] Since diazepam is a compound with relatively low water solubility, solubilization formulations are needed to enable intravenous administration. Consequently, Pharmaceutical Form Line Extensions were introduced on the market, which used mixed micelles of soybean lecithin and glycocholic acid (Valium MM, Roche)[21] and o/w emulsions with egg lecithin as emulsifier[22] (Diazepam-Lipuro, B. Braun Melsungen AG),[23] respectively. Diazepam dissolves in the mixed micelles or the oil phase of the o/w emulsion. In both cases, the phospholipid is an essential component in these formulations, which either eliminates the haemolytic effect of the bile salt in the mixed micellar formulation or serves as a non-toxic emulsifier in the o/w emulsion.[9] The o/w emulsion further prevents adsorption of the drug by infusion sets.[24] The mixed micellar product is, however, not on the market anymore.

2.1.5. Flurbiprofen Axetil

Flurbiprofen is a member of the phenylalkanoic acid derivative group of NSAIDs available in 50–100 mg tablets. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents.[25] To enable parenteral administration of this drug, to reduce gastric mucomembranous disturbances caused by oral flurbiprofen, and to enable a fast onset of action, a prodrug of flurbiprofen, flurbiprofen axetil, was developed. Due to its high solubility in oils, flurbiprofen axetil is formulated in o/w emulsion with egg yolk lecithin as the key excipient (Axetil, Kaken Pharmaceuticals Co. Ltd., Tokyo, Japan).[26]

2.1.6. Vitamin A, D, and E

Multivitamin supplements are on the market in oral tablets.[27] In some indications, the parenteral administration, in case of prevented or reduced food intake by, e.g., oesophagus and gastrointestinal (GI) stenosis, coma, persistent vomiting, is required.[28] These multivitamin preparations containing lipophilic vitamins, such as vitamin A (retinol), vitamin D3 (cholecalciferol), and vitamin E (α-tocopherol), need solubilization to enable parenteral administration. Mixed micelles containing soybean phospholipids and glycocholic acid are used in these Pharmaceutical Form Line Extension to solubilise these vitamins (Cernevit, Baxter Germany GmbH, Unterschleißheim, Germany).[28]

Interestingly, the lipophilic vitamin K1 (phytomenadion) is solubilised for oral and parenteral administration with the same mixed micelles. At this way, the developers of this formulation profited from the fact that mixed micelles are suitable for parenteral as well as oral administration and no additional reformulation from an oral to a parenteral line extension was necessary. Also, the orally used mixed micellar formulation may be better absorbed in children with cholestatic disease condition compared to the Cremophor-based products.[29] The mixed micellar formulation is also a clear improvement compared to polyoxyethylated fatty acid containing injectables,[30] which may cause fatal allergic reactions.[31]

2.1.7. Estradiol

A further example of a parenteral Pharmaceutical Form Line Extension is related to estradiol. Estradiol is available in oral dosage forms[32] and a transdermal system (Vivelle TTS). (Note: transdermal administration is grammatically considered as parenteral administration, since oral administration is avoided;

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Table 2. Examples of parenteral Pharmaceutical Form Line Extension, based on liposomes/emulsions, resulting in an increased therapeutic index of the drug substance.

API (Class)	Originator product dosage form and (product example)	Line extension product dosage form and (product)
Cisplatin (Cytostatic)	Aqueous solution (Platinol)	Liposomal suspension, with DPPG, HSPC, MPEG 2000-DSPE (Lipoplatin)
Daunorubicin citrate (Cytostatic)	Lyophilisate (Daunoblastin)	Liposomal suspension, with DSPC and cholesterol (DaunoXome)
Daunorubicin/cytarabine (Cytostatics)	Lyophilisate/aqueous solution (Daunoblastin/Cytarabin USP)	Lyophilised liposomal suspension, with DSPC, DSPG, and cholesterol (Vyxeos)
Doxorubicin HCl (Cytostatic)	Lyophilisate/aqueous solution (Adriamycin, doxorubicin HCl injectable)	Liposomal suspension, with HSPC, MPEG 2000-DSPE and cholesterol (Doxil/Caelyx, Lipodox) Liposomal suspension, with EPC and cholesterol (Myocet)
Doxorubicin HCl (Cytostatic)	Liposomal suspension, with HSPC, MPEG 2000-DSPE, and cholesterol (Doxil/Caelyx, Lipodox) Liposomal suspension with EPC and cholesterol (Myocet)	Liposomal suspension with MPEG 2000-DSPE, DPPC, and MSPC (ThermoDox)
Irinotecan HCl (Cytostatic)	Lyophilisate (Camptosar)	Liposomal suspension with MPEG 2000-DSPE, DSPC, and cholesterol (Onivyde)
Mifamurtide (Immunomodulator)	Micelles MTP-PE (Development stage)	Lyophilised phospholipids followed by in situ preparation of liposomal suspension, with POPC and DOPS (Mepact)
Prostaglandin (Smooth muscle relaxant)	Lyophilizate, α-cyclodextrin complex (Prostavasin)	o/w emulsion with EPC (Liple)
Vincristine sulfate (Cytostatic)	Aqueous solution (Vincristine sulfate USP)	Lyophilised liposomal suspension with sphingomyelin and cholesterol (Marqibo)

however, from the pharmacopoeial point of view, parenterals are sterile dosage forms and transdermal dosage forms are considered as a distinct type of dosage form.) Vivelle, which belongs to parenteral administration forms, is a line extension with several benefits, such as the application of a new transdermal system for once a week administration, instead of taking many tablets, and the assurance of a constant drug level for the entire duration of wear. The Vivelle system comprises three layers. Starting from the visible surface toward the surface attached to the skin, these layers are: 1) a translucent flexible film consisting of ethylene-vinyl alcohol copolymer, polyurethane, urethane polymer, and epoxy resin, 2) an adhesive formulation containing estradiol USP (United States Pharmacopoeia), acrylic adhesive, polyisobutylene, ethylene-vinyl acetate copolymer, 1,3-butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol, and 3) a polyester release liner that is attached to the adhesive surface, which must be removed before the system can be used.[33] Lecithin plays in this type of formulation the role as skin flux enhancer, probably in combination with propylene glycol and oleic acid.

2.2. Improving the Therapeutic Index

From a pharmaceutical-technological point of view, Pharmaceutical Form Line Extensions resulting in a more efficacious drug product and drug products with fewer side effects are most striking. Phospholipids can play a key role in this option, because they are the main building blocks of liposomes and o/w emulsions, as these dosage forms are quite often used to achieve this goal. Both colloidal types of formulations have the potentials to change the body distribution of the associated drug after parenteral administration, resulting in an enrichment of the drug in the diseased target tissues and/or avoidance of "tox-target" organs. In addition, they can replace synthetic detergents in parenteral formulations of whose parenteral application is hampered by the risk of allergic reactions up to anaphylactic shock.

To allow a systematic discussion of all these options, the parenteral Pharmaceutical Form Line Extensions are presented into three product categories which 1) show an improvement of the therapeutic index employing drug targeting to the diseased site and/or avoidance of "tox target" organs, 2) same as 1) and additionally eliminates potentially toxic excipients, and 3) show a less toxic formulation by removal of potentially toxic excipients.

The improvement of therapeutic index is qualitatively described by the increase of efficacy and/or improvement of the safety profile. The exact factor at which the therapeutic index is increased cannot be provided, because of the lack of clinical research data comparing directly, ideally in the same patient population, the line extension and the originator product. **Table 2** shows such product examples of the use of liposomes/emulsions to optimise the therapeutic index of intravenously administered drug substances. For more details on the characteristics of liposome products and sales, refer to Crommelin et al., 2020.[34] Further line extensions, which increase the therapeutic index and additionally eliminate suspect potentially toxic excipients, are discussed in Section 2.3. A recent update on the clinical performance of these line extensions based on liposomes can be found in Beltrán-Gracia et al., 2019.[35]

2.2.1. Cisplatin

Cisplatin is a chemotherapy medication to treat several cancers. It is available as Cisplatin Injection, which is a sterile aqueous solution, each milliliter containing 1 mg of cisplatin and 9 mg sodium chloride in water for injection and hydrochloric acid

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and/or sodium hydroxide added to adjust pH to 3.5–4.5. It is indicated for metastatic testicular tumors, advanced bladder cancer, and metastatic ovarian tumors.[36]

For this cytostatic drug, a parenteral Pharmaceutical Form Line Extension was developed. On November 30, 2007 the European Medicines Agency (EMA, prior to 2010 named EMEA) granted the orphan drug status to liposomal cisplatin of Regulon Inc., Athens, Greece for the treatment of pancreatic cancer.[37] The product Lipoplatin is a liposomal formulation of cisplatin. The liposomes are composed of 1,2-dipalmitoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol), sodium salt (DPPG), hydrogenated soybean PC (HSPC), cholesterol, and *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE). It was developed to reduce the toxicity rendered by cisplatin and to improve the targeting of the drug to the primary tumor and metastases by enhancing its half-life circulation time in body fluids and tissues. Preclinical studies have shown Lipoplatin's lower toxicity in rats, in comparison to cisplatin.[38] Lipoplatin has also shown a high concentration in tumors and metastases at levels up to 200-fold higher compared to the adjacent normal tissue in surgical specimens from patients.[39] Phase I, II, and III studies have been published,[40] and a relevant patent for this product is US Patent 6 511 676.[41]

2.2.2. Daunorubicin

Daunorubicin is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a sterile lyophilised powder in vials for intravenous administration only. Cerubidine (daunorubicin) is indicated for remission induction in acute non-lymphocytic leukaemia of adults and for remission induction in acute lymphocytic leukaemia of children and adults.[42] Myocardial toxicity may occur either during therapy or months to years after termination of treatment.[42]

To suppress the cardiotoxicity and possibly enhance the tumor efficacy, an improved parenteral Pharmaceutical Form Line Extension, DaunoXome, was developed based on the preparation of liposomes with lipid composition 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and cholesterol in a 2:1 molar ratio.[43] Based on imaging studies with ^{111}In-labeled liposomes, it was postulated that DaunoXome extravasates selectively into solid tumors through discontinuities in the capillary beads arising in tumor neovasculature. Preclinical studies have indicated that DaunoXome increases in vivo daunorubicin tumor delivery by about tenfold over a conventional drug, yielding a comparable increase in therapeutic efficacy. Studies on the modes of delivery and action indicated that DaunoXome arrives at and accumulates within tumor cells primarily in an intact form. Once within the tumor cells, the liposomes release drug over a prolonged period (36 h or more), providing sustained, high levels of cytotoxic material within tumor cells.[44] Clinical PK paralleled findings from animal studies. In humans, DaunoXome produced daunorubicin plasma area under the curve (AUC) levels that were more than 35-fold higher than those reported for comparable doses of non-encapsulated drug at 80 mg m^{-2}. Cardiotoxicity was not clinically observed even for patients receiving more than 1 g m^{-2} cumulative daunorubicin.[45]

Based on these findings, the orphan drug status was granted to DaunoXome for the treatment of Kaposi´s sarcoma.[46] Later, DaunoXome was granted the orphan drug status in the EU for the treatment of acute myeloid leukaemia.[47]

2.2.3. Daunorubicin/Cytarabine

In oncology, often various cytostatic compounds are combined. For treatment of acute myeloid leukaemia, the combination of cytarabine and daunorubicin is being used.[48] They act synergistically, because daunorubicin inhibits deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Cytarabine, in turn, decreases DNA synthesis by inhibiting DNA polymerase. Daunorubicin is provided as a sterile lyophilised powder in vials for intravenous administration only (see above),[42] whereas Cytarabine for Injection USP, commonly known as ara-C, is provided as sterile lyophilised cytarabine for intravenous, intrathecal, or subcutaneous administration.[49]

The company CELATOR Pharmaceuticals Inc (Ewing, NJ) later Jazz Pharmaceuticals plc (Dublin, Ireland) combined the use of the two coencapsulated drug substances in liposomes to make a Pharmaceutical Form Line Extension.[50] Basically, this line extension is a double line extension by combining two drugs and additionally introducing a new dosage form of both combined drugs.

Liposomes containing daunorubicin and cytarabine at the same time are the first dual-drug liposomal encapsulation product approved by the US Food & Drug Administration (FDA). The fixed 1:5 molar ratio of daunorubicin/cytarabine was shown to be the most synergistic ratio for killing leukaemia cells in vitro and in murine models. The resulting product Vyxeos comprises, besides the drug substances daunorubicin and cytarabine, the following inactive ingredients: DSPC, 1,2-distearoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol), sodium salt (DSPG), cholesterol, copper gluconate, triethanolamine, and sucrose.[51]

These daunorubicin/cytarabine liposomes are approved for the treatment of adults with newly diagnosed therapy-related acute myeloid leukaemia (AML) or AML with myelodysplasia-related changes (AML-MRC).[51,52] The efficacy of this liposomal combination of two cytostatic compounds is based on the fact that the liposomes have a propensity for uptake by the bone marrow, which is the target site for AML treatment. In leukaemia-bearing mice, the liposomes are taken up by leukaemia cells to a greater extent than by normal bone marrow cells, and the liposomes undergo degradation thereby releasing daunorubicin and cytarabine within the intracellular environment.[53]

This product is an exciting example of how liposome technology can be applied to deliver even combinations of (coencapsulated) drugs to the diseased target sites.

2.2.4. Doxorubicin HCl

Doxorubicin hydrochloride is a cytotoxic, anthracycline, topoisomerase II inhibitor isolated from cultures of *Streptomyces peucetius var. caesius*. Doxorubicin HCl for Injection USP, is a sterile lyophilised powder.[54] The occurrence of cardiomyopathy complicates the use of this drug. The risk of cardiomyopathy is proportional to the cumulative exposure with incidence

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rates from 1% to 20% for cumulative doses ranging from 300 to 500 mg m^{-2} when doxorubicin HCl is administered every 3 weeks. Doxorubicin HCl is indicated as a component of multi-agent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer. Also, many other cancers can be treated with doxorubicin HCl.[54]

To suppress this cardiotoxicity, Pharmaceutical Form Line Extensions of doxorubicin HCl were developed based on the use of PEGylated liposomes (Doxil/Caelyx/Lipodox; Doxil and Caelyx are the brand names of the doxorubicin liposomes in the US and EU, respectively, whereas Lipodox is the generic version) and non-PEGylated liposomes (Myocet). Here, the abbreviation PEG stands for polyethylene glycol.

Doxil is a sterile, liposomal dispersion of so-called "stealth liposome" carriers, which are composed of cholesterol, HSPC, and MPEG 2000-DSPE. The "stealth effect" is related to the presence of PEG on the liposomal surface, which extends the blood-circulation time by reducing recognition by the mononuclear phagocyte system uptake. More than 90% of the drug is encapsulated in the PEGylated liposomes.

Doxil is considered as the first FDA-approved nanodrug (1995).[55] Its efficacy is based on four unrelated principles

1) prolonged drug circulation time and avoidance of the premature clearance by the mononuclear phagocytic system (MPS) owing to PEGylation,
2) high and stable remote loading of doxorubicin driven by a transmembrane ammonium sulfate gradient, which also allows for drug release at the tumor,
3) having the liposomal lipid bilayer in a "liquid ordered" phase since HSPC—a lipid with a high transition temperature (T_m about 53 °C)—and cholesterol are used, making the liposomes stable in blood circulation and suppressing the leakage of the encapsulated drug substance. Due to the PEGylated lipid in the liposomal membran and the enhanced permeability and retention (EPR) effect, Doxil liposomes are "passively targeted" to tumors, and the encapsulated doxorubicin is released and becomes available to tumor cells.[55]
4) Finally, it is further proposed that the release of the drug substance from the liposomes within the tumor is triggered by the ammonia production caused by glutaminolysis.[56]

The Doxil line extension shows superior efficacy over former conventional therapy in case of Kaposi's sarcoma, recurrent ovarian cancer over comparator drug and equivalent efficacy in metastatic breast cancer and reduced cardiotoxicity compared to doxorubicin HCl. In addition, Doxil demonstrates a significant reduction of cardiotoxicity as compared to doxorubicin HCl in all settings.[55] A drawback of this new formulation is, however, the occurrence of the so-called Palmar-Plantar Erythrodysesthesia Syndrome (Hand-Foot Syndrome), which has become the dose-limiting toxicity. Furthermore, the widespread use of this product revealed the possibility of (pseudo)allergic infusion reactions (often referred to as complement activation-related pseudoallergy or CARPA). Most of these hypersensitivity reactions are transient and mild, but life-threatening reactions also have been documented in hypersensitive patients (see, for example, van den Hoven et al.,[57] and references therein). These reactions usually occur at the start of infusion. While this seems to be a general side effect of intravenous administration of colloidal particles, it is currently unclear whether the specific lipid composition of the product plays a role. This CARPA effect can, however, be reduced by premedication and slowing down the initial infusion rate.[58]

Doxil was not protected by a formulation patent but indirectly by patents covering the use of a transmembrane gradient to load liposomes with weak bases like doxorubicin[59] and the use of PEGylated lipids to prolong the circulation time of liposomes.[60] Upon entering the USA market, Doxil sales benefited from 14 years of patent protection in the USA.

The non-PEGylated liposomal product Myocet with doxorubicin (initially developed by The Liposome Company, later Elan Pharmaceuticals, Princeton, NJ and other companies) comprises the lipids cholesterol and egg phosphatidylcholine (EPC). US Patent 5 616 341, describing the compositions used for in situ loading of the liposomes with doxorubicin, covered the product.[61]

The liposomes show after intravenous administration an increased blood level of total doxorubicin over time suggesting a minor prolonged residence time in the blood circulation.[62] In clinical practice, Myocet shows comparable efficacy as doxorubicin HCl but, just like Doxil, reduced cardiotoxicity. In contrast to Doxil, there is no occurrence of the Hand-Foot Syndrome. Myocet is approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide. Despite these positive features, the product is not popular. A severe limitation of Myocet is related to its administration form which is presented as a three-vial system: Myocet doxorubicin HCl (lyophilised), Myocet liposomes (aqueous dispersion), and Myocet buffer, used for in situ loading of the liposomes with doxorubicin. Additionally, the high costs are a hindrance.[63]

A further Pharmaceutical Form Line Extension based on Doxil and doxorubicin HCl with the aim to further increase the therapeutic index of doxorubicin HCl, is ThermoDox. ThermoDox is an intravenous liposomal dosage form of doxorubicin, whose phospholipid composition is optimised to release the doxorubicin HCl content at localised tumor site or intratumorally by locally applied hyperthermia. The target indication of this line extension is the treatment of primary liver tumor, whereas the two original/parent products Doxil and doxorubicin HCl are not used for this indication.[54,64] This product has been developed by Celsion Corporation (Lawrenceville, NJ) and is covered by patents.[65] At present, ThermoDox has the orphan drug designation in EU[66] and US.[67]

The ThermoDox product comprises 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), the lysolipid 1-stearoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (monostearoylphosphatidylcholine, MSPC), and MPEG 2000-DSPE. The addition of MSPC to the composition accelerates drug release by a slight reduction in the transition temperature of DPPC enabling local release by hyperthermia treatment through non-invasive focused ultrasound. The presence of the PEGylated lipid helps in attaining lysolipid-induced permeability at a faster rate.[68] The use of these thermosensitive liposomes and the local release result in a 25-fold higher drug concentration at the target site as compared to intravenous infusion of the unencapsulated drug and fivefold higher drug concentration compared to Doxil.

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Despite these promising features, obtaining clinical evidence for the usefulness of this approach appears challenging.[69] Exploring other localised cancer indication, such as bladder cancer may be a more promising indication.[70] An impression on the patents covering the product can be obtained from the web.[71]

2.2.5. Irinotecan

Irinotecan hydrochloride (Camptosar Injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Camptosar is supplied as a sterile, aqueous solution.[72] Camptosar Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum and is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea.

As with the previously discussed cytostatic compounds, the motivation to make a Pharmaceutical Form Line Extension was to improve either the efficacy and/or suppress the toxicity of irinotecan. It was found that irinotecan encapsulated in liposomes—liposomal irinotecan was originally developed by Hermes Bioscience (D. Papahadjopoulos) and patented,[73] further developed by Merrimack Pharmaceuticals, and now owned by Ipsen Biopharmaceuticals Inc.; the Onivyde trademark was filed in 2013[74]—showed in preclinical studies a maximum tolerated dose in normal mice of 80 mg kg^{-1} for free irinotecan and >320 mg kg^{-1} for the liposomal counterpart, respectively. Liposomal irinotecan showed markedly superior efficacy when compared with free irinotecan in human breast and colon cancer xenograft models.[68c,75] In clinical studies, it was found to be efficacious in the treatment of pancreatic cancer. In 2014, Onivyde received the orphan drug status from the FDA[76] and in 2015 from the EMA.[77] Onivyde is the first FDA-approved therapy in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. The formulation comprises cholesterol, DSPC, and MPEG 2000-DSPE. The drug is loaded into and kept inside the liposomes following a rather elaborate procedure using polymeric or non-polymeric highly charged anions and intraliposomal trapping agents-like polyphosphate or sucrose octasulfate in combination with a high-pK_a polyalkylamine gradient, which facilitates the encapsulation of irinotecan at a high drug-to-lipid ratio. An extensive IP umbrella covers the product and concomitant therapy (see orange book of the FDA,[78] owned by Ipsen Biopharmaceuticals Inc). It should be noted that the line extension is used for another cancer indication than the original parent product. The irinotecan HCl injectable was approved in the US in 1996, whereas Onivyde received FDA approval 19 years later.

2.2.6. Mifamurtide

The product based on mifamurtide (Mepact) is not a Pharmaceutical Form Line Extension derived from a parent drug product but is an example of the development of a line extension during the R&D stage to convert an aqueous solution of the drug into a liposomal dosage form, which showed an increased therapeutic index. The efficacy of the product is based on the finding that macrophages can be activated to a tumoricidal, microbicidal, and antiviral state by a wide variety of naturally occurring and synthetic agents. Muramyldipeptide (MDP) is the minimal structural unit of the cell wall of *Mycobacteria* with immune-potentiating activity[79] that is capable of activating macrophages.[80] A lipophilic analogue of MDP, MTP-PE (muramyltripeptide-phosphatidylethanolamine), has been synthesised to obtain a more stable association with liposomes, because MTP-PE can be inserted into the phospholipid bilayer structure. Liposomal MTP-PE has been shown in vitro to enhance the activation of murine macrophages and human monocytes by 100-fold compared with free MDP. In addition, systemic administration of liposomes containing MTP-PE has been shown to eradicate spontaneous metastases in several animal tumor models, including dogs with autochthonous osteogenic sarcoma metastases.[81] Based on these findings, a stable and reproducible preparation of liposomal MTP-PE, with total entrapment of MTP-PE, was developed by Ciba-Geigy Ltd. (Basel, Switzerland) for clinical use in humans.[82]

This product, which can be considered as a double line extension (conversion of the water-soluble MDP to the phospholipid derivative MTP-PE with amphiphilic properties and simultaneously conversion of the micellar solution of MTP-PE to MTP-PE liposomes) comprises a sterile lyophilisate of the synthetic phospholipids POPC and 1,2-dioleoyl-*sn*-glycero-3-phospho-L-serine, sodium salt (DOPS) in a 7:3 weight ratio containing the MTP-PE at a 1:250 w/w drug-to-lipid weight ratio. The multilamellar liposomes are in situ prepared by addition of saline to the lyophilisate. The phosphatidylserine (PS) component in the formulation was selected to mimic the phospholipid components of the outer leaflet of the membrane of senescent erythrocytes, which are preferably taken up by macrophages. The application of this formulation in toxicity-sensitive species caused a tenfold reduction in adverse side effects compared with free MTP-PE in aqueous solution.[83] At this way, the MTP-PE is efficiently targeted to (lung) macrophages, which activates their tumoricidal state. This therapy concept was explored in the clinic with children suffering from osteosarcoma to eradicate lung metastases after removal of the primary tumor by activated lung macrophages.[84] After assessment of the clinical efficacy by the EMA,[85] the European Commission formally granted in 2009 a centralised marketing authorization for Mepact for the treatment of patients with non-metastatic, resectable osteosarcoma.[86] Mepact was already granted orphan medicinal product status in Europe in 2004 and in the US in 2001.[87] Mepact was protected by patents[88] and is nowadays marketed by Takeda Pharmaceutical Company (Tokyo, Japan) in Europe. This example illustrates how phospholipids can be used to deliver selected drugs to macrophages as part of immunotherapy.

2.2.7. Prostaglandin

Alprostadil (prostaglandin E1, PGE1) is one of the prostaglandins, a family of naturally occurring acidic lipids with various pharmacological effects. As an endogenous substance, PGE1 exerts its biological effects either directly or

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indirectly by regulating and modifying the synthesis and effects of other hormones and mediators. Alprostadil is a smooth muscle relaxant.

The drug substance is on the market in an injectable cyclodextrin formulation (Prostavasin). The purpose of the cyclodextrin is to solubilise the lipophilic prostaglandin compound.[89] The product is used for the therapy of peripheral arterial occlusive disease stages III and IV according to Fontaine et al.[90]

Japanese researchers found that incorporation of the prostaglandin in an o/w emulsion with soybean oil as oil phase (10%) and EPC (1.8%) as emulsifier was more effective than the comparable cyclodextrin formulation for the treatment of peripheral vascular diseases.[91] The o/w emulsion product Liple of Mitsubishi Tanabe Pharmaceutical (Osaka, Japan)—initially developed by Green Cross and covered by US Patent 4 684 633,[92]which is based on the described findings—, is used for indications, such as improvement of extremital ulcers, resting pains in chronic occlusive arterial diseases (Buerger´s disease) and others.[93] The egg phospholipid permits the formulation of this drug substance in an emulsion and is, as emulsifier, a key component of this Pharmaceutical Form Line Extension.

2.2.8. Vincristine Sulfate

Vincristine sulfate Injection (USP) is a sterile, preservative-free, single-use only solution available for intravenous administration. It is indicated in acute leukaemia and has also been shown to be effective in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor. The most common adverse reaction is hair loss; the most troublesome adverse reactions are of neuromuscular origin.[94]

As pointed out by Cullis,[95] vincristine sulfate was selected for inclusion in a phospholipid-based (liposomal) Pharmaceutical Form Line Extension for three reasons. First, it is one of the most commonly used anticancer drugs, second, vincristine is a cell-cycle specific drug and an extended release from liposomes may result in enhanced potency, and third, neurotoxicity as dose-limiting side effect of vincristine sulfate, which may be reduced as result of encapsulation in liposomes. Preclinical development indeed showed that the efficacy of the liposomal vincristine was increased and the general toxicity decreased, when the release from the liposomes in the blood circulation was delayed.[96] The optimal lipids were the natural lipids egg sphingomyelin (ESM) and cholesterol prepared as relatively small liposomes.

Based on these findings, a clinical dosage form was developed[97] showing an increased efficacy against non-Hodgkin's lymphoma and reduced toxicity compared to the original vincristine sulfate injectable.[98] The clinical dosage form is a kit with three vials for in situ preparation of the vincristine sulfate liposomes, which comprises vials with vincristine sulfate injection, sphingomyelin/cholesterol liposome injection, and sodium phosphate injection, respectively. Just like the in situ preparation of Myocet, the procedure needs a controlled heating step in a water bath,[99] which makes the procedure elaborate.

Despite favorable Phase II/III results in 2004, the FDA did not approve the product.[100] The FDA[101] granted the orphan drug status in 2007; the EMA did this in 2008.[102] The company Talon Therapeutics (San Francisco, CA) took the vincristine sulfate liposomes successfully forward for another indication, that is Philadelphia chromosome-negative acute lymphoblastic leukaemia, and in 2012, it received approval by the FDA, 25 years after the market introduction of the Vincristine sulfate injectable originator product. The product is now marketed by Spectrum Pharmaceuticals (Irvine, CA) under the trade name Marqibo. Marqibo is covered by several patents;[103] data taken from ref. [104]. This product is another example of the use of phospholipids to develop a superior parenteral Pharmaceutical Form Line Extension. However, Marqibo is only approved for one disease indication (acute leukaemia) compared to vincristine sulfate injection (see above).[94]

Several interesting line extension developments in this category are ongoing. In the following, a few selected examples are discussed.

2.2.9. Corticosteroid Liposomes

The company Enceladus Pharmaceuticals BV (Naarden, The Netherlands) is developing Nanocort, which is a liposomal prednisolone formulation for treatment of acute manifestations of inflammatory diseases, such as rheumatoid arthritis and ulcerative colitis.[105] Prednisolone is a glucocorticoid, which is available for oral therapy in, e.g., tablet form or as injectable suspension for intra-articular administration (e.g., Predni H Injekt of Winthrop Arzneimittel GmbH, Frankfurt am Main, Germany). Water-soluble esters, such as the phosphate (Prednisolone Sodium Phosphate Injection USP) or hemisuccinate esters (Prednisolut, Mibe Arzneimittel GmbH, Brehna, Germany) are used for intravenous administration.

Glucocorticoids are highly effective anti-inflammatory drugs, but their use in arthritis therapy is controversial due to a high incidence of serious adverse effects occurring during chronic treatment.[106] As a result of rapid elimination from the circulation and unfavorable tissue distribution, systemic therapy with glucocorticoid results in poor target localization of the drug, which often necessitates the use of high doses and intensive dosing schedules.[107] Targeted delivery of glucocorticoids may significantly increase the concentration of the drug in the inflamed tissue.[108] The liposomal formulation in development is composed of DPPC, cholesterol, and MPEG 2000-DSPE in a molar ratio of 1.85:1.0:0.15.[108a]

In 2016, Enceladus announced positive results from a Phase IIa study in patients with active rheumatoid arthritis or in ulcerative colitis using Nanocort.[109]

Another product under development by Enceladus is Oncocort,[105] which is liposomal dexamethasone for castration-resistant prostate carcinoma and metastasised multiple myeloma. In both indications, corticosteroids are part of the standard-of-care and have proven to be efficacious, albeit with limitations due to other potential side effects. Preclinical studies have shown that targeted delivery of corticosteroids in animal models for these indications can be a promising strategy to improve efficacy and reduce toxicity.[110]

Since infusion reactions as a result of complement activation as shown with PEGylated liposomal doxorubicin are less acceptable in a non-life-threatening disease, such as inflammation, the

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development of Nanocort triggered further attempts to minimise these reactions.[111] Recently, it was discovered that a very slow initial rate of infusion followed by carefully step by step increasing the infusion rate is key for avoiding these reactions. These protocols are now implemented in clinical practice.[112] The glucocorticoid liposomes are covered by an extensive IP portfolio.[113]

2.2.10. Gemcitabine

Gemcitabine, a nucleoside analogue and deoxycytidine antimetabolite, is characterised by activity against many kinds of tumors. It is available as the HCl salt in lyophilised form (Gemzar)[114] for intravenous treatment of ovarian, breast, non-small cell lung, and pancreatic cancer. Primary dose-limiting toxic effects are myelosuppression, neutropenia, leucopoenia, anemia, and thrombocytopenia. The main limitation of using this active compound is the rapid inactivation by deoxycytidine deaminase following intravenous administration in vivo. As a result, the compound needs to be administered at a high-dose level, and because of the narrow therapeutic index, this high dosing may give rise to severe side effects.

In the past, several attempts were made to improve the therapeutic index of gemcitabine. High hopes were raised for liposomes as potential tumor delivery (e.g., GemLip).[115] Although this approach seemed successful in the preclinic, this liposomal form of gemcitabine has never been clinically tested.

In addition, lipid derivatives of gemcitabine, such as CP-4126 of Clavis Pharma ASA (Oslo, Norway) and Clovis Oncology Inc. (Boulder, CO) were explored;[116] so far without success.[117] Nevertheless, the Japanese company Fujifilm (Tokyo, Japan) is now pursuing clinical research with a Pharmaceutical Form Line Extension based on liposomal gemcitabine (FF-10832) and presented favorable preclinical findings.[118] In contrast to the liposomal form of twenty years ago, which comprises hydrogenated EPC and cholesterol,[119] the liposomal dosage form of Fujifilm comprises cholesterol, HSPC, and MPEG 2000-DSPE in a 4:15:1 molar ratio and therefore has a longer circulation half-life. The optimised lipid composition allows for effective drug encapsulation over 97.5% for the total amount of gemcitabine (0.5 mg mL^{-1}). Electron microscopy (EM) data revealed that FF-10832 had a homogeneous appearance and consisted of unilamellar liposomes with a mean particle size of 80 nm.[118b] In 2018, Fujifilm started clinical trials in the US for its patented[120] anticancer agent FF-10832 to assess it as a potential treatment for advanced solid tumors.[121]

2.3. Replacing Potentially Toxic Excipients

Organic solvents (for example, ethanol and propylene glycol) and synthetic detergents, such as polysorbates (e.g., Tween 20 and 80) and Polyoxyl 35 Castor Oil (Kolliphor EL, Cremophor EL)[30] are used in some products to enable intravenous administration of poorly water-soluble drug substances. Depending on the type and quantity/concentration, organic solvents may cause side effects,[122] such as pain at the injection site and/or thrombophlebitis.[123] Certain (synthetic) detergents, in turn, possess allergic properties after intravenous administration, which may even give rise to the occurrence of anaphylactic shocks. To avoid these undesired side effects, phospholipids can serve as alternative solubilisers in liposomes or mixed micelles or as emulsifier in solubilising o/w emulsions[9] to make superior Pharmaceutical Form Line Extensions. Examples of such reformulated products are presented in **Table 3**.

2.3.1. Aprepitant

EMEND (fosaprepitant) for injection is a sterile, lyophilised formulation containing fosaprepitant dimeglumine. This is a prodrug of aprepitant, a substance P/NK_1 receptor antagonist, acting as antiemetic agent for the prevention of CINV. The final dosage form for intravenous infusion contains polysorbate 80. Hypersensitivity reactions including anaphylactic reaction[124] and irritation of blood vessels resulting in infusion-site pain have been reported.[125] In general, the allergic properties of polysorbates and other synthetic detergents are well described in the literature.[126]

To overcome the disadvantages of polysorbates, the company Heron Therapeutics (San Diego, CA) developed a Pharmaceutical Form Line Extension based on an emulsion-like formulation with egg lecithin as the emulsifier (Cinvanti).[11] This product was approved by the FDA in 2017.[104,127] The weight ratio of the oil phase to phospholipid, ranging from 1.7 to 2.7 in the formulation, suggests, however, that this formulation may be better described as swollen liposomes than emulsion particles. Cinvanti is the first and only polysorbate 80-free, intravenous formulation of a NK_1 receptor antagonist.[128]

A similar product to the aprepitant formulation, but with another drug substance (Varubi, rolapitant) using polyoxyl-15-hydroxystearate (Kolliphor HS15, in the past termed as Solutol HS 15) as alternative emulsifier to EPC developed by TESARO Inc. (Waltham, MA) was withdrawn from the market due to the high incidence of anaphylactic shocks[129] likely due to the polyoxyl-15-hydroxystearate component in the product. This event underscores the relative safe use of EPC as emulsifier compared to synthetic emulsifiers.[130]

The Cinvanti product is covered by US patents,[131] which all expire in 2035.[104] Interestingly, the patents covering the original product expire in 2027, which means that the line extension could be launched ten years before the original product will lose its IP protection. This line extension showed that by considering lipid-based solubilization technologies, the elaborate development of the EMEND formulation based on a pro-drug and a polysorbate formulation could have been avoided.

2.3.2. Diazepam

The tranquilliser diazepam (described above) was originally on the market in an injectable dosage form comprising organic solvents and water. This dosage forms caused discomfort at the injection site and thrombophlebitis.[123] Compared to the formulation of diazepam using water-miscible solvents (40% propylene glycol, 10% alcohol, 5% sodium benzoate and benzoic acid added as buffers, and 1.5% benzyl alcohol added as a preservative),[132] o/w emulsions suppresses the risk for complications at the injection site, such as pain and thrombophlebitis, and possible

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Table 3. Examples of parenteral Pharmaceutical Form Line Extension, eliminating potentially toxic excipients.

API (Class)	Originator product dosage form and (product example)	Line extension product dosage form and (product)	Advantage of line extension
Aprepitant (Anti-emetic)	Aqueous polysorbate containing prodrug formulation (EMEND injection)	o/w emulsion, with egg lecithin (Cinvanti)	Replacement of polysorbate, no prodrug
Diazepam (Tranquilliser)	Organic solvent/water mixture (Valium Roche)	Mixed micelles with soybean lecithin (Valium MM) o/w emulsion with egg lecithin (Diazepam-Lipuro)	Replacement of organic solvents, reduction of side effects at injection site
Etomidate (Anesthetic)	Organic solvent/ water mixture (Hypnomidate)	o/w emulsion with egg lecithin (Etomidat-Lipuro)	Replacement of organic solvents, reduction of side effects at injection site
Propofol (Anesthetic)	Cremophor-based formulation (Development stage)	o/w emulsion with egg yolk lecithin (Diprivan)	Replacement of Cremophor, reduction of side effects

toxicity caused by the organic solvent can be avoided.[133] Also, when diazepam was formulated in mixed micelles of soybean lecithin and sodium glycocholate, no thrombophlebitis at the injection site was observed.[134] Both phospholipid-based Pharmaceutical Form Line Extensions appear to be superior formulations compared to the organic solvent formulation. Nevertheless, the injectable formulation based on mixed micelles, Valium Roche MM, is not on the market anymore for undisclosed reasons and in, e.g., Germany still the organic solvent formulation of diazepam is being used.[135]

2.3.3. Etomidate

Etomidate is a short-acting, intravenous anesthetic agent used for the induction of general anesthesia and sedation for a short procedure, such as the reduction of, e.g., dislocated joints or tracheal intubation.[136] It was developed at Janssen Pharmaceutica N.V. (Beerse, Belgium) in 1964 and was introduced as an intravenous agent in 1972 in Europe and 1983 in the US.[137] The original product Hypnomidate, which was formulated in a mixture of propylene glycol and water,[138] causes severe pain at the injection site.[139] By incorporating the drug substance in an o/w emulsion (Etomidate-Lipuro, B. Braun Melsungen AG, Melsungen, Germany),[139a] with egg lecithin as a key emulsifier, a Pharmaceutical Form Line Extension was developed showing improved tolerability at the injection site. The product was protected by a general patent on emulsions[140] and was introduced on the German market in 1991.[141]

2.3.4. Propofol

Propofol (Diprivan; 2,6-diisopropylphenol) is an intravenous, sedative-hypnotic agent that can serve for initiation and maintenance of Monitored Anaesthesia Care sedation.[142] The anesthetic properties of propofol were initially reported in 1973 by ICI (Cheshire, UK).[143] The first clinical trials were conducted in Europe in 1977 using a 1% preparation formulated in Cremophor EL,[144] but this formulation was not clinically tested in the US. High incidences of anaphylaxis with the Cremophor EL formulation prompted its withdrawal from development.[145] Propofol in an o/w or lipid-based emulsion was evaluated in clinical trials in Europe in 1983 and in the US in 1984.[143b] Its anesthetic properties were found to be similar to the Cremophor EL formulation but without the anaphylactic reactions.[146] The emulsion formulation ultimately chosen for development was one having the same components as the parenteral fat formulation Intralipid (Kabi/Pfrimmer, Munich, Germany), comprising soybean oil and egg yolk lecithin as the key emulsifier.[142] Although this example is not a classical line extension development in which an original product is converted in another product, it is an excellent example showing that also during the development phase the timely selection of line extensions with improved performance plays a role.

2.4. Improving Both the Therapeutic Index and Replacing Potentially Toxic Excipients

The previously discussed advantages based on phospholipid-based line extensions, which on the one hand can be the increase of therapeutic index and on the other hand the elimination of potentially toxic excipients, can also be combined in a line extension product. In **Table 4**, such product examples are provided.

2.4.1. Amphotericin B

Fungizone contains amphotericin B, an antifungal polyene antibiotic obtained from a strain of *Streptomyces nodosus*.[147] Each vial contains a sterile, non-pyrogenic, lyophilised cake providing 50 mg amphotericin B and 41 mg sodium deoxycholate with 20.2 mg sodium phosphate as a buffer. Amphotericin B is insoluble in water. Therefore, the antibiotic is solubilised by the addition of sodium deoxycholate to form a mixture which provides a colloidal dispersion for intravenous infusion following reconstitution. Due to the presence of the strong detergent sodium deoxycholate, the product has haemolytic properties and may cause thrombophlebitis and pain at the injection site.[148] In addition, the drug is nephrotoxic. To increase the therapeutic index of amphotericin B and to replace the potentially toxic excipient sodium deoxycholate, several Pharmaceutical Form Line Extensions with phospholipids as key excipients were developed.

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Table 4. Examples of parenteral Pharmaceutical Form Line Extension, based on phospholipid formulations, resulting in an increased therapeutic index of the drug substance as well as allowing the replacement of potentially toxic excipients.

API(Class)	Originator product dosage form and (product example)	Line extension product dosage form and (product)	Advantage of line extension
Amphotericin B (Antifungal)	Lyophilizate (Fungizone)	Lyophilised complex of drug with DMPC, DMPG (Abelcet) Lyophilised complex of drug with cholesterol sulfate (Amphotec) Lyophilised liposomal suspension, with HSPC, DSPG, and cholesterol (AmBisome) o/w emulsion with purified egg lecithin as emulsifier (Amphomul)	Increase therapeutic index and replacement of sodium deoxycholate by phospholipids
Cyclosporin (Immuno-suppressant)	Solution with Cremophor EL (Sandimmune)	o/w emulsion with phospholipids (NeuroSTAT, development stage)	Increased therapeutic index and replacement of Cremophor
Docetaxel (Cytostatic)	Concentrate with polysorbate and ethanol (Taxotere)	Liposomal suspension with PC and sodium cholesteryl sulfate (DoceAqualip)	Increased therapeutic index and replacement polysorbate and ethanol by phospholipids
Paclitaxel (Cytostatic)	Aqueous concentrate with Cremophor (Taxol)	Lyophilised liposomal suspension with lecithin and cholesterol (Lipusu) Liposomal suspension with DOPC and DOTAP (EndoTag; development stage)	Increased therapeutic index and replacement Cremophor by phospholipids

Abelcet (amphotericin B) is a lipid complex formulation, developed by The Liposome Company in 1995. Abelcet is a drug lipid complex with 1:1 drug-to-lipid weight ratio bearing the synthetic phospholipids 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) and 1,2-dimyristoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol), sodium salt (DMPG) in a 7:3 molar ratio.[149] PK studies demonstrate that there is deposition in the MPS.[150] This "depot" form releases the drug at local sites of infection, maybe through the action of lipases.[151] Compared to Fungizone, site-effects at the injection site and nephrotoxicity are reduced.[152] The product was covered by US patents.[153]

Amphotec, an amphotericin B cholesteryl sulfate complex for injection, in the past manufactured at Ben Venue Laboratories Inc. (Bedford, OH), is another lipid-based line extension of Fungizone.[154] The formulation is based on the specific property of amphotericin B to form complexes with cholesterol, which is covered by US patents.[155] It shows that in particular cases also alternative lipids may be used attempting to increase the therapeutic index of amphotericin B and to eliminate suspect excipients from the formulation. The increased safety profile of Amphotec (compared to Fungizone) was demonstrated in preclinical[156] as well as clinical settings[157] and is possibly related with an accumulation of the drug in a non-toxic form in the MPS tissue. Amphotec was significantly less nephrotoxic than conventional amphotericin B and could be given to patients with renal disease. Despite these positive features, the sales of this product were discontinued.[158]

AmBisome, developed initially by NeXstar Pharmaceuticals Inc. (Boulder, CO), is the best-selling lipid-based injectable of amphotericin B.[34] AmBisome is a liposomal formulation with low content of amphotericin B.[159] The lipid bilayer of AmBisome is composed of HSPC, cholesterol, DSPG, and amphotericin B in a 2:1:0.8:0.4 molar ratio.[160] Amphotericin B forms a complex in the liposomal membrane with cholesterol. The superiority of this line extension compared to Fungizone is underscored by preclinical data reports showing negligible haemolysis caused by AmBisome.[159] In addition, AmBisome demonstrated increased safety in animal models with systemic fungal infection. It was tolerated at doses higher than those of conventional amphotericin B and possessed a higher therapeutic index.[160] The product was protected by several patents.[161]

Further liposomal formulations of amphotericin B and line extension of Fungizone, not discussed here in detail, are PhoSome, AmBil, Lambin, AmbiHope, Lipholyn, Ampholip, and Fungisome. For details please refer to Adler-Moore et al.[162]

Besides liposomes or lipid complexes, also an o/w emulsion with purified egg lecithin as essential component[163] can be used to suppress the toxicity of amphotericin B and, hence, as a solubilising formulation of amphotericin B. An example of such a Pharmaceutical Form Line Extension is the product Amphomul, which comprises soybean oil as oil phase, glycerol as isotonising agent, and purified egg lecithin as emulsifier. Amphomul is manufactured by Bharat Serum and Vaccines Ltd (Mumbai, India). This product is covered by patents.[163,164] After administration of Amphomul, amphotericin B gets released from the oily phase in the monomeric form, which is less toxic compared to oligomeric form present in conventional (Fungizone) formulation. In rodents, Amphomul is at least 80-fold less toxic than conventional deoxycholate formulations of amphotericin B. Amphomul gets distributed rapidly into the MPS and, hence, a rapidly increased amphotericin B concentration is achieved in liver and spleen, the target organs in patients of Visceral leishmaniasis (kala-azar).

In general, all liposome-based Pharmaceutical Form Line Extensions of amphotericin B show a similar increase in therapeutic index in preclinical studies.[165] However, comparative clinical studies have never been performed. A conclusion on which line extension is best can therefore not be drawn.

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2.4.2. Cyclosporine

Cyclosporine, the active ingredient in Sandimmune, is a cyclic polypeptide immunosuppressant agent. The injectable form of cyclosporin is formulated with Cremophor EL. Sandimmune is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. The injectable form is always to be applied with adrenal corticosteroids. Sandimmune Injection (cyclosporine injection, USP) is mostly used shortly before and after transplantation and when patients are unable to take the Sandimmune Soft Gelatin Capsules or Oral Solution.[166] This daily single-dose is continued postoperatively until the patient can take the Sandimmune Soft Gelatin Capsules or the Oral Solution. This switch should be performed as soon as possible after surgery.

While cyclosporine has been widely used to prevent graft rejection in patients undergoing organ transplantation, it was also used to treat several systemic and local autoimmune disorders. The neuro- and cardio-protective effects of cyclosporine were tested in Phase II and III trials with an o/w emulsion formulation with phospholipids as the key emulsifier[167] including 1.2% egg phospholipid and 10% soybean oil as oil phase (NeuroSTAT). This product received orphan drug status from FDA and EMA in 2010.[168] The reformulation strategies focused on developing Cremophor EL-free formulations.[169] This intravenous formulation of cyclosporine did not significantly affect the glomerular filtration rate (GFR) in an acute nephrotoxicity rat model, while the Cremophor EL-based Sandimmune and the Cremophor EL itself reduced GFR to ≈70% and 75%, respectively, of the baseline level. These results indicate that the main contributor to the acute nephrotoxic effects in this model was associated to the Cremophor EL in the vehicle.[133,170]

In 2016, NeuroVive Pharmaceutical AB (at present Abliva, Lund, Sweden) announced that the Phase II clinical trial, although well conducted, showed that patients treated with CicloMulsion during open heart surgery had no benefit from the treatment in terms of preventing acute kidney injury. The company therefore discontinued the development.[171] The development of the other cyclosporine o/w formulation (NeuroSTAT), for treatment of traumatic brain injury, is still continuing.[172]

2.4.3. Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. The docetaxel injectable product (Taxotere) contains 20 mg docetaxel (anhydrous) in 0.54 g polysorbate 80 and 0.395 g dehydrated alcohol solution to solubilise the poorly water-soluble drug. Severe hypersensitivity reactions characterised by generalised rash/erythema, hypotension, bronchospasm, or very rarely fatal anaphylaxis have been reported even in patients who received a 3-day dexamethasone premedication.[173] To eliminate these side effects probably caused by polysorbate 80, a Pharmaceutical Form Line Extension was developed by the Indian company Intas (Ahmedabad, India) in cooperation with the US company Jina Pharmaceuticals Inc. (Libertyville, IL).[174] This product is based on the Nanoaqualip technology in which the therapeutic drugs are formulated in an aqueous medium without the use of any toxic solvents during the manufacturing process yielding a homogenous nanosized product comprising PC and sodium cholesteryl sulfate. DoceAqualip is protected by patent.[175] The phospholipid in the formulation plays an essential role as (co)solubiliser together with the sodium cholesteryl sulfate, possibly forming mixed micelles. DoceAqualip is indicated for treatment of breast cancer, non-small cell lung cancer, prostate cancer, cancer of head, and neck, which are the same indications as for Taxotere.[176]

2.4.4. Paclitaxel

Paclitaxel is on the market in an injectable form bearing Cremophor EL (Kolliphor EL, polyoxyl 35 castor oil) (Taxol, approved by the FDA in 1992). The injectable has as side effects anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea, hypotension, angioedema, and generalised urticaria. These side effects have occurred in 2–4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication.[177]

For these reasons, this product has been reformulated to a Pharmaceutical Form Line Extension with more efficacy and reduction of undesired side-effects by the elimination of Cremophor EL from the product and encapsulating the drug in liposomes.[178] While not yet approved in American or European countries, this liposomal paclitaxel product, called Lipusu (initially developed by Sike Pharmaceutical Nanjing, Jiangsu, China[179]), received market approval in China in 2003. This freeze-dried intravenous liposome formulation is prepared with lecithin and cholesterol at a mass ratio of 87:13.[180] Compared to Taxol, Lipusu shows comparable activity against breast, gastric, and non small lung cancer, but with less severe side effects. In Phase I clinical trials, Lipusu was administered at 175 mg m^{-2}, the same dose as Taxol, premedicated with corticosteroids.[181] Side effects included diarrhoea, anaemia, neutropenia, thrombocytopenia, hepatotoxicity, and chest pain, but these were milder than those of patients treated with Taxol.[182] In addition, it was shown that due to the elimination of Cremophor EL from the formulation, Lipusu displayed a much higher safety margin and did not induce hypersensitivity or hypersensitivity-related lung lesions, which may be associated with the fact that Lipusu did not activate the complement system or increase histamine release in vivo. Indeed, Lipusu did not promote complement activation in healthy human serum in vitro.[183] Lipusu has been approved for the treatment of ovarian cancer, breast cancer, and non-small cell lung cancer in China.[184] Luye Pharma claims that Lipusu has more favorable clinical and industrial advantages over albumin-bound Paclitaxel (Abraxane) in terms of safer formulation medium, less dosage needed and the ease of production.

Lipusu was the most popular pharmaceutical product for cancer treatment in China in 2018, as well as the most popular paclitaxel product in China in 2018. The patents Luye holds with respect to Lipusu will expire in 2021. This paclitaxel liposome product is a prominent example of how phospholipids can be used to increase the therapeutic index of the formulated drug and to eliminate potentially toxic excipients from the original formulation.

An alternative liposomal formulation of paclitaxel (EndoTag), containing dioleoyl-3-trimethylammonium propane

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Table 5. Examples of parenteral Pharmaceutical Form Line Extensions, based on liposomes, with extended drug release properties.

API (Class)	Originator product dosage form and (product example)	Line extension product dosage form and (product)
Bupivacaine HCl (Local anesthetic)	Aqueous solution (Marcaine, Sensorcaine)	Liposomal (DepoFoam) suspension with DEPC, DPPG, tricaprylin, and cholesterol (Exparel)
Buprenorphine HCl (Opioid-related disorders)	Sublingual tablet (Subutex, Sublocade)	Lipid-based solution for subcutaneous injection with phosphatidylcholine (soybean), glycerol dioleate, and ethanol anhydrous (Buvidal)
Cytarabin (Cytostatic)	Aqueous solution (Cytarabin for Inj. USP)	Liposomal (DepoFoam) suspension with DOPC and DPPG (DepoCyt)
Morphine sulfate (Anesthetic)	Aqueous solution (Infumorph, Duramorph)	Liposomal (DepoFoam) suspension with DOPC and DPPG (DepoDur)

(DOTAP) as positively charged lipid and 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) in a 53:47 molar ratio, is in the clinical development stage since a long time.[185] The company Medigene AG (Martinsried, Germany) started the development based on favorable preclinical findings in tumor models.[186] Due to the presence of the positive charge in the liposomes, the encapsulated paclitaxel is targeted to tumor endothelium. In 2006, Medigene AG exclusively licensed the newly issued patent.[187] In 2015, Medigene AG transferred the product development to the company SynCore Biotechnology Co., Ltd. (Taipei City, Taiwan).[188] In 2006, an orphan designation was granted by the European Commission to Medigene AG for paclitaxel (liposomal) for the treatment of pancreatic cancer.[189] In 2019, clinical trials with EndoTag in China were announced by SynCore Biotechnology.[190] Further alternative lipid-based line extensions for paclitaxel, which are in the development stage, can be found in Sun et al.[182b]

2.5. Extending Release Properties

In the 1980s, the possibility to use liposomes as parenteral slow release vehicle for encapsulated water-soluble drugs, especially for proteins, was explored at the preclinical level.[191] This research direction was driven by the advent of highly potent (biological) drugs with a shorter biological half-life for which the oral administration route is not feasible. Therefore, dosage forms allowing a lower frequency of injection and avoiding probable toxic drug plasma level after bolus injection needed to be developed.

For obtaining a depot effect at an intramuscular or subcutaneous injection site it is necessary that the depot formulation stays at the injection site. It was shown that larger liposomes with diameters above 300 nm were indeed retained at the subcutaneous or intramuscular injection site.[192] In addition, the entrapped water-soluble drug or model compound was slowly released from the aqueous compartment(s) of the liposomes.[193]

A technological breakthrough in this area was obtained after introduction of the DepoFoam technology initially developed for delivering proteins and peptides.[194] This technology is based on the use of large multivesicular liposomes. This structure renders a higher aqueous volume-to-lipid ratio and a much larger particle diameter (about 24–31 μm) than ordinary single-vesicle liposomes. More recently, the FluidCrystal injectable depot technology, based on the in situ formation of a lipid depot, with PC as an essential component, was also used to develop lipid-based products (see below).

Several Pharmaceutical Form Line Extensions based on these technologies for low molecular weight drugs were introduced on the market (**Table 5**).

2.5.1. Bupivacaine HCl

Bupivacaine HCl injectable solution is a prescription medication used as a local anesthetic (numbing medicine). Bupivacaine is available under the following different brand names: Marcaine and Sensorcaine. Marcaine was introduced on the market by Hospira Inc. (Lake Forest, IL) in 1984.[195]

Bupivacaine is a potent local anesthetic with increased cardiotoxicity risks compared to lidocaine.[196] In general, long-acting local anesthetic formulations hold great promise for the management of acute pain, as long-lasting analgesia could be realised with a single dose administered after surgery or trauma. Liposomal bupivacaine formulations prolong analgesic duration in animals and humans. The slow release of drug from the liposomal depot decreases the potential for systemic toxicity and allows for administration of a higher bupivacaine dose.[197] In addition, the better and more prolonged the local anesthesia is acting the further use of systemic opioids to suppress pain after the operation is reduced.

The Pharmaceutical Form Line Extension developed for these reasons for bupivacaine Exparel (a bupivacaine liposome injectable suspension) by DepoTech Corp. (San Diego, CA) and SkyePharma Production SAS (Saint-Quentin-Fallavier, France) was introduced on the US market in 2011 by Pacira Pharmaceuticals (Parsippany, NJ)—27 years after the introduction of the original bupivacaine injectable. The product is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks. Exparel combines bupivacaine with DepoFoam, a drug delivery technology that delivers medication over a desired period (see above). The liposomes comprise the lipids 1,2-dierucoyl-*sn*-glycero-3-phosphocholine (DEPC), DPPG, cholesterol, and tricaprylin.

Exparel represents the first and only multivesicular liposome local anesthetic that can be utilised in the peri- or postsurgical setting. By utilising the DepoFoam platform, a single dose of Exparel delivers bupivacaine over time, providing significant reductions in cumulative pain scores with up to a 78% decrease in opioid consumption. The clinical benefit of the opioid reduction was not demonstrated. The product is covered by US patent.[198]

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2.5.2. Buprenorphine HCl

Buprenorphine HCl is an opioid used to treat opioid use disorder, acute pain, and chronic pain.[199] The compound is available in sublingual tablets (Subutex[200]) and also in extended release injectable form (Sublocade[201]). The Sublocade (buprenorphine extended-release) injection is a clear, sterile solution for subcutaneous injection only. It is designed to deliver buprenorphine at a controlled rate over a 1 month period. Buprenorphine is dissolved in the ATRIGEL delivery system at 18% by weight. The ATRIGEL delivery system is a biodegradable 50:50 poly(DL-lactide-*co*-glycolide) polymer and a biocompatible solvent, *N*-methyl-2-pyrrolidone (NMP). The usage safety of NMP is, however, controversially discussed.[202]

Camurus AB (Lund, Sweden) developed an alternative line extension to this product by applying their FluidCrystal injectable depot technology. A liquid solution with low viscosity comprising soybean phosphatidylcholine (SPC), glycerol dioleate, and a small amount of alcohol (in the weekly formulation) or NMP (in the monthly formulation)[203] is transformed into a controlled-release liquid crystal gel matrix in situ on contact with minute quantities of aqueous fluid at the site of injection. It is claimed that the release duration can be tuned to meet dosing interval specifications ranging from once-daily to once-weekly or once-monthly.[204] In a Phase III study, it was shown that subcutaneous buprenorphine delivered weekly or monthly was well tolerated, with a systemic safety profile consistent with the known profile of sublingual buprenorphine. Both the weekly and monthly injectable were associated with high retention rates and low levels of illicit opioid use throughout this study.[205]

The product Buvidal received market authorization in the EU in 2018.[206] In the US, the registration status of this product is complicated. Braeburn Inc. (Princeton, NJ)—obtaining a licence for the product from Camurus AB in the US[207]—announced that it is eligible for marketing approval for Brixadi (the product name in the US) as of 2020. This follows from the decision by the FDA to grant Braeburn's Citizen Petition (filed in 2019) and thereby revoke Indivior PLC's (Chesterfield Court House, VA) orphan designation for buprenorphine treatment for opioid use disorder. By revoking Indivior's orphan designation, Sublocade injection is not eligible for any period of orphan exclusivity.[208] Patents protecting the product are US 9937164[209] and EP 3045162.[210]

2.5.3. Cytarabine

To address the need for an improved therapy of leptomeningeal cancer dissemination, a Pharmaceutical Form Line Extension for cytarabine was developed.[211] Cytarabine was encapsulated in multivesicular liposome preparation using the DepoFoam technology. This product, known as DepoCyt,[212] was introduced on the US market in 1999 by Pacira Pharmaceuticals (Parsippany, NJ) and SkyePharma Production SAS (Saint-Quentin-Fallavier, France). The liposomal formulation comprises DOPC, DPPG, cholesterol, and triolein.

The encapsulation of the drug in lipid changes drastically the PK of the free cytarabine released by liposomes in the cerebrospinal fluid, such that the mean elimination $t_{1/2}$ of the depot formulation of free cytarabine in the cerebrospinal fluid is between 130 and 277 versus 3.4 h for native cytarabine.[213] Furthermore, the cytotoxic concentrations of the slow release formulation of the cytarabine in cerebrospinal fluid were maintained for as long as 14 days or more, depending on the target cell threshold concentration that is cytotoxic.[211] In addition, DepoCyt has distinct advantages for the patients compared to the standard therapy of leptomeningeal cancer dissemination fusing intrathecal injection of methotrexate at a lower frequency of administration. However, DepoCyt was discontinued in 2017.

2.5.4. Morphine Sulfate

Infumorph by Hikma Pharmaceuticals USA Inc. (Eatontown, NJ) is a sterile solution of morphine sulfate intended for use in continuous microinfusion devices for intraspinal administration in the management of pain. This product was introduced on the market in 1984.[214]

DepoDur is a Pharmaceutical Form Line Extension of morphine sulfate injectable. It is an extended-release liposome injection, developed by Endo Pharmaceuticals (Chadds Ford, PA) and SkyePharma PLC (London, UK) intended for single-dose administration by the epidural route for the treatment of pain following major surgery. DepoDur is administered prior to surgery or after clamping the umbilical cord during caesarean section.[215] DepoDur was introduced on the market in 2004—18 years after introduction of the regular morphine sulfate injection.[104] The product comprises multivesicular liposomes with DOPC, DPPG, cholesterol, and triolein as lipid components.[215]

Administered epidurally as a single dose either before or during surgery, DepoDur provides sustained release of morphine sulfate for as long as 48 h. As stated by Rios, the release profile is a considerable improvement over current therapy, which requires the use of an in-dwelling epidural catheter and/or administration via continuous intravenous infusion with patient-controlled analgesia.[216] The pharmaceutical profile of the drug product is described in ref. [217]. The product was marketed by Pacira Pharmaceuticals and covered by patents which last expiry date in 2017.[104] In spite of the positive features of the product, sales of the product were discontinued in 2012.[218]

3. Inhalation Pharmaceutical Form Line Extensions

Interestingly, phospholipids are used/explored in many ways in dosage forms for inhalation. They are used 1) to replace a solution for nebulization by a dry powder inhalation formulation (example tobramycin), 2) to convert a dosage form of a drug, which is usually orally and parenterally administered into an inhalation form enabling local lung treatment (example ciprofloxacin), 3) to enable systemic administration with a fast onset of action (examples levodopa and acetyl salicylic acid), and 4) to allow slow release of the drug substance reducing the administration frequency (examples amikacin and ciprofloxacin). These options are summarised in **Table 6**. Options 1), 2), and 4) are also designed to reduce systemic side effects as result of the local administration.

The safety of administration of phospholipids to the lung was already proven in 1964 when phospholipids were administered

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Table 6. Example of inhalation Pharmaceutical Form Line Extensions using phospholipids as key excipients.

API (Class)	Originator oral product dosage form and (product example)	Line extension product dosage form and (product)
1) Converting a liquid inhalation form into a solid form (dry powder inhalation form)		
Tobramycin (Antibiotic)	Aqueous solution Tobramycin injection (Bethkis, inhalation solution)	Powder for inhalation with DSPC-$CaCl_2$ (Tobi Podhaler)
2) Enabling local treatment with a dry powder inhalation form		
Ciprofloxacin (Antibiotic)	Tablet (Cipro)	Powder for inhalation with DSPC-$CaCl_2$ (Ciprofloxacin DPI, development stage)
3) Enabling systemic treatment		
Levodopa (Parkinson's disease)	Oral tablets in combination with carbidopa (Sinemet)	Powder for inhalation with DPPC (Inbrija)
Acetylsalicylic acid	Oral tablets (Aspirin)	Powder for inhalation with DPPC (Asprihale, development stage)
4) Extending release properties		
Amikacin (Antibiotic)	Aqueous solution (Amikacin sulfate injection)	Liposomal suspension with DPPC and cholesterol (Arikayce)
Cisplatin (Cytostatic)	Aqueous solution (Cisplatin injection)	Liposomal suspension with DPPC and cholesterol (Inhaled Lipid Complex of cisplatin, development stage)
Ciprofloxacin (Antibiotic)	Aqueous solution (CIPRO intravenous injection)	Liposomal suspension with HSPC and cholesterol (Pulmaquin, later Linhaliq)

to infants to treat the Respiratory Distress Syndrome caused by lack of phospholipid surfactants in these infants. Interestingly, lung tissues comprise saturated phospholipids,[219] which are the same phospholipids as used to make suitable inhalable formulations (utilising their powder forming properties and slow-release features) as will be demonstrated in this Section.

3.1. Converting a Liquid Form into a Solid Form

Tobramycin is available as an injection and in an ophthalmic ointment and solution. It is also available as solution for inhalation as an antipseudomonal antibiotic for chronic pulmonary infections in patients with cystic fibrosis.[220] The solutions for inhalation of tobramycin and the use of nebulisers require prolonged administration and cleaning times and high administration frequency, resulting in a high treatment burden in this patient population. A dry powder formulation for inhalation, eliminating these disadvantages, would therefore be a viable alternative.

The dry powder Pharmaceutical Form Line Extension of tobramycin, Tobi Podhaler, was developed using PulmoSphere technology—initially developed by Chiron Corporation (Emeryville, CA)—wherein phospholipids are key excipients.[221] PulmoSphere particles are manufactured by an emulsion-based spray-drying process, designed to create porous particles with a sponge-like morphology.[222] The availability of a dry powder formulation for inhalation offers a genuine alternative to oral administration. It provides substantially improved intrapulmonary deposition efficiency, faster delivery, and more convenient administration over nebulised formulations. The availability of more efficient and convenient treatment options may improve treatment adherence and thereby therapeutic outcomes in cystic fibrosis.

The dispersed oil droplets are stabilised against coarsening by a monolayer of the saturated long-chain phospholipid DSPC. Such saturated long-chain PCs, for example DPPC, are the principal components of endogenous pulmonary surfactant.[223] The active pharmaceutical ingredient (tobramycin) is incorporated in the emulsion by dissolving it in the continuous water phase. Owing to the short spray drying time (in the order of milliseconds), tobramycin is present as an amorphous solid in the spray-dried particles. DSPC acts as emulsifier and hydrophobic shell former. The product was introduced on the market in 2013. The product and technology are covered by various patents (see ref. [224] for details).

3.2. Enabling Local Treatment

The same technology is used for the antibiotic ciprofloxacin, to create a dry powder inhalation form and to enable treatment of local infections in the lung.

Ciprofloxacin is an antibiotic used to treat several bacterial infections.[225] This includes bone and joint infections, intra-abdominal infections, certain types of infectious diarrhoea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections. Ciprofloxacin is on the market in several dosage forms, that are tablet and injectable form.[226] A Pharmaceutical Form Line Extension for ciprofloxacin, the Ciprofloxacin DPI, whereas DPI stands for "dry powder inhaler," is in development as a long-term, intermittent therapy to reduce exacerbations in patients with non-cystic fibrosis bronchiectasis and evidence of respiratory pathogens using the same PulmoSphere technology as for tobramycin.[227] Besides, this formulation approach would have the advantages of a dry powder inhalation form.

As with Tobi Podhaler, the principal excipient is DSPC. Although DSPC makes up just 21.5% w/w of the bulk composition, the surface of the PulmoSphere particles comprises more than 96% DSPC. The porous hydrophobic phospholipid shell formed with DSPC reduces interparticle attractive forces, enabling efficient powder dispersion and delivery of ciprofloxacin inhalation powder to the lungs. Following deposition of ciprofloxacin

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inhalation powder, DSPC is catabolised and ultimately recycled by type II cells in the lungs.[228] The other excipient, calcium chloride, is present in ciprofloxacin inhalation powder at a concentration of 1.5% w/w and helps to modify the phase behavior of the phospholipid by binding to the phosphate portion of the PC headgroup on DSPC.

3.3. Enabling Systemic Treatment

Remarkably, the dry powder inhalation approach with synthetic saturated phospholipids can also be used to achieve enhanced systemic delivery via uptake by the lungs as opposed to local lung delivery as shown with the example antibiotic formulation described above. This can be advantageous for drugs that require a fast onset of action. Here, the added phospholipid also acts as a diluent excipient to develop a suitable dry powder formulation for inhalation.

3.3.1. Levodopa

Levodopa (L-Dopa, L-3,4-dihydroxyphenylalanine) crosses the protective blood–brain barrier, whereas dopamine itself cannot.[229] Thus, L-DOPA is used to increase dopamine concentrations in the treatment of Parkinson's disease and dopamine-responsive dystonia.

Quite recently (in 2019), a dry powder formulation product for inhalation, Inbrija[230] by Arcoda Therapeutics Inc. (Ardsley, NY) and Civitas Therapeutics Inc. (Chelsea, MA; which is a subsidiary of Arcoda) was introduced on the market as parenteral Pharmaceutical Form Line Extension of the oral levodopa products (in combination with carbidopa, an inhibitor of dopamine decarboxylase[231]). Inbrija, which acts systematically after inhalation, is intending to treat symptoms during "off" periods that occur, while patients are taking their usual treatment, a combination of levodopa and carbidopa. The advantage of this line extension is the faster onset of action of levodopa. This product contains DPPC as excipient in the powder formulation,[232] with two main advantages. First, on the technical side, it is the improved flowability of the powder and the high powder density enabling high drug dose inhalation.[233] Second, on the physiological side, it is the compatibility of saturated phospholipids with the lung tissue. Since after inhalation the active ingredient is systemically absorbed. Hence, this treatment belongs to parenteral administration. The product was introduced on the market in the US in 2018 and in the EU in 2019. The IP related to the product is found in ref. [233].

3.3.2. Acetylsalicylic Acid

Concerning Inbrija, it is worth mentioning that also acetylicsalicylic acid (commonly orally administered) is being developed by the company Otitopic Inc. (Los Angeles, CA) in a Pharmaceutical Form Line Extension for inhalation, using DSPC as essential formulation component, with a fast onset of systemic action. The company Otitopic Inc. claims that the effects of their product Asprihale are distinctly more rapid, potent, and assure a consistent pharmacodynamic response in the treatment of acute thrombotic conditions such as stroke and heart attack than the current standard of care.[234] It is touted as revolutionising the myocardial infarction management by providing a portable, single-use therapy for the treatment of acute myocardial infarction.[235] Several patent applications have been published and patents have been granted.[236] The phospholipid component is added to coat the active, suppressing its bitter taste and irritation potential upon inhalation and simultaneously acts as a viable alternative for lactose, which is typically used to blend powders for inhalation.[236c]

3.4. Extending Release Properties

Phospholipids in the form of liposomes also have the potential to act as slow-release formulation for drug substances after inhalation to reduce the required frequency of inhalation dosing for local treatment of lung diseases. Pharmaceutical Form Line Extensions based on this principle were discussed by Cipolla et al.[237] In this article, Cipolla mentions: "There have been a wide range of drugs evaluated in liposomal formulations with the intention to treat lung disease. The earliest examples were liposomal formulations of oncology compounds to target lung cancer [...]".

Later development efforts have focused on the antibiotics ciprofloxacin and amikacin, resulting in (for the time being) a clinical failure for ciprofloxacin and a successful market introduction of a liposomal amikacin slow-release inhalation product (Arikayce).

The discussed products do not have direct comparators as original product, being the same inhaled drug substances without a slow-release formulation, but in Table 6, the original intravenous products are provided. In fact, tobramycin and aztreonam (Cayston) are the only antibiotics approved for inhalation therapy of lung infections in the US and polymixins (colistin and the related colomycin) are the only ones in Europe.[238] Inhaled cytostatics are not on the market. Therefore, the liposomal slow-release formulations for amikacin or ciprofloxacin would also represent the first inhalation therapy with these antibiotics and the inhalation form of cisplatin would be the first inhaled cytostatic. Thus, these line extension products can also be considered as conversions of the parenteral dosage forms used for the original administration routes.

In general, delivery of an antibiotic formulation *via* the inhalation route has the potential to provide high concentrations at the site of infection with reduced systemic exposure to limit systemic side effects. A slow-release liposomal formulation may improve tolerability controlled release, thereby reducing the dosing frequency, enhanced penetration of biofilms and better treatment of intracellular infections.[239] The same rationale may apply for inhaled cytostatics but potentially resulting in a more efficacious local tumor treatment.

3.4.1. Amikacin

Amikacin sulfate is a semisynthetic aminoglycoside antibiotic derived from kanamycin. It is on the market in the US (Amikin) since 1994 as an injectable dosage for intravenous and intramuscular use. The injectable form is also used for the treatment of respiratory infections. Aminoglycosides are, however, potentially nephrotoxic and ototoxic.[240] The development of an injectable

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Pharmaceutical Form Line Extension with amikacin sulfate using liposomes was explored by Gilead Sciences Inc. (La Verne, CA) named MiKasome.[241] MiKasome showed substantially reduced nephrotoxicity and reduced ototoxicity in preclinical studies. In humans, however, it was assumed that therapeutic dose monitoring would virtually eliminate the toxicity in control arms in clinical studies for the cystic fibrosis indication, and so proof of improvement and label claim would be very difficult to obtain. With these issues, there was less commercial incentive leading to cessation of further development of this product.[241]

Still, local administration of this product was considered a potentially viable therapeutic strategy, and the company Transave (South Brunswick Township, NJ) decided to develop liposomal amikacin (Arikace, later named Arikayce) originally for treatment of *Pseudomonas* lung infections and lung infections due to non-tuberculous *Mycobacteria* in cystic fibrosis patients.[242] After obtaining the orphan drug status in the US and EU, Insmed Inc. (Bridgewater Township, NJ) acquired Transave and further developed the product. This product is a liquid dispersion of liposomes composed of DPPC and cholesterol.

Although it could be shown that targeting amikacin (without liposomes) to the lung by inhalation leads to a >3000-fold increased lung-to-serum drug concentration ratio as compared to intravenous administration,[239] the liposomal product is until now only registered in the US (in 2018; 24 years after introduction of the original product) and only for a limited population, and only as part of a combination antibacterial drug regimen.[243] In addition, the product is still nephrotoxic and ototoxic. It has additional product-specific side effects, such as respiratory adverse reactions including, hypersensitivity, pneumonitis, haemoptysis, bronchospasm, or exacerbation of the underlying pulmonary disease.[244] In the EU, the marketing authorization application for Arikayce was withdrawn in 2016.[245] Clinical research for other indications like non-cystic fibrosis bronchiectasis is, however, ongoing.[246] Several patents protect Arikayce; the most recent ones[247] expire in 2035 at the latest.

3.4.2. Cisplatin

Eleison Pharmaceuticals LLC (Princeton, NJ) is developing an inhaled cisplatin lipid complex with sustained-release properties for prevention and treatment of lung metastases as a result of pediatric osteosarcoma. Approximately 35% of patients fail first-line therapy, mostly with metastatic recurrence only in the lungs, and with poor prognosis (5-year survival of such patients is below 25%).[248] In 2013, the product received the orphan drug designation from the EMA.[249]

Eleison is currently enrolling patients in a Phase II clinical study by leading osteosarcoma clinical investigators throughout the US, to evaluate the safety and efficacy of inhaled lipid cisplatin in patients with osteosarcoma lung metastases. The product comprises cisplatin (1 mg mL^{-1}), DPPC (16 mg mL^{-1}), and cholesterol in 0.9% NaCl.[250]

Eleison has sublicensed the marketing rights of inhaled lipid cisplatin for the Chinese market to an emerging Hong Kong-based pharmaceutical company. In conjunction with this agreement, Eleison and the Chinese partner plan to commence in 2020 a large Phase II study of inhaled lipid cisplatin in patients with non-small cell lung cancer, the leading cause of cancer deaths worldwide. Eleison cooperates with Windtree Therapeutics (Warrington, PA) to further develop inhaled lipid cisplatin.[251]

3.4.3. Ciprofloxacin

For ciprofloxacin it is known that intravenous administration of this antibiotic to treat lower respiratory tract infections or severe pneumonia is often ineffective for patients infected with *Pseudomonas aeruginosa*. Observations included failure to eradicate the organism, persistence of infection, and the emergence of resistance. Thus, an inhaled ciprofloxacin product achieving higher drug concentrations in the lung may be more effective and simultaneously reduce the potential for the development of resistance.[239]

The company Aradigm Corp. (Hayward, CA) explored the inhalation use of liposomal ciprofloxacin. This product, Pulmaquin, was a successor of Lipoquin of the same company. The difference between Lipoquin and Pulmaquin is that with Lipoquin practically all ciprofloxacin is liposome-encapsulated, while with Pulmaquin, a portion of the drug is not encapsulated to provide an initial high peak concentration of ciprofloxacin in the lung. Pulmaquin comprises the lipids HSPC and cholesterol.[252] Linhaliq, the later tradename for Pulmaquin, was intended for once-daily inhalation with the additional aim to reduce adverse lung reactions such as bronchospasm that have historically hampered the development of inhaled antibiotics in bronchiectasis.

PK studies in a mouse model showed that aerosolised Lipoquin (1 mg kg^{-1}) provides an $AUC_{0\text{-}24}$ in the lungs that is over 80-fold larger than oral ciprofloxacin (50 mg kg^{-1}), which is rapidly eliminated from the lungs (half-life 4.2 h). In contrast, aerosolised Lipoquin has an 80% longer half-life (7.4 h).[253] Despite a promising preclinical profile and clinical results showing that Linhaliq was safe and, compared with placebo, its use extended the time before a patient experienced a pulmonary exacerbation and Linhaliq-treated patients experienced a decrease in the frequency of severe exacerbations including those that required antibiotic treatment,[254] the FDA rejected the New Drug Application (NDA) for Linhaliq in 2018 because of concerns related to the clinical data, human factors validation study (that is usage of devices by intended users without serious use errors), and the product quality.[255] In Europe, Aradigm withdrew its application in 2019.[256] The development and marketing rights were then acquired by the Spanish company Grifols SA (Barcelona, Spain) in 2020.[257] The product was further licensed in April 2020 to Savara Pharmaceuticals (West Lake Hills, TX) for bronchiectasis, and this company plans a confirmatory Phase III trial of ciprofloxacin (for inhalation) in non-cystic fibrosis-related bronchiectasis.[258]

4. Dermal Pharmaceutical Form Line Extensions

4.1. Converting from the Oral to the Dermal Administration Route

Phospholipids can also be used to convert oral products into Pharmaceutical Form Line Extensions for topical administration to

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Table 7. Examples of pharmaceutical form line extensions using phospholipids as key excipients to convert an oral form into a dermal form.

API (Class)	Originator product dosage form and (product)	Line extension product dosage form and (product)	Advantage of line extension
Diclofenac sodium (NSAID)	Tablet (Voltaren)	Liposomal gel with PC (Diclac Liposomal Gel, Voltaren Spray, and other)	Improved skin interaction; lower systemic availability compared to oral administration
Ketoprofen (NSAID)	Capsule (Orudis)	Ethanolic solution with soybean lecithin (Ketospray)	
Nimesulide (NSAID)	Tablet (Nisulid)	Foam formulation with HSPC (Erreflog topical foam)	

the skin or mucosa. The choice of phospholipids is motivated by their excellent skin compatibility and the potential of liposomes to enhance the skin interaction with drugs. In general, for this type of line extensions topical administration should result in less systemic side effects compared to oral therapy. The original products mentioned in **Table 7** are also available in injectable form to treat emergency (e.g., lumbago in case of NSAIDs). The presented topical line extensions are not intended for treatment of emergency indication but serve more as an alternative for more prolonged treatment with an oral product.

4.1.1. Diclofenac

The dermal NSAID Pharmaceutical Form Line Extensions were developed as an alternative to oral medications with this class of drug products to circumvent gastric side effects of these drugs.[259] Several formulation approaches to achieve this goal have been described. In addition, certain salt forms of diclofenac, such as diclofenac hydroxyethyl pyrrolidine[260] and diethylamine, respectively,[261] can permeate through the human stratum corneum from aqueous solutions, whereas diclofenac sodium seems to profit from phospholipid-based formulations.[262] It is, however, unclear whether the phospholipids should be used in form of liposomes or mixed micelles. Anyway, several clinical studies in animals (veterinarian) and osteoarthritis patients showed the benefit of this type of phospholipid-based products—gels[263] (Diclac Schmerzgel, Hexal AG, Holzkirchen, Germany) including "(3-*sn*-Phosphatidyl)-choline" and sprays[264] (Voltaren spray, Novartis Consumer Health, Munich, Germany) with deoiled soybean phospholipids—on their own in relief of pain and morning stiffness. Still, in all cases, no critical comparison with a comparator having a different formulation composition has been made.[265] Also, the justification for the selection of the phospholipid type (saturated or unsaturated) is not presented in any study. However, it is known that the phase transition temperature of phospholipids dramatically influences whether phospholipids are suitable for skin penetration or skin barrier enhancement.[266] The concept of local treatment of arthritis inflammations was underscored by a study showing that after administration of a diclofenac sodium 4% spray gel, the diclofenac concertation was found to penetrate the skin locally in substantial amounts. The median diclofenac concentration was approximately 10- to 20-fold higher in synovial tissue of the knee than in synovial fluid or plasma.[267] For this reason, such NSAID products can be considered not only as dermatological products, but also as partially parenteral products since they are aimed for an enrichment of the drug in the synovial compartments or tissues surrounding joints, without further systemic bioavailability.

4.1.2. Ketoprofen and Nimesulide

A similar type of studies, with the same lack of comparators, can be found for other NSAIDs, which are on the market as oral products and are reformulated for dermal use bearing phospholipids as key excipients. These are ketoprofen and nimesulide.[268]

Ketoprofen is on the market as Ketospray (CYATHUS Exquirere Pharmaforschungs GmbH, Bisamberg, Austria) which contains soybean lecithin as stabiliser to enable the formulation of the high concentration (10%) of ketoprofen. It is further claimed that the lecithin acts together with ethanol and isopropanol in the formulation as flux enhancer.[269] The efficacy and tolerability of these spray products have been shown in a safety study as it is defined by Article 21 of the European Clinical Trials Directive 2001/20/EC.[270]

Nimesulide was found to have excellent skin interaction when using multilamellar liposomes. Anti-inflammatory studies, using the carrageenan-induced rat paw oedema model, indicated significantly higher efficacy of liposomal entrapped nimesulide in comparison to the marketed gel formulation and the Carbopol gel containing nimesulide.[271] In Italy, a cream and a spray formulation are on the market, including nimesulide.[272]

Although the scientific evidence that phospholipids exclusively enhance the skin interaction of NSAIDs is on debate, the corresponding products enjoy much interest in local symptomatic treatment in arthrosis patients.

4.2. Converting from the Parenteral to the Dermal Administration Route

There are a few parenteral products for which a dermal Pharmaceutical Form Line Extension could offer a more convenient alternative. For instance, for an antifungal that needs to be repeatedly intravenously injected to treat local infections, a topical product can be a less painful and more cost-effective alternative. Examples at which phospholipids play a key role in such line extensions are provided in **Table 8**.

4.2.1. Amphotericin B

Amphotericin B was first on the market in a parenteral dosage form (Fungizone) which used sodium deoxycholate as

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Table 8. Examples of Pharmaceutical Form Line Extensions using phospholipids as key excipients to convert a parenteral form into a topical form.

API (Class)	Originator product dosage form and (product example)	Topical line extension product dosage form and (product)	Advantages of line extension
Amphotericin B (Antifungal)	Parenteral micellar solution or liposome (Fungizone or Ambisome)	Liposomal gel, with HSPC and cholesterol (Fungisome)	Drug solubilisation and improved skin interaction
Minoxidil (Hair loss)	Solution, intradermal injection (Minoxidil injection)	Solution with SPC (Morr F) (Tugain, spray)	Increased tolerability and improved skin interaction
Heparin (Venous thrombosis)	Solution (Heparin Sodium Injection, USP)	Liposomal suspension with soybean lecithin (ViaTromb spray)	Improved skin interaction
Lidocaine HCl (Local Anesthetic)	Solution Xylocaine (lidocaine HCl and epinephrine Injection, USP)	Liposomal gel with HSPC (LMX cream)	Improved skin interaction

solubiliser[147] to enable injection of this water-insoluble drug (see above). In 2007, a parenteral and dermal Pharmaceutical Form Line Extension was developed by the company Lifecare Innovations Pvt Ltd. (Gurgaon, Haryana, India), based on a liposomal formulation of amphotericin B with HSPC and cholesterol as liposome components.[162] For the dermal treatment of acute and recurrent chronic fungal infections of the skin and cutaneous leishmaniosis, the liposomes were formulated in a gel (Fungisome gel).[273] The liposomes solubilise amphotericin and offer a formulation with less irritation potential and increased skin interaction.

4.2.2. Minoxidil

The drug minoxidil is on the market for treatment of hair loss (androgenic alopecia) and is available in tablet form (Minoxidil Tablets, USP)[274] and administered through intradermal injection (Minoxidil Injection of Swiss Healthcare Pharmaceutical Ltd; Montreux, Switzerland), respectively. As Pharmaceutical Form Line Extension, Morr F by Intas Pharmaceuticals Ltd (Ahmedabad, India) and JINA Pharmaceuticals Inc (Libertyville, IL), a dermal liquid comprising minoxidil liposomes based on US patent 9 750 812[275] was introduced. In addition, a dermal spray/foam with phospholipids is on the market (Tugain of Cipla Ltd, Mumbai, India).

The benefits of liposomal forms for skin treatment, in general,[276] and of minoxidil (SPC dissolved in isopropyl alcohol-propylene glycol-water solution) in comparison to a minoxidil solution (isopropyl alcohol-propylene glycol-water), for treatment of androgenic alopecia are well described in the literature.[277] A topical formulation of Morr F (combination of Minoxidil and Finasteride) was shown to have clinically significant improvement in terms of hair growth as compared to Minoxidil alone.

4.2.3. Heparin

Heparin acts as an anticoagulant, preventing the formation of clots and extension of existing clots within the blood. Heparin and its low-molecular-weight derivatives (low molecular weight heparin, LMWH), for example, enoxaparin, dalteparin, or tinzaparin, are effective in preventing deep vein thromboses and pulmonary emboli in people at risk[278] and is given as a subcutaneous injection. Since a topically applied dosage form of heparin would be a more convenient way to administer the drug compared to injection, dermal Pharmaceutical Form Line Extensions were developed. In addition, liposomal dosage forms to enhance the skin penetration of heparin were explored. Just like with dermal forms of NSAIDs, the clinical applicability of the dermal use of heparin in liposomes is controversial. Betz et al.[279] found that the extent of LMWH penetration was independent of the formulation. LMWH, however, showed a trend to accumulate in deeper epidermal layers of the liposomal formulation compared to the aqueous formulation. The molecular weight of the heparin and liposomal formulations influenced the penetration pattern of heparin in the epidermis. They could not conclude whether the concentration of LMWH achieved at the blood capillaries is sufficient to exert a pharmacological effect. For these reasons, such applications are more suitable to treat superficial venous thrombosis rather than deep venous thrombosis. Indeed, Górski et al.[280] were able to clinically prove that the dermal application of a liposomal heparin spray (Lipohep spray gel) combined with compression shows a comparable efficacy as subcutaneous administration of LMWH in the treatment of superficial thrombosis.[280b]

Vecchio and Frisinghelli[281] reviewed the literature on dermally applied heparins for the treatment of vascular disorders. They concluded that still more clinical research is needed to clarify which formulation is best regarding the treatment of thrombosis and that so far, all reviewed products are about the same in efficacy and tolerability. Nevertheless, a product such as ViaTromb by CYATHUS Exquirere Pharmaforschungs GmbH (Vienna, Austria) uses the "magic" of the liposome (with soybean phospholipids[282]) in the product to suggest a superiority of this dermal heparin product versus products without liposomes, which makes, despite the absence of convincing clinical evidence, such Pharmaceutical Form Line Extensions from marketing perspective attractive products.

4.2.4. Lidocaine

Lidocaine is another drug substance used for local anesthesia through injection (Xylocaine; lidocaine HCl and epinephrine Injection, USP),[283] which could be made more attractive for the patient by reformulating the drug in a dermal dosage form. An example of such product is LMX4 (ELA-Max), a lidocaine cream (4 weight%) of Ferndale Pharmaceuticals Ltd (Wetherby, UK), which contains benzyl alcohol, carbomers, cholesterol,

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Table 9. Examples of dermal/topical pharmaceutical form line extensions.

API (Class)	Originator product dosage form and (product example)	Line extension product dosage form and (product)	Advantages line extension
Azelaic acid (Antibiotic, anti-acne)	Cream 20% (Azelex)	Gel 15% with lecithin (Skinoren Gel/Finacea)	Increased efficacy
Clindamycin phosphate (Antibiotic)	Cream (Cleocin)	Water-in-oil-in-water (w/o/w) emulsion with soybean lecithin as emulsifier (Clindesse intravaginal cream)	Increased efficacy
Dexpanthenol (Provitamin)	Ointment, gel solution (Bepanthen)	Spray with HSPC (Sensiderm, Physiogel AI)	Cooling effect, excellent spreading and skin interaction
Diclofenac sodium (NSAID)	(Voltaren Emulgel)	Liposomal gel with PC (Diclac)	Equivalent to original product
Dithranol/salicylic acid (Anti-psoriatic)	Ointment (Psoralon MT)	Liposomal gel with egg lecithin (Psorisome)	Efficacy enhancement (50% less dithranol); no salicylic acid; increased skin interaction

hydrogenated soy lecithin, polysorbate 80, propylene glycol, trolamine, vitamin E acetate, and purified water.[284] LMX4 is a liposomal formulation in a gel base, which because of the presence of liposomes[285] enhances the skin penetration of the drug, leading to a rapid onset of action,[286] and prevents metabolic degradation at the application site. This, in turn, leads to a prolonged duration of action[287] and further helps in sustained release of the drug.[288] More extensive clinical research and comparison with eutectic mixture of local anesthetics (composed of lidocaine 25 mg mL^{-1} and prilocaine 25 mg mL^{-1}, polyoxyethylene fatty acid esters that are emulsifiers, carboxypolymethylene that is a thickening agent, distilled water with pH adjusted approximately to 9, and without any preservative) was performed. It was shown that LMX4 and the product of an eutectic mixture of local anesthetics were equally efficacious.[289] These results indicate that the presence of liposomes in the LMX4 product may act as an additional sales/marketing factor to create an attractive Pharmaceutical Form Line Extension.

4.3. Improving Interaction with the Skin

Phospholipids can also be used as key excipients in Pharmaceutical Form Line Extension to improve (either in the form of skin penetration or restoring the skin barrier) the skin interaction profile of the formulated drug in existing skin products. Some examples are provided in **Table 9**.

4.3.1. Azelaic Acid

Azelaic acid, a naturally-occurring saturated dicarboxylic acid, is used to treat mild to moderate acne, both comedonal acne and inflammatory acne.[290] Azelaic acid was introduced on the US market in a topical gel by Amirall S.A. (Barcelona, Spain) in 1995, for treatment of rosacea, due to its ability to reduce inflammation.[290b] This product, Azelex cream (20%),[291] contains cetearyl octanoate, glycerine, glyceryl stearate, cetearyl alcohol, cetyl palmitate, cocoglycerides, PEG-5 glyceryl stearate, propylene glycol, and purified water as excipients. Benzoic acid is present as a preservative.

As Pharmaceutical Form Line Extension—initially developed by Schering AG (Berlin, Germany)—, an alternative dermal product containing lecithin for the same indication containing less azelaic acid (15%) compared to Azelex was introduced on the US market by Leo Pharma AS (Ballerup, Denmark) in 2015; 20 years later. This product, Finacea/Skinoren Gel, has been developed to meet the needs of acne patients with greasy skin.[292] A reason to select 15% drug content instead of 20% was that the galenically acceptable maximal concentration in the gel was only 15%.[292b] The Austrian product approval documentation mentions that SPC is used as phospholipid component.[292b] Burchacka et al.[293] found in a Franz cell diffusion system that a liposomal gel formulation showed a higher concentration of azelaic acid in the stratum corneum compared to the standard non-liposomal product. The only preclinical experiment to study skin PK, which has been published with azelaic acid containing hydrogels by Schering, was a test on an in vitro skin penetration, using hairless mouse skin. Azelaic acid containing hydrogels delivered a higher dose fraction into the viable skin layers than Skinoren cream. Since the number of experiments was low and since the variation between the single experiments was high, these differences should not be overestimated.[292b]

Schering performed two Phase II/III clinical studies with Skinoren Gel controlled by the azelaic acid-free vehicle ("placebo") and 5% benzoyl peroxide hydrogel, respectively. Moreover, Schering has performed a Phase II study between Skinoren Gel and Skinoren Cream in small groups of 15 patients each to underscore the clinical efficacy. No clinical studies in comparison with the cream formulations were made.[292b]

Since the phospholipid-containing product Finacea, which bears 15% azelaic acid, and the Azelex cream product containing 20% azelaic acid are used for the same indication, it can be assumed that the phospholipid-based line extension product shows an increased efficacy.[292b] To underscore the commercial importance, this product is protected by patents.[294]

4.3.2. Clindamycin

For treatment of local vaginal infections clindamycin is used in a cream formulation.[295] The Pharmaceutical Form Line Extension Clindesse was originally developed by the company KV Pharmaceutical Company, which was acquired by the company Perrigo (Dublin, Ireland). The Clindesse product is covered by patents.[296] Clindesse is indicated for the treatment of bacterial vaginosis in non-pregnant women.[297] The formulation

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comprises a pH neutral o/w emulsion, which oil globules have two phases, an internal water-soluble phase and an external water-insoluble phase. The internal water phase contains the clindamycin and has an acidic buffer.[296a] The phospholipid (SPC)[296b] probably acts as essential emulsifier in this complex water-in-oil-in-water (w/o/w) emulsion formulation. In a clinical study, which compared Clindesse with a conventional vaginal cream, it was shown that Clindesse was more efficacious compared to a conventional cream since a single dose of Clindesse was equivalent in safety and efficacy to a regimen of once daily for seven days of the conventional cream, Cleocin, in the treatment of bacterial vaginosis.[295,298]

4.3.3. Dexpanthenol

Dexpanthenol (provitamin B5) is a well-known substance used in skincare and topical treatment of skin and mucous membrane related diseases. Most of these diseases are characterised by a decrease or damage of the barrier function of the skin or mucous membrane. A popular method to strengthen the barrier function is to add, together with the drug substance, hydrogenated natural phospholipids, such as HSPC to the formulation, generating dermatological interesting Pharmaceutical Form Line Extensions. These phospholipids have a phase transition temperature above skin temperature, which brings these molecules in the rigid gel state. Together with other high-melting lipids in the formulation, they form lamellar structures able to form a skin barrier increasing lipid film.[266,299] In the case of dexpanthenol, the product Sensiderm are using this "lamellar" technology.[300] A similar use of hydrogenated phospholipids from soybean can be found in the product Physiogel AI of GlaxoSmithKline (London, UK)[301] for treatment of atopic dermatitis and in the product Repithel of Mundipharma Deutschland GmbH & Co. KG (Frankfurt/Main, Germany) containing polyvinyl-pyrrolidone iodine of for the local treatment of burn wounds.[302]

4.3.4. Diclofenac Sodium

Diclofenac sodium (Voltaren) was introduced as oral NSAID by Ciba-Geigy Ltd (Basel, Switzerland) in 1973/1974.[303] Based on the success of this product as an anti-inflammatory drug, topical Pharmaceutical Form Line Extensions were developed for local anti-inflammatory effects in, e.g., joints, also to eliminate possible systemic side effects. The first topical product to achieve this was Voltaren Emulgel of Ciba Geigy Ltd. This Voltaren gel containing the diethylammonium salt of diclofenac received US regulatory approval as the first topical prescription treatment for pain associated with osteoarthritis in 2007.[304] To circumvent patent protection of this topical product,[305] liposome-based dermal Pharmaceutical Form Line Extensions of diclofenac (for example Diclac of Hexal AG including 1% diclofenac and SPC)[263,306] was developed, having at least the same benefits as the original Emulgel product.[307]

4.3.5. Dithranol

The drug substance combination of dithranol (patented by Bayer AG, Leverkusen, Germany in 1916) and salicylic acid is topically applied to the skin for a short period for treatment of psoriasis. A side effect of the use of dithranol is a reversible brown coloration of the skin. This combination is on the market in the product Psoralon MT ointment (including 0.5–3% dithranol) with paraffin and vaseline of Hermal Kurt Herrmann GmbH & Co oHG (Reinbek, Germany).[308] A further problem is the oxidative sensitivity of dithranol.

Research in the nineties showed that dithranol incorporated in liposomes shows a favorable skin interaction.[309] The Indian company Lifecare Innovations Pvt Ltd. (Haryana, India) developed a Pharmaceutical Form Line Extension based on liposomes. This new dosage form should increase the stability of the drug and enhance skin penetration at a lower dithranol dose and formation of a micro reservoir in the skin. Lifecare Innovations claims that the resulting product Psorisome (without salicylic acid) has minimised cloth-staining and discoloration problems, reduced irritation, perilesional erythema, burning, sensation, sustained moisturising effect, improved patient acceptability, dose reduction up to 50%, and improved drug stability.[310] The product is covered in the EU by a patent.[311] In this patent, clinical research on the comparison between a dithranol ointment with salicylic acid and a liposomal formulation with egg lecithin is presented. The lecithin containing formulations were found to be non-irritating and therapeutically more effective even at dithranol concentrations of 0.5% as compared to a dithranol ointment containing 1.1% dithranol.

5. Oral Pharmaceutical Form Line Extensions

5.1. Suppressing Gastric Irritation of NSAIDs

Phospholipids can also be used to optimise oral products. An example is to use phospholipids to make Pharmaceutical Form Line Extension to reduce gastric side effects of NSAIDs (**Table 10**).

Gastric mucosal injury occurs when the causative agents such as gastric acid and NSAIDs overwhelm the mucosal defence. It is well documented that external application of phospholipids to the stomach had the potential to reduce gastric side effects of oral NSAIDs such as ibuprofen and acetylsalicylic acid.[313] Also, the gastric irritation caused by acetylsalicylic acid (Aspirin) could be reduced in preclinical models by using PHOSAL 35 SB (the composition of PHOSAL 35 SB can be found in ref. [312]). These observations were the impetus for the commercial development of PL2200 Aspirin (Vazalore) by PLx Pharma Inc. (Houston, USA) combining aspirin with PHOSAL 35 SB.[314] Vazalore was approved in 2013[315] for temporary relief of minor aches and pains associated with a cold, headache, backache, toothache, premenstrual and menstrual cramps, minor pain of arthritis, and for a temporary reduction in fever. Several US patents cover this product.[316] The focus of the clinical development is to provide patients with vascular disease and diabetic patients, who are candidates for aspirin therapy with more reliable and predictable antiplatelet efficacy as compared to enteric-coated aspirin, while also reducing the adverse gastric events common in an acute setting. PLx Pharma is reported to perform soon a bioequivalence study of Vazalore 325 mg dose (in comparison of the original formulation of 2013 and a new formulation), and a corresponding sNDA (subordination, non-disturbance and attornment agreement) submission is expected by year-end of 2021.[317] The

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Table 10. Examples of oral Pharmaceutical Form Line Extensions of NSAID with reduced gastric side effects.

API (Class)	Originator product dosage form, (product example)	Line extension product dosage form and (product)	Advantages of line extension
Acetylsalicylic acid (NSAID)	Aspirin	Complex of API with PHOSAL 35 SB[a] (Vazalore)	PLxGuard delivery system, decrease stomach irritation
Ibuprofen (NSAID)	Ibuprofen USP tablets (*e.g.*, Motrin)	Complex of API with phospholipid (PL1100/PL1200 Ibuprofen, development stage)	

[a] For composition of PHOSAL 35 SB refer to van Hoogevest.[312]

company develops similar phospholipid-based Pharmaceutical Form Line Extensions for ibuprofen (Phase I), indomethacin, and diclofenac, which show improved GI safety in preclinical models.

5.2. Alternative Bioequivalent Oral Liquid Form

Phospholipids can also be used in liquid oral dosage forms as an alternative to a solid dosage form. The typical example of such a liquid dosage form is the product, based on the use of a non-aqueous PC concentrate from soybean PHOSAL 50 PG trademark of PHOSPHOLIPID GmbH (Cologne, Germany),[318] developed for the lipophilic compound sirolimus, marketed under the trade name Rapamune by Wyeth-Pharmaceuticals (Madison, USA; a subsidiary of Pfizer Inc).[312] Sirolimus is a naturally occurring compound which is mainly used to prevent rejection of kidney transplants. The inactive ingredients in Rapamune Oral Solution are PHOSAL 50 PG (including PC, propylene glycol, mono- and diglycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and Tween 80. Rapamune Oral Solution contains 1.5–2.5% ethanol and is supplied in amber glass bottles with 60 mg sirolimus per 60 mL. The sirolimus product based on the liquid PHOSAL formulation got the generic status in the US in 2019.[319]

Although this liquid dosage form was the first oral dosage form developed for this product and the solid dosage form, based on the use of nanocrystals, came later, both forms can be considered as line extensions of each other. In fact, sirolimus was the first approved drug using nanocrystal technology. The tablet form provides a common administration form, but the liquid form may be more convenient for a flexible-dose regime.[320] The systemic availability of sirolimus is low and was estimated to be approximately 14% after the administration of Rapamune Oral Solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level.[312]

6. Suitability of Phospholipids for Pediatric Pharmaceutical Form Line Extensions

Regulatory authorities require the development of pediatric line extensions, i.e., dosage forms suitable for pediatric use for products developed exclusively for adults.[321] Formulators are then possibly forced to replace excipients in formulations for adults by excipients which are unproblematic or approved for pediatric use. Phospholipids can be found in many products for pediatric use and may offer viable alternative solubilisers/dispersants to polysorbates, ethanol, and propylene glycol.[322]

Polysorbates (Tween 80, Tween 20) and polyoxyl castor oil derivatives are particularly problematic because, as outlined above, they may cause hypersensitivity reactions, especially after parenteral administration. In addition, the use of Tween 80 and 20, respectively, may give rise to the occurrence of the E-Ferol syndrome observed with Low-Birth-Weight Infants.[323] Phospholipids present an alternative when parenteral formulation should contain wetting agents (for suspension injections) or a solubiliser to enable unproblematic parenteral administration. In that respect, products containing solubilising formulations, such as mixed micelles, o/w emulsions, and liposomes are approved for application in children explained as follows. Mixed micelles with SPC containing the lipophilic vitamin K is allowed for oral and intravenous use in children.[324] The product Diprivan comprising an o/w emulsion with EPC as essential emulsifier as solubilising formulation for the lipophilic drug propofol can be used in children ≥3 years for induction of general anesthesia and in children of ≥ 3 months for maintenance of general anesthesia. Pediatric patients, aged one month to 16 years, with presumed fungal infection (empirical therapy), confirmed systemic fungal infections or with visceral leishmaniosis have been successfully treated with AmBisome comprising amphotericin B and the phospholipids HSPC and DSPC[325] as well as with Abelcet (DMPC/DMPG).

Phospholipids could also be used in injectable products for poorly water-soluble drugs to replace organic solvents, such as ethanol and propylene glycol as solubilisers. Both solvents should be avoided in pediatric formulations. Accumulation of propylene glycol can occur in neonates and young children as they cannot adequately metabolise and eliminate the excipient. This reduced metabolism and elimination can lead to depression of the central nervous system.[322,326]

The permitted pediatric use of phospholipids after intravenous administration can be derived from the prescribing information of phospholipid-based products for intravenous use (**Table 11**).

Since for oral administration liquid products for pediatric use are preferred, excipients with a bitter taste need to be avoided in these liquid products and could be replaced by phospholipids. Phospholipids of natural (soybean) origin are odorless or have a characteristic, slight nutlike odor and bland taste[330] in contrast to polysorbates, which have a bitter taste.[331] Phospholipids are even able to suppress bitter taste without affecting other taste qualities.[332] SPC is used in oral products[9] and the European Food Safety Authority recently assessed the safety of oral use of lecithin (E 322, food codex) and concluded that there was no safety concern for the general population from more than 1 year of age and infants (from 12 weeks up to 11 months of age) at the refined exposure assessment for the reported uses of lecithins (E 322) as a food additive.[333] The product Konakion MM, containing SPC, can be orally administered to children from born before

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Table 11. Intravenous products with phospholipids permitted for pediatric use.

Product	Pediatric use (Age category)	Phospholipid component
Abelcet[152a]	1 month – 16 years	DMPC and DMPG
AmBisome[327]	1 month – 18 years	HSPC and DSPG
Konakion MM[328]	From born before finishing 37th pregnancy week; or less than 2500 g birthweight – 18 years	SPC
Intralipid[329]	From born before finishing 37th pregnancy week; or less than 2500 g birthweight – 18 years	Egg yolk phospholipids
Mepact[86]	2–18 years	POPC DOPS monosodium salt

finishing 37th pregnancy week (or less than 2500 g birthweight) up to 18 years.[328b]

The acceptability of pediatric dermal use of soybean phospholipids (which are mainly present in dermatological products) in children can also be derived from the product prescribing information. For instance, the product LidoGalen (including lidocaine) containing HSPC can be used in children older than one month. The product ViaTromb Spray gel (including heparin), which contains soybean lecithin, can be used in children older than 2 years.[334]

7. Discussion

This review shows the manifold options to make Pharmaceutical Form Line Extensions with the aid of phospholipid excipients. These numerous options are the result of favorable physiological properties of phospholipids, such as biocompatibility, biodegradability, and non-toxicity in combination with their multifunctional technological properties as surfactant excipient, being emulsifier, solubiliser, liposome former, and wetting agent. Regarding the versatility, phospholipids are superior compared to synthetic non-biodegradable excipients which are not always suitable for every administration route and which are, by definition, non-physiological.

Phospholipids are a family of compounds differing in fatty acid composition and polar headgroup, which give the specific species unique properties and use in pharmaceutical technology. Also, the availability of both natural and synthetic phospholipids provides the formulation scientist with a valuable treasure of options to optimise phospholipid-based line extension products.[9] The use of phospholipids (documented by drug master files according to 21 CFR 314.420 of the FDA)[335] in many registered products all around the world render them well-known to regulatory authorities. Therefore, when phospholipids need to be selected for formulation development, phospholipids documented through a drug master file are preferred. In case natural phospholipids derived from hen egg yolk or soybean are selected, attention should be paid to the grade of the product regarding minimal PC-phospholipid content, which is dependent on the administration route. For oral and dermal administration, natural phospholipids with at least 45% PC can be used, whereas for parenteral use at least 70% PC is typical.[336] For specific high-tech parenteral products more expensive, high purity, synthetic phospholipids may be the best choice, whereas for dermal and oral administration cost-effective natural phospholipids are the first choice.

The product examples provided in this review rely on the official description of the composition and phospholipids therein found in the literature. With synthetic phospholipids, there are hardly any question marks as to which phospholipid has been used in a product. In the case of natural phospholipids, it is much harder to find out which phospholipid grade actually has been used. An important reason for the poor description of phospholipids relates to the confusion that exists, especially in American literature, regarding the difference between the term "lecithin" and "phosphatidylcholine". According to the USP Convention, 2014, lecithin is a complex mixture of acetone-insoluble phosphatides (i.e., phospholipids), which consist chiefly of PC, PE, phosphatidylinositol (PI), and PA, present in conjunction with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. Unfortunately, "lecithin" is also used as a synonym of PC, which is the pure compound. Description of the phospholipid component in a product as "lecithin" leaves open which lipid was used. We therefore recommend to use for natural phospholipids the term "lecithin" only when the product contains less than 80% by weight total phospholipids (which could be, e.g., PC, PE, PA); the term "phospholipids" is used when the product contains 80–100% by weight phospholipids (which could be, e.g., PC, PE, PA); the specific phospholipid is mentioned (e.g., PC) when the product contains more than 90% by weight of that specific phospholipid. The European Pharmacopoeia, the USP, and the Chinese Pharmacopoeia are continuously upgrading and extending the monographs on phospholipids, and the nomenclature used in these pharmacopoeias should unequivocally define the phospholipids used in pharmaceutical products.

The product and development examples described in this review only represent a fraction of the ongoing activities in the pharmaceutical industry regarding the use of liposomes and other phospholipid-based formulations. Reference is made to, for instance, www.orpha.net, www.clinicaltrials.gov, the United States Patent and Trademark Office (www.uspto.gov), and the European Patent Office (www.epo.org) databases.

The examples of conversion of an oral dosage to a parenteral dosage form are mainly related to poorly water-soluble drug substances in need for low toxic solubilization formulation to enable parenteral administration (Table 1). The provided examples encompass also transdermal and inhalation products (Table 6), which are, because of the obtained systemic bioavailability, considered as parenteral dosage forms: they again underscore the versatility and suitability of phospholipids for any route of administration. The (parenteral) inhalation line extensions Inbrija and Asprihale (Table 6) with systemic activity show the use of phospholipids to create line extension products with fast onset of action. In contrast, phospholipids can also be used in liposomal form to develop inhalation line extensions with (local) slow-release properties (Table 6). From a pharmaceutical technological perspective, saturated phospholipids are a viable alternative for lactose as diluent for inhalation powders.

The parenteral line extensions, which show an increased therapeutic index of the employed drug substance (without discarding

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of a potentially toxic solubiliser in the original formulation) compared to a formulation without phospholipids, are mainly related to (water-soluble) cytostatics for cancer treatment (Table 2). These, in most cases, cytostatics have a narrow therapeutic index and/or drug-specific toxicity (for instance cardiotoxicity for doxorubicin HCl) and are reducing the quality of life of cancer patients. The increase of efficacy of the liposomal dosage forms and/or the reduction of toxicity may be linked to the EPR effect, which results in an enrichment of the liposomal cytostatic in tumor tissue and simultaneously avoidance of "tox target" organs, as demonstrated with the Doxil product. Jensen and Hodgson[241] reviewed the properties of DaunoXome in comparison to Doxil and mention the short shelf-life of the DaunoXome product. In addition, DaunoXome is only applied to treat liquid tumors, whereas Doxil is used for both liquid and solid tumors.

The resulting line extensions mainly aim to the same disease indications as the original product. An example that the line extension is used for another cancer indication as the original product is Onivyde (pancreas cancer). It is remarkable to note that the original non-liposomal injectables with a worse therapeutic index are still on the market. This may be the consequence of the fact that in the clinical research stage, the liposomal products are compared to another anticancer drug.[337] For instance, liposomal doxorubicin has only once tested (crossover, double-blind) against the original product of doxorubicin HCl.[338]

The provided examples (Table 2) display that a plethora of lipids are applied in liposomes. A minimal requirement is that the liposomes employed are not leaky for the encapsulated drug to carry the cargo efficiently to the tumor site. Many lipid compositions and different methods, such as ion gradient to keep the drug in the liposomes are now available to achieve the desired targeting profile. An interesting example in this direction is provided by the liposomal forms for doxorubicin HCl, Doxil (Caelyx), and Myocet (both used in combination with cyclophosphamide). Both have reduced cardiotoxicity, but Doxil is using PEGylated lipids to prolong the circulation time after intravenous administration, whereas Myocet and DaunoXome do not contain PEGylated liposomes.[241,339]

The Hand-Foot Syndrome is a major side effect of Doxil, whereas Myocet does not show this syndrome. Myocet seems to be expensive and requires an elaborate in situ preparation method of the dosage form for injection (needing a controlled heating step in a water bath[340]) whereas Doxil is a ready-for-use liquid injectable dosage form. From this comparison, it looks like that Myocet is the interesting alternative line extension from a clinical use point of view. A conclusion, however, cannot be drawn, since clinical trials comparing these two line extensions were never performed.

A further remarkable observation regarding these line extensions is that the original product, although being more toxic and/or less efficacious than the liposomal line extension (e.g., doxorubicin HCl, vincristine sulfates etc.) is still registered and clinically used for the same medical indication and not withdrawn from the market. A rational explanation for that can be found in the fact that the original products are probably much cheaper and/or clinicians still are not convinced that the liposomal line extension is better. Another explanation could be that oncologists tend to use combination therapies and such combinations with the liposomal line extensions are not approved/tested, whereas for the non-liposomal form such combinations have a long(er) track record of use.

The product Mepact, in this class of (development stage) line extensions, is an example of a different way (instead of EPR effect) to use phospholipids/liposomes to increase the therapeutic of an immunomodulator by using liposomes which are optimised to interact with macrophages, to activate them to become tumoricidal to eliminate metastases. Also, parenteral emulsions, with EPC as emulsifier, can be used to optimise the efficacy of an oil-soluble drug-like prostaglandin (PGE1) for the treatment of peripheral vascular diseases.

The analysis of the parenteral line extension products in this review (Tables 3 and 4), characterised by the replacement of potentially toxic excipients by phospholipids, shows that phospholipid-based formulations, such as mixed micelles, o/w emulsions, and liposomes are clearly an alternative, with reduced risks for anaphylactic reactions compared to formulations with synthetic detergents, such as polysorbates, Kolliphor EL (Cremophor EL, Polyoxyl 35 Castor Oil), and Polyoxyl-15-hydroxystearate for solubilising poorly water-soluble drugs for parenteral administration. In addition, these phospholipid-based formulations can avoid or reduce formulations with potentially toxic organic solvents. Regarding the latter issue, it is remarkable that the injectable form of diazepam with mixed micelles has now been replaced by the original manufacturer by an organic solvent formulation which causes pain at the injection site.

A recent exciting example replacing synthetic detergents in parenteral formulations is the product Cinvanti, which belongs to two categories of line extensions: it enables the parenteral administration of the original oral product and, simultaneously, replaces the polysorbate in the injectable formulation of the prodrug of the original compound.[124] The original Emend for Injection product is an example of suboptimal pharmaceutical development. When lipid-based formulation alternatives would have been considered adequately, the development of the prodrug and its salt form and the addition of polysorbate, which makes the coadministration of dexamethasone necessary, probably to suppress hypersensitivity reactions, would not have been necessary.

The examples in Table 4 show that the use of phospholipids in parenteral line extensions has, in comparison to the original product, two advantages simultaneously: replacement of excipients (eliminating corresponding infusion reactions) and further improving the therapeutic index of the drug by means of targeting. One of these examples, AmBisome, is considered as an improvement compared to the original product Fungizone, but still Fungizone is on the market. This may be related to the costs of treatment and reimbursement policies of health insurances. This same price pressure and medical need in developing countries (treatment of kala-azar, *visceral leishmaniasis*) urged local companies to develop their own line extensions. Which line extension of amphotericin B is clinically best cannot be judged, since comparative clinical trials have never been performed. The line extensions with docetaxel and paclitaxel are only present in India and China, respectively.

Although, parenteral mixed micelles and o/w emulsions are clearly alternative solubilisers compared to synthetic detergent containing formulations, it should be noted that intravenous administration of (especially PEGylated) liposomes as part of

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such Pharmaceutical Form Line Extensions is also not without complications. Repeated administration of PEGylated liposomes can cause an Accelerated Blood Clearance (ABC) phenomenon. ABC involves the production of antibodies toward nanocarrier components, including PEG, which reduces the safety and effectiveness of encapsulated therapeutic agents.[341] Another immune response is the hypersensitivity or infusion reaction referred to as CARPA.[341] In that respect, it is of interest to compare the clinical data of these liposomal products and alternative (solubilising) formulations regarding the occurrence of infusion-related hypersensitivity reactions.

The available product leaflet on Caelyx (that is the product name of Doxil in Europe) mentions that serious and sometimes life-threatening reaction may occur within minutes after the start of the intravenous infusion of the PEGylated liposomes. After resolving the symptoms, in most patients, the treatment can be continued, without reoccurrence of the hypersensitivity symptoms. It is recommended to start the first infusion with an infusion rate of less than 1 mg drug substance per minute to reduce the risk for hypersensitivity reactions.[338,342] This recommendation agrees with Szebeni et al.[58] who recommended to slow the rate of administration to an initial rate of 0.1–0.15 mg Doxil per minute in the first Doxil treatment. If the patient does not experience any reaction or other symptoms, this infusion rate can be gradually increased after 10–15 min up to 1–1.5 mg per minute. Non-PEGylated liposomes such as AmBisome show the same infusion reactions, but also here it is mentioned that these reactions can be prevented by applying slow infusion rates.[343]

In contrast to liposomes, other intravenous phospholipid-based solubilising formulation types such as o/w emulsions and mixed micelles show hardly any infusion-related reactions. The available product leaflet of the intravenous mixed micellar products comprising SPC and sodium glycocholate in the product Konakion MM mentions that side effects regarding the immune system are scarce, meaning that the frequency of occurrence is less than 1 out of 10 000.[324] An intravenous o/w emulsion with EPC as emulsifier used for parenteral nutrition (Intralipid) show in less than 1% of the administrations, an increase of body temperature and chills, which cannot be considered as severe hypersensitivity reactions. In addition, it is mentioned that the reporting frequency of other undesired side effects is less than 1 out of a million.[329a]

In sharp contrast, the synthetic detergent-containing solubilising formulations show a higher tendency toward the occurrence of hypersensitivity infusion reactions. For instance, Taxotere containing polysorbate 80 shows very often (i.e., $\geq$ 1/10 cases) the event of significant reactions; 5.3% with grade 3/4. In addition, it is not allowed to repeat the treatment.[344] Also, paclitaxel shows significant hypersensitive response in less than 1% of the patients. Repeating the treatment is also not allowed. The Cremophor EL (Polyoxyl 35 Castor Oil) component is mentioned as a possible cause for the hypersensitivity reactions.[345] Also Polyoxyl-15-hydroxystearate (Kolliphor HS15, in the past Solutol HS 15) failed as solubiliser because an aprepitant product using this solubiliser (Varubi) was withdrawn from the market due to the high incidence of anaphylaxis shock.[129] In addition, synthetic detergents may be disadvantageous after oral administration as well. Recent studies on the impact of polysorbate 80 on the microbiome in the gut showed that polysorbate may cause bacterial translocation across the intestinal epithelium, intestinal inflammation, and metabolic syndrome.[346]

Although phospholipids on their own do not have an allergy potential, phospholipids derived from soybean and hen egg yolk must be labeled as potential allergens because of the soy and egg origin.[347] It is known that residues of soy and egg proteins may cause these allergies. In purified soybean phospholipids used for pharmaceutical application, the protein residues were found to be below the lower limit of detection (LLOD) of a soybean specific ELISA (enzyme-linked immunosorbent assay) assay which was 3 ppm.[348] The egg protein content of purified egg lecithin for parenteral administration was tested by Lipoid GmbH.[349] The most sensitive immunological detection method of proteins showed less than a LLOD of 2 ppm of egg protein in purified egg phospholipids. However, from the immunological perspective regardless of any protein present, the origin of such products has, according to regulatory authorities, to be labeled to alert allergic individuals. In a recent study on propofol emulsion with soybean oil and egg lecithin as emulsifier and its parenteral use in children with allergies to egg, peanut, soybean, or other legumes, it was concluded that genuine severe allergic reaction to the product was rare and was not reliably predicted by a history of food allergy.[350]

Based on these findings, the authors believe that as part of pharmaceutical development activities, (phospho)lipid-based systems should always be considered as viable alternatives to synthetic detergent formulations for solubilising poorly water-soluble compounds for intravenous administration. In contrast to synthetic detergent formulations, liposomes, mixed micelles, and o/w emulsions are preferred as solubilising formulations, as there is no hypersensitivity risk. Due to the presence of bile salts, mixed micelles are typically used for small volume parenterals as well as oral liquids. A significant advantage is that a mixed micellar solution is thermodynamically stable and can be produced without high pressure homogenization. The rare incidence of allergic reactions to purified natural phospholipids is restricted to small patient populations, which are mostly aware of their allergies. In contrast, allergic reactions to synthetic detergents may occur in any patient.

The examples in Table 5 show that liposomes/phospholipids can also be used for making injectable line extensions with retarded release properties. So far, this approach is limited to the use of the DepoFoam technology (see above). This technology is challenging with respect to manufacturing since the entire production process must be carried out under aseptic conditions. A terminal sterilization procedure is not possible. Therefore, it is to be expected that alternative technologies will be developed. Ideas in this direction are using in situ aggregated negatively charged liposomes[351] or injectable extrudates with hydrogenated soybean phospholipids as depot formulations.[352] These depots should cover the drug release window from days up to 2–4 weeks, which are presently not covered by formulations with polymers like poly(lactic-*co*-glycolic acid) (PLGA). The FluidCrystal injectable depot technology of Camurus, based on in situ formation may be a simpler alternative. The introduction of the slow-release injectable for buprenorphine (Buvidal/Brixadi) on the market underscores the viability of this technology.

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Conversion from an oral dosage form to an inhalation form, which should act locally, show an interesting novel use of saturated phospholipids and $CaCl_2$ to develop inhalation powders (Table 6). Also, in this case, the physicochemical properties of these phospholipids are ideally combined with the biocompatibility of these saturated phospholipids with lung tissue, which also contains saturated phospholipids.[353] The resulting products with antibiotic allow the local treatment of lung infections. The possible clinical benefits of Tobi Podhaler were, however, only compared to a placebo and not to the oral therapy with Tobramycin.[354]

The phospholipid-based line extension for inhalation purposes are challenging from clinical and technical development point of view (Table 6). For administration of antibiotic for local effects, the PulmoSphere technology had to be developed, and the usefulness of the inhaled antibiotic had to be proven clinically. For tobramycin this is the case, for ciprofloxacin not (yet). The inhalation forms of levodopa and acetylsalicylic acid use saturated phospholipids to make powders for inhalation, which must meet the highest requirements for particle size, particle size distribution, and flowability. The clinical development of this type of line extensions maybe less demanding compared to the locally acting line extensions because a fast onset of action and systemic absorption is envisaged, the latter one being well-described for the original oral products. Much more demanding is the development of liposomes for a desired slow-release use for antibiotics acting locally. Such development requires nebulization of the liposomes, analysis of change of particle size, loss of encapsulated drug, coadministration of an initial dose, etc. The development of such a concept was successful for amikacine (Arikayce) but failed for ciprofloxacin. The Arikayce product is, however, for the time being only approved for a very limited medical indication in the US. The EMA was not convinced by the therapeutic profile of this product. The development difficulties of this type of slow-release formulations may be related to the absence of data of the inhaled antibiotics without liposomes. Basically, two steps toward potentially better products have been made simultaneously, by exploring inhalation therapy with an antibiotic which has never been used like that before and on top of that the development of a sophisticated, technologically challenging, dosage form.

Conversion from an oral dosage form to a dermal product using phospholipids (Table 7) is mainly related to the reputation of liposomes and their claimed excellent skin interaction. It cannot be objectively assessed whether the favorable skin interaction of the developed dermal Pharmaceutical Form Line Extension is caused exclusively by the liposomes. Alternatively, these positive effects may be achieved by other dosage forms (either without phospholipids or alternative phospholipid-based formulations such as o/w emulsions or mixed micelles). Nevertheless, the liposomes represent a skin-compatible and cosmetically appealing formulation with an excellent marketing story. The drug class in focus of this approach is the NSAIDs. The popularity of this approach offering a local treatment without systemic side effects (mainly gastric irritation) underscore that this type of line extensions are valuable products, also in terms of sales of such products.

The conversion from a parenteral dosage form to a dermal dosage form (Table 8) addresses the medical need that for some indications only local treatment may be beneficial while the toxicity of systemic administration of the drug can be avoided/suppressed (e.g., example with amphotericin B). Such line extensions also address that some patients have a needle phobia. For instance, a locally acting anesthetic instead of a local injection is a relief for such patients. Such an approach requires that the guaranteed effect obtained by the local injection is maintained after local treatment with a dermal dosage form during an adequate period. In case of heparin (LMWH), the liposomal formulation cannot penetrate that deeply into the skin as an injectable since the dermal form is more suitable to treat superficial venous thrombosis rather than deep venous thrombosis.

The dermal line extensions provided in Table 9 are examples of products containing phospholipids with claimed advantages. The azelaic acid gel with phospholipid contains a lower concentration of the active compared to the cream, suggesting that the gel is more efficacious. The actual reason to take the lower percentage of azelaic acid was, however, not a difference in efficacy, but a galenical issue preventing a higher percentage of azelaic acid in the line extension with the phospholipid-containing gel formulation. As far this increase of efficacy is caused by the presence of the phospholipid is unclear, since systematic studies on this aspect are missing.

The dermal products (e.g., Sensiderm and Physiogel AI) with added saturated phospholipids like HSPC are claimed to have skin barrier restoring effect, due to the presence of skin-like, lamellar structures, which ideally fit in the skin structure.

The Diclac liposomal gel is an interesting example to circumvent existing patents protecting an attractive commercial product, which does not contain phospholipids. The Diclac gel demonstrates that the skin interaction of the liposomal gel with diclofenac sodium is equivalent to the Emulgel which uses a specific lipophilic diethylamine salt of diclofenac. The liposomal gel with dithranol was at least as clinically efficacious as a dithranol ointment with salicylic acid. The phospholipid-containing formulations were found to be non-irritating and therapeutically more effective even at dithranol concentrations of 0.5% as compared to a dithranol ointment containing 1.1% dithranol. The specificity of the effect caused by solubilization of the compound in comparison with other solubilising formulations has not been presented. As mentioned above, regarding line extension converted to the dermal application, the value of these line extensions is also based on marketing statements rather than sound scientific evidence. The comparison of the degree of skin interaction of original and line extension product using in vitro models using healthy (fresh) skin samples (e.g., Franz Cell) may show qualitative differences but may be irrelevant for the diseased skin on the patient. Also, preclinical assessment using animal skin models are at the maximum indicative for differences in skin interaction because the skin of animals is different from the human skin. In the assignment of a claimed skin effect on a specific component, the presence of other excipients in a dermal product must be considered which may have overlapping properties.

The oral line extensions in Table 10 are based on the property of phospholipids to complex with NSAIDs and to suppress the gastric irritation potential of this compound class. It appears that the product development of these products takes a very long time. The future will show whether these products with acetylsalicylic acid and ibuprofen, respectively, can conquer significant market shares of the oral NSAIDs. Another example of oral use of

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phospholipids is demonstrated by the product Rapamune. A non-aqueous concentrate of phospholipids (e.g., PHOSAL 50 PG) is utilised here to solubilise the poorly soluble drug substance. The liquid oral dosage form is a viable line extension and it is used as immunosuppressant besides tablets, which contain the nano-sized drug substance. Such liquid concentrates may accelerate the pharmaceutical dosage form development, gives great dose flexibility, and enable a quick introduction of the product on the market.[312]

Most databases on the pediatric use of excipients only mention the excipients, which may cause problems for this patient population.[355] The developer of a dosage form would like to know as well which excipients can be used. Based on the prescription information and the phospholipid compositions, this review should provide some information on the pediatric intravenous administration of selected phospholipids. The pediatric oral use of phospholipids (soybean) is in general allowed, of course with precautions for soybean allergy. Sunflower phospholipids, with no allergy warnings, are available today. Also, the pediatric dermal use of soybean phospholipids, natural and hydrated, is unproblematic.

It is out of the scope of this review to analyze the ROI of the provided line extensions. Anyway, the presented products were, in most cases, protected by additional patents. It is not exceptional that patents covering the line extensions have been issued 10–20 years after the market introduction date of the original product. These patents should carefully describe the phospholipids, which are suitable and preferred for the envisaged products. To do this accurately, a piece of in-depth knowledge on the availability of the many eligible phospholipids and formulation options is necessary to define the protecting IP of the product accurately. It is also clear from the description of the obtained line extensions that in all cases, such products must represent clear advantages for the patients. Together with the existence of these products on the market, it can be assumed that the line extensions represent commercially attractive products.

From the mentioned companies involved in the development of the line extensions, it can be derived that mostly small and mid-size companies are playing a role nowadays. In contrast, most big-pharma companies do not pursue the development of line extension products as a priority but may prefer to license in commercially attractive options. An example how such line extension enters the market is Doxil, which was developed by the small liposome company LTI (Menlo Park, CA) and through the acquisition of Alza Corporation (Palo Alto, CA) ended at J&J Pharmaceuticals. Gilead Sciences Inc.[241] and Taiwan Liposome Company,[356] respectively, are examples of companies pursuing and exploring especially liposome-based line extensions. Since mainly smaller companies are involved, it is no surprise that many line extensions change their owner or even developer during the development phase and marketing phase. The available resources of such companies are apparently not adequate to perform and finance the complete technical and clinical development.

Recently, Metselaar and Lammers reviewed the challenges in nanomedicine clinical translation.[4] They define the challenges in the categories of commercial and practical feasibility, clinical development feasibility, translating preclinical efficacy to clinical outcome, bridging preclinical toxicity to patient safety, and fulfilling CMC (chemistry, manufacturing, and control) requirements. These considerations partially overlap with the general challenges a developer of Pharmaceutical Form Line Extension is facing. They apply particularly for liposomal products with increased therapeutic index. These authors refer to comparator products as a clinical reference. In most cases of line extensions, the comparator is the original product without the nanomedicine carrier, in this case, the liposome. The clinical research strategy is clear most of the time: suppression of toxicity and at least maintenance of efficacy of the original product. Recently, Jensen and Hodgson[241] presented a few examples of the development of liposomal line extensions at Gilead. They conclude that also technical issues, such as lack of stability or cumbersome manufacturing methods, may be hurdles. At the end of the day, however, the overall ROI of such line extensions played a decisive role. Other line extensions, not related to challenging intravenous carriers like liposomes, which change the distribution and kinetics of the drug substance, may have lower technical hurdles to develop. The clinical development may, however, be equally challenging, dependent on the benefits the line extensions should have and which product will be used as a comparator (placebo or original product). The technological hurdles for the Pharmaceutical Form Line Extensions are relatively low because of the versatility, biocompatibility, and biodegradability of the phospholipids in combination with standard formulation technology. Also, the large-scale availability of pharmaceutical-grade phospholipids is helpful. In some cases, however, the dosage form development for the inhalation route may be quite challenging. The presented products in this review demonstrate that phospholipid-based Pharmaceutical Form Line Extensions are not restricted to parenteral liposome products, but that phospholipids are well-suited pharmaceutical excipients in many other formulation types and any route of administration.

8. Conclusions

This review describes the use of phospholipids as key excipients for the development of Pharmaceutical Form Line Extensions as part of Product Life Cycle Management. Based on the provided product and development examples, conclusions can be drawn that phospholipids 1) are suitable to convert dosage forms for other administration routes, 2) can act as an alternative solubiliser to reformulate products containing potentially toxic synthetic detergents and/or organic solvents for parenteral administration of lipophilic compounds, 3) can be used in liposomal form to increase the therapeutic index of toxic cytostatics and antifungals for parenteral administration, 4) allow in liposomal form for slow release of the encapsulated drug substance, 5) serve to formulate inhalation products, for local treatment, systemic treatment, or local slow release, 6) improve the oral administration of NSAIDs, 7) may serve as a component in liquid oral dosage forms as alternative to solid dosage forms for lipophilic compounds, 8) are suitable in dermal products for enhancing the skin interaction of the drug substance, and 9) are very well suited for application in pediatric products.

These versatile properties are related to the non-toxicity, biodegradability, and biocompatibility of phospholipids for any administration route and their technical function as natural surfactant with emulsifying, wetting, liposome forming properties, which are very suitable to make dosage forms with drug

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targeting, solubilizing, bioavailability enhancing, and drug release retarding properties.

The resulting line extensions present more attractive innovative products. Compared to the original products, they may have a better safety profile and/or are more efficacious and, in general, they may have an increased convenience of use.

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Conflict of Interest

Peter van Hoogevest is also Head of the Scientific Department of Lipoid GmbH, Ludwigshafen am Rhein, Germany.

Author Contributions

Peter van Hoogevest: Conceptualization; Data curation; Investigation; Project administration; Supervision; Writing-original draft; Writing-review & editing. Harry Tiemessen: Conceptualization; Data curation; Validation; Writing-review & editing. Josbert M. Metselaar: Conceptualization; Data curation; Validation; Writing-review & editing. Simon Drescher: Data curation; Investigation; Methodology; Validation; Visualization; Writing-review & editing. Alfred Fahr: Data curation; Investigation; Methodology; Validation; Writing-review & editing.

Keywords

dermal, inhalation, line extension, oral, parenteral, phospholipids, product life cycle management

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Review Article

The use of natural and synthetic phospholipids as pharmaceutical excipients*

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In pharmaceutical formulations, phospholipids obtained from plant or animal sources and synthetic phospholipids are used. Natural phospholipids are purified from, e.g., soybeans or egg yolk using non-toxic solvent extraction and chromatographic procedures with low consumption of energy and minimum possible waste. Because of the use of validated purification procedures and sourcing of raw materials with consistent quality, the resulting products differing in phosphatidylcholine content possess an excellent batch to batch reproducibility with respect to phospholipid and fatty acid composition. The natural phospholipids are described in pharmacopeias and relevant regulatory guidance documentation of the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Synthetic phospholipids with specific polar head group, fatty acid composition can be manufactured using various synthesis routes. Synthetic phospholipids with the natural stereochemical configuration are preferably synthesized from glycerophosphocholine (GPC), which is obtained from natural phospholipids, using acylation and enzyme catalyzed reactions. Synthetic phospholipids play compared to natural phospholipid (includ- ing hydrogenated phospholipids), as derived from the number of drug products containing synthetic phospholipids, a minor role. Only in a few pharmaceutical products synthetic phospholipids are used. Natural phospholipids are used in oral, dermal, and parenteral products including liposomes. Natural phospholipids instead of synthetic phospholipids should be selected as phospholipid excipients for formulation development, whenever possible, because natural phospholipids are derived from renewable sources and produced with more ecologically friendly processes and are available in larger scale at relatively low costs compared to synthetic phospholipids.

Practical applications: For selection of phospholipid excipients for pharmaceutical formulations, natural phospholipids are preferred compared to synthetic phospholipids because they are available at large scale with reproducible quality at lower costs of goods. They are well accepted by regulatory authorities and are produced using less chemicals and solvents at higher yields. In order to avoid scale up problems during pharmaceutical development and production, natural phospholipid excipients instead of synthetic phospholipids should be selected whenever possible.

Keywords: Emulsifier / Lecithin / Liposomes / Natural phospholipids / Phosphatidylcholine / Solubilizer / Synthetic phospholipids

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Abbreviations: BSE, bovine spongiform encephalopathy; **CP,** Chinese pharmacopeia; **DEPC,** 1,2-dierucoylphosphatidylcholine; **DMPC,** 1,2-dimyristoylphosphatidylcholine; **DOPC,** 1,2-dioleoylphosphatidylcholine; **DOPS,** 1,2-dioleoylphosphatidylserine; **DPPC,** 1,2-dipalmitoylphosphatidylcholine; **DSPC,** 1,2-distearoylphosphatidylcholine; **DSPG,** 1,2-distearoylphosphatidylglycerol; **EC,** European commission; **ELSD,** evaporative light scattering detector; **EMA,** European Medicines Agency; **E PC,** egg phosphatidylcholine; **E PG,** egg phosphatidylglycerol; **FDA,** Food and Drug Administration; **GPC,** glycerophosphocholine; **HSPC,** hydrogenated soybean phosphatidylcholine; **HSPG,** hydrogenated soybean phosphatidylglycerol; **ICH,** The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; **LOD,** limit of detection; **JPE,** Japanese Pharmaceutical Excipients; **LPC,** lysophosphatidylcholine; **LPE,** lysophosphatidylethanolamine; **MCT,** medium chain triglycerides; **MPEG-DSPE,** *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoylphosphatidylethanolamine sodium salt; **MTP-PE,** muramyltripeptide-phosphatidylethanolamine; **NF,** National Formulary; **PA,** phosphatidic acid; **PC,** phosphatidylcholine; **PE,** phosphatidylethanolamine; **PG,** phosphatidylglycerol; **PI,** phosphatidylinositol; **PLPC,** 1-palmitoyl-2-linoleoylphosphatidylcholine; **PLPG,** 1-palmitoyl-2-linoleoylphosphatidylglycerol; **POPC,** 1-palmitoyl-2-oleoylphosphatidylcholine; **POPG,** 1-palmitoyl-2-oleoylphosphatidylglycerol; **PPC,** polyenylphosphatidylcholine; **PSPC,** 1-palmitoyl-2-stearoylphosphatidylcholine; **PSPG,** 1-palmitoyl-2-stearoylphosphatidylglycerol; **SLPC,** 1-stearoyl-2-linoleoylphosphatidylcholine; **SLPG,** 1-stearoyl-2-linoleoylphosphatidylglycerol; **SM, s**phingomyelin; **SOPC,** 1-stearoyl-2-oleoyl phosphatidylcholine; **SOPG,** 1-stearoyl-2-oleoyl phosphatidylglycerol; **TSE,** transmissible spongiform encephalopathy; **USP,** United States Pharmacopeia

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1 Introduction

Phospholipids are well-established excipients for pharmaceutical applications. They are used in many types of formulations, like fat emulsions, mixed micelles, suspensions, and liposomal preparations for any administration route. They are natural compounds and effective alternatives to synthetic, unnatural emulsifiers, like polysorbates, polyoxyethylene castor oil derivatives, and sucrose fatty acid esters.

All lipids that contain phosphorus are called phospholipids. Phospholipids are surface-active, amphiphilic molecules, which comprise a polar head group and a lipophilic tail. Because of this amphiphilic character they are used as emulsifier, wetting agent, solubilizer, and liposome former. The phospholipid molecule comprises a glycerol backbone, which is esterified in positions 1 and 2 with fatty acids and in position 3 with phosphate. The systematic designation of, e.g., phosphatidic acid (PA) is 1,2-diacyl-*sn*-glycero-3-phosphate (where *sn* means stereospecific numbering). The *sn*-2 carbon atom of glycerophospholipids is a chiral center, and natural phospholipids occur in enantiomerically pure form. In typical membrane phospholipids, the phosphate group is further esterified with an additional alcohol, for instance in phosphatidylcholine (PC) with choline, in phosphatidylethanolamine (PE) with ethanolamine, and in phosphatidylglycerol (PG) with glycerol. Depending upon the structure of the polar region and pH of the medium, PE and PC are zwitterionic and have a neutral charge at pH values of about 7, whereas, e.g., PG is negatively charged. The most common phospholipid is PC, and PC is the main component of lecithin. Lecithin is described, e.g., in the United States Pharmacopoeia (USP) as a "complex mixture of acetone-insoluble phosphatides, which consists chiefly of PC, PE, phosphatidylserine, and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. It contains not less than 50% of acetone-insoluble matter." Normally, lecithin grades containing more than 80% PC do not comply anymore with the phamacopoeial definition and are called arbitrarily PC, whereas grades containing less than 80% PC can be arbitrarily called lecithin. However, there is still some confusion on the term "lecithin," which was originally assigned to the pure PC, but is still used in medicinal literature and documents of health authorities (US-FDA, C-FDA, BfArm). Today "lecithin" has become the trade name for the mixture of phosphatides as typically used in the food and cosmetic industry [1].

Phospholipids are structural and functional components of all cell membranes and therefore endogenous substances. The phospholipid content of membranes and the distribution of fatty acid residues vary within a cell and from one cell type to another [2]. Until now, the biological function of membrane asymmetry and the distribution of different types of phospholipids in organs are not completely understood, but the interaction of the manifold of phospholipids and further membrane components seem to fulfil important roles in signal-transduction cascades. To illustrate the importance of phospholipids for the physiological functioning of the body, besides the functional role of phospholipids in cell membranes, phospholipids, mainly PC, have digestion/metabolic functions in bile (as monoacyl-phospholipids) to solubilize cholesterol and fatty components in food and lipophilic drug substances [3], as lipoprotein components for transport of fat between gut and liver, as source for acetylcholine (in case of PC) and as source of (essential) fatty acids and energy [4]. In addition, in lung surfactant a specific phospholipid dipalmitoylphosphatidylcholine occurs [4]. Phosphatidylserine is a component of the lipid–calcium–phosphate complex for deposition during bone formation [5], regulation of apoptosis (programmed cell death) [6] and blood coagulation [7].

Natural phospholipid excipients are defined as phospholipids isolated from natural sources like, e.g., soybean, rapeseed, and sunflower seed. Natural phospholipids may be further converted to saturated phospholipids by means of hydrogenation or further treated with enzymes to, e.g., remove partially fatty acids (phospholipase A2) or to convert a polar head group (phospholipase D). The saturated phospholipids are considered as natural phospholipids because the resulting saturated lipids are also occurring in nature (i.e., natural identical). For instance, saturated PC can be found in rat tissue at rather high levels in the lung, spleen, brain, and kidney (36, 22, 20, and 16% of total PC, respectively) [8]. The additional hydrogenation step represents a minor chemical modification compared to the overall production process of natural phospholipids. Also, enzymatically modified natural (saturated as well as unsaturated) phospholipids are considered as natural phospholipids because the resulting phospholipids occur as well in nature and the enzymatic process used to generate the phospholipids is also natural. Typical for all these natural phospholipids is that the eventual fatty acid and polar head group composition is determined by the (phospholipid and fatty acid) composition of the starting natural material and applied isolation procedures. In contrast, synthetic phospholipid excipients are phospholipids where defined specific molecular species of polar head groups or fatty acids are introduced by means of a tailor made chemical synthesis process.

In this review, the production, use, and properties of natural phospholipids and synthetic phospholipids excipients are compared from the industrial pharmaceutical technical development perspective. The synthetic phospholipids discussed are synthetic analogs to natural alternatives. Chemically modified phospholipids, like, e.g., *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoylphosphatidylethanolamine sodium salt (MPEG-DSPE), which do not occur in nature, are out of the scope of this review.

This comparison offers a rational to select the preferred phospholipid class for pharmaceutical formulation development purposes.

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Table 1. Phospholipid composition of vegetable de-oiled lecithins, as derived from corresponding product specifications (%) [11]

	Lecithin		
Phospholipid	Soybean	Sunflower seed	Rapeseed
PC	20–22	20–26	23–31
PE	16–22	4–10	9–15
PI	13–16	15–19	15–18
PA	5–10	2–5	5–10
LPC	<3	<3	<3

Table 2. Fatty acid composition of typical batches of vegetable de-oiled lecithins (area %) [11]

	Lecithin		
Fatty acid	Soybean	Sunflower seed	Rapeseed
C14:0	0.1	0.1	0.1
C16:0	21	16	10
C18:0	4.7	5.3	0.8
C18:1	9.9	21	49
C18:2	57	54	31
C18:3	5.0	0.2	4.4
C20:0	0.1	0.3	0.1
C22:0	0.4	1.5	0.1

2 Natural phospholipids

Natural phospholipids can be obtained from vegetable sources like, e.g., soybeans, rape (canola) seed, wheat germ, sunflower, and flax seed, and animal material, like egg yolk, milk, or krill. These raw materials are world-wide produced at very large scale. The world-wide harvest of soybeans was in 2013, 280 million tons and the annual world-wide production of soybean oil is about 42 million tons [9]. During 2002, 53.4 million tons of table eggs were produced. This represents approximately 17 million tons egg yolk [10]. Although only a part of these huge amounts is used for the production of natural phospholipid excipients, it is clear that there is adequate supply for this purpose.

The phospholipid and fatty acid profiles of the lecithin are dependent on the raw material sources. The profiles for de-oiled soybean-, sunflower seed-, and rapeseed lecithin are provided as example (Tables 1 and 2). For an example of the phospholipid and fatty acid composition of a lecithin derived from animal source (egg lecithin), reference is made to the corresponding section below.

In all cases, PC is the main phospholipid component. In order to convert these raw materials into high quality pharmaceutical excipients, meeting pharmacopeial and regulatory requirements for parenteral and other specific formulations, extraction and chromatography procedures are applied.

2.1 Soybean lecithin

To illustrate the production process of natural phospholipid excipients starting from plant oil, the production process of soybean lecithin is given as example. As a first step crude soybean lecithin is isolated by degumming of the crude soybean oil as obtained by extraction from soybeans (Fig. 1) [12].

The crude soybean lecithin obtained serves as starting material for production at large scale of soybean lecithin fractions with higher PC content. They are obtained in high

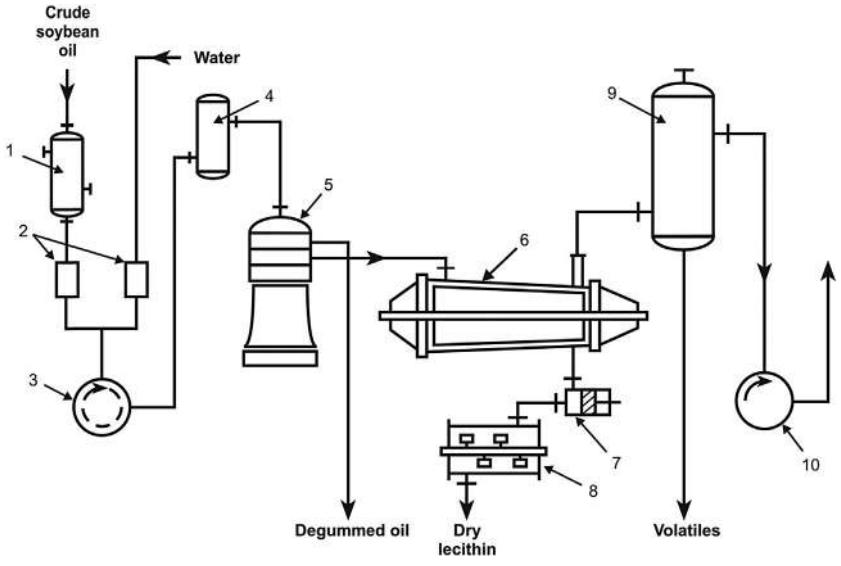

Figure 1. Flow sheet of a lecithin producing unit. Crude soybean oil is heated in the preheater, (1) to 80°C, mixed with 2% water in the proportion control unit, (2) and intensively agitated in (3). The mixture goes to a dwelling container, (4), and is then centrifuged after a residence time of 2–5 min. The degummed oil flows without further drying to the storage tanks. The lecithin sludge is dried in the thin-film evaporator, (6), at 100°C and 6 kPa (60 mbar) for 1–2 min and is discharged after cooling to 50–60°C in the cooler, (8). (9) and (10) are the condenser and vacuum pump, respectively [12].

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yields by extraction methods using the non-toxic solvents acetone and ethanol followed by chromatographic purification procedures and appropriate solvent removal methods (Fig. 2A (flow chart) and Fig. 2B (visual aspect of phospholipids)). All solvents can be recycled and reused. By selecting appropriate sequential extraction and chromatography methods several lecithin fractions differing in the PC content (20–80%) up to pure PC (to 98%), and in the ratio of phospholipids to non-polar lipids can be reproducibly achieved. This procedure applies to soybean oil and all vegetable oils used to produce lecithin/PC.

The original fatty acid composition of the starting material is reflected in the fatty acid composition of the purified fractions. The PC content and purity of the various soybean lecithin extraction and chromatography fractions, as measured with normal phase HPLC equipped with an ELSD are demonstrated (Fig. 3). The various phospholipids present in soybean lecithin, *N*-acyl-PE, PA, PE, PC, PI, and Lyso-PC (LPC) are separated at increasing retention time.

As derived from these HPLC chromatograms and additional TLC studies (not shown), the more detailed lipid profile shows dependent on the number of extraction and chromatography steps an increase of the PC content to 98%, and concomitantly a decrease of the other lipid components (Table 3).

The typical fatty acid composition of the soybean lecithin extraction and chromatography fractions differing in PC content is provided in Table 4.

The results in Table 4 indicate that in the fatty acid pattern of the soybean derived lecithin fractions, phospholipids and PCs obtained by extraction and chromatography five fatty acid types account for about 95% of the total fatty acid composition. These are palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), and linolenic acid (C18:3). There is a slight variation in the ratio of the fatty acids between the different fractions. The fatty acid composition is influenced by the climate conditions (temperature and humidity) prevailing during the maturation of the soybeans and the genetic origin of the plants.

Control on the quality of the raw material and use of validated purification method guarantees the reproducibility of the composition of the resulting phospholipid excipients. An impression on the inter-batch reproducibility of the quality of the soybean lecithin extraction and chromatography fractions differing in PC content can be obtained from Tables 5A and 5B.

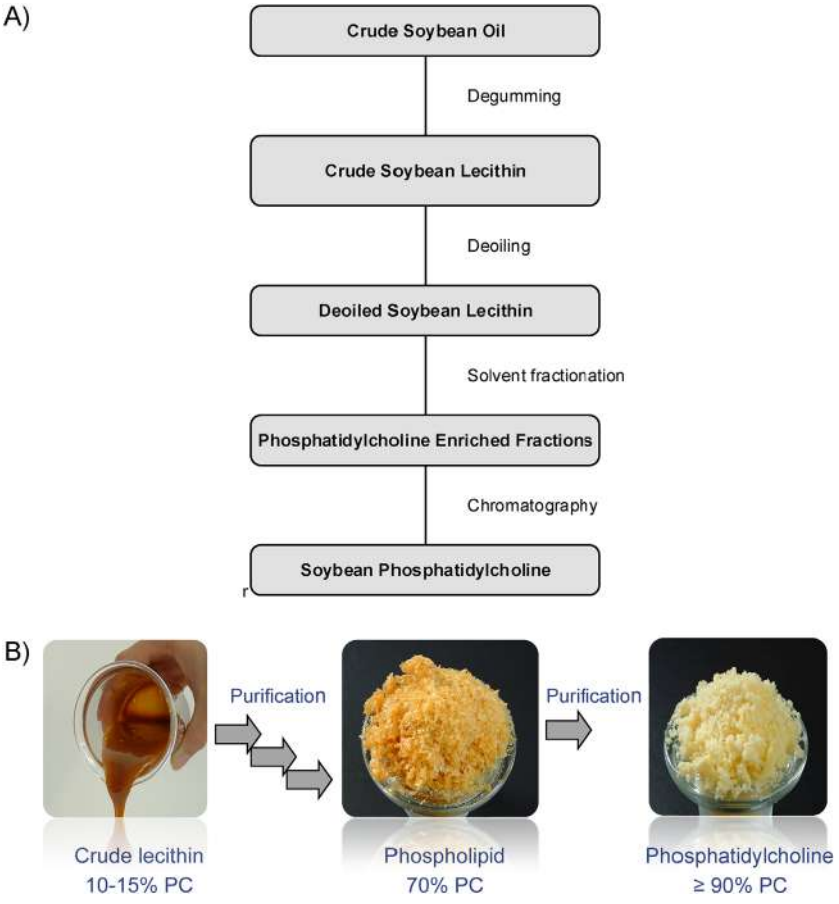

Figure 2. (A) Flow chart of the isolation process steps of soybean phosphatidylcholine from crude soybean oil. (B) Visual aspect of soybean lecithin fractions with varying PC content.

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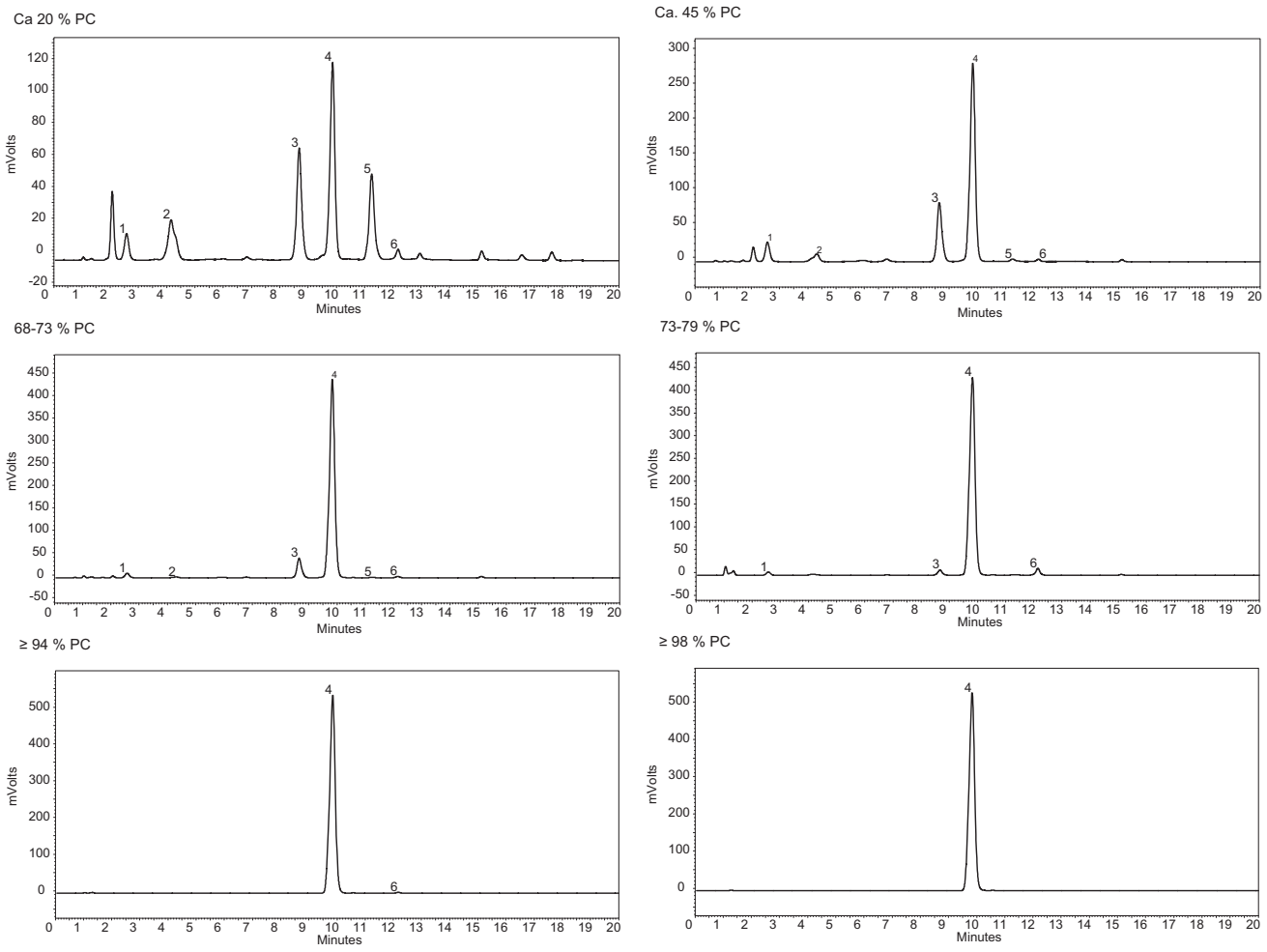

Figure 3. HPLC (normal phase chromatography)-ELSD chromatograms of soybean lecithin extraction and chromatography fractions differing in PC content. Peak numbers reference 1: *N*-acyl-PE, 2:PA, 3:PE, 4:PC, 5: PI, 6: LPC [11].

The data in the Tables 5A and 5B indicate that the inter-batch reproducibility increases at increasing PC purity. Materials with high PC contents undergo a number of purification steps leading to more constant chemical

Table 3. Phospholipid composition of the soybean lecithin extraction and chromatography fractions differing in PC content [13]

	Fraction					
Component (%w/w)	Ca. 20% PC	Ca. 45% PC	68–73% PC	73–79% PC	≥94% PC	≥98% PC
PC	22	51	70	79	97	99
PE	15	18	10	3.3	0	0
PI	15	1.7	0.7	0.2	0	0
PA	9.7	4.5	1.3	1.6	0	0
LPC	3.2	1.9	1.4	6.1	0.4	0.1
N-Acyl-PE	3.2	5.0	2.3	1.7	0	0

Table 4. Typical fatty acid composition (area % of total) of soybean lecithin extraction and chromatography fractions differing in PC content [13]

	Fraction					
Fatty acid	Ca. 20% PC	Ca. 45% PC	68–73% PC	73–79% PC	≥94% PC	≥98% PC
C14:0	0.1	0.1	0.1	0.1	0.1	0.1
C16:0	21	16	15	15	15	12
C18:0	4.7	3.4	3.5	3.7	3.7	3.3
C18:1	9.9	9.5	10	12	12	9.7
C18:2	57	63	64	63	63	67
C18:3	5.0	6.0	5.8	5.2	4.7	6.1
C20:0	0.1	0.1	0.1	0.1	0.1	0.1
C22:0	0.4	0.1	0.1	0.1	0.1	0.1

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Table 5A. Inter-batch reproducibility of the composition of soy bean lecithin extraction and chromatography fractions with PC content 20–70% w/w [11]

	Fraction					
	Ca. 20% PC		Ca. 45% PC		68–73% PC	
Component (% w/w)	Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
PC	20–22[a)]	20–22[a)]	53	55	71	68
PE	16–22[a)]	16–22[a)]	14	13	9.9	9.5
LPC	2.0	0.5	2.5	2.5	1.5	1.8
Triglycerides	0.2	1.1	<0.5	<0.5	1.0	0.6
Free fatty acids	0.2	0.5	≤0.5[a)]	≤0.5[a)]	≤0.5[a)]	≤0.5[a)]
Phosphorus	3.1	3.0	3.2	3.1	3.4	3.5
D,L-α-Tocopherol	<0.1	<0.1	0.1	0.2	0.2	0.1
Water	0.4	0.4	0.2	0.2	0.5	0.5
Peroxide value	0.8	2.5	1.1	1.1	1.0	1.1
Iodine value	n.d.[b)]	n.d.	n.d.	n.d.	87	87
Acid value	24	23	16	16	n.d.	n.d.

[a)]Typical values, not routinely tested.
[b)]n.d., not determined.

Table 5B. Inter-batch reproducibility of the quality of soybean lecithin extraction and chromatography fractions with PC content 76–98% w/w [11]

	Fraction					
	73–79% PC		≥94% PC		≥98% PC	
Component (% w/w)	Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
PC	75	74	96	96	99	98
PE	3.9	3.8	<LOD	<LOD	<LOD	<LOD
LPC	3.3	3.3	0.7	0.8	0.1	0.2
Triglycerides	5.0	5.0	0.1	0.8	0.2	0.2
Free fatty acids	≤0.5	≤0.5	<LOD	<LOD	<LOD	<LOD
Phosphorus	3.7	3.7	3.9	3.9	3.9	4.0
D,L-α-Tocopherol	0.2	0.2	0.2	0.2	0.2	0.2
Water	0.5	0.5	0.5	0.5	1.2	0.8
Peroxide value	1.2	1.2	1.7	2.0	1.7	1.3
Iodine value	90–105	90–105	104	99	105	103
Acid value	n.d	n.d.	0.2	0.1	0.1.	0.1

LOD, limit of detection; n.d., not determined.

compositions. For that reason, products with high PC contents are more suited for pharmaceutical applications requiring higher phospholipid purity, like parenteral administration, whereas the lecithin qualities starting at PC 20 are suitable for oral and topical administration.

2.2 Egg lecithin

Egg phospholipids are isolated from egg yolk with similar extraction and chromatography methods as for soybean lecithin. The phospholipid profiles of egg lecithin extraction/chromatography fractions as measured with HPLC, equipped with ELSD shows the presence of PC, PE, SM, LPE, and LPC in the fractions with 64–79% PC, whereas upon further purification, the content of PC increases up to ≥98% and the other lipids are removed with exception of a small amount of SM (Fig. 4 and Table 6A).

In the fatty acid pattern of the egg derived phospholipids and PCs, five fatty acid types account for about 92% of the total fatty acid composition (Table 6B).

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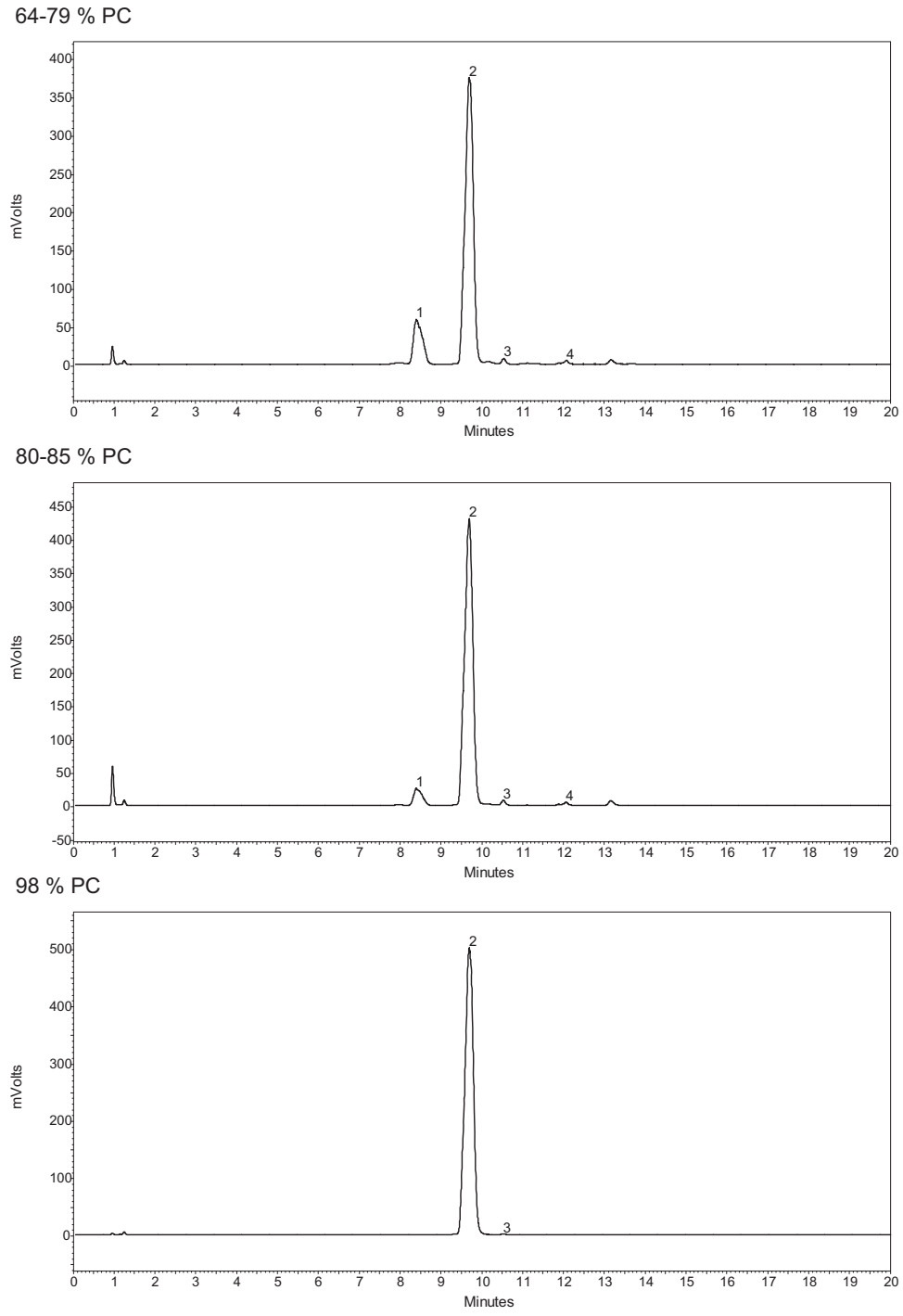

Figure 4. HPLC (normal phase chromatography)-ELSD chromatograms of egg lecithin extraction and chromatography fractions differing in PC content. Peak numbers reference 1: PE, 2: PC, 3: SM, 4: LPC [11].

These are palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), and arachidonic acid (C20:4). The presence of the polyunsaturated fatty acids C 20:4 (n-6) and C22:6 (n-3) is typical for egg phospholipids. There is a slight variation in the ratio of the fatty acids between the different fractions. Considering the position of the fatty acid within the phospholipid molecule, egg PC comprises about 40% 1-palmitoyl-2-oleoylphosphatidylcholine.

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Table 6A. Phospholipid composition (% w/w) of the egg lecithin extraction and chromatography fractions differing in PC content [14]

	Fraction		
Component	64–79% PC	80–85% PC	≥98% PC
PC	72	81	99
PE	17	8.5	0.0
SM	2.0	2.0	0.4
LPE	1.0	0.3	0.0
LPC	2.0	2.0	0.0

Table 6B. Typical fatty acid composition (area % of total) of egg lecithin extraction and chromatography fractions differing in PC content [14]

	Fraction		
Fatty acid	64–79% PC	80–85% PC	≥98% PC
C14:0	0.2	0.1	0.2
C16:0	31	31	34
C18:0	15	14	12
C18:1	24	28	28
C18:2	16	15	16
C20:4	5.6	4.8	3.6
C22:4	0.3	0.3	0.2
C22:5	0.2	0.2	0.1
C22:6	2.2	1.8	1.8

2.3 Hydrogenated lecithin

Due to the presence of unsaturated fatty acids in natural phospholipids the liquid crystalline to gel phase transition temperature is below 0°C. These phospholipids are at ambient and body temperature in the liquid crystalline state and form upon hydration flexible structures/mesophases, suitable for specific pharmaceutical technological applications. In some formulations, however, when, e.g., more physically stable liposomes with increased stability in blood plasma or when phospholipids with more powder like properties are required, phospholipids with higher phase transition temperatures are preferred [15].

Phospholipids with saturated fatty acids possess these properties and can be obtained by hydrogenation of natural phospholipids with unsaturated fatty acids.

In this process, the unsaturated fatty acids are saturated by hydrogen gas in a catalytic reaction involving metal catalysts (e.g., nickel, palladium, and platinum) bound to porous carrier, typically in a heterogeneous system [16]. The progress of the reaction can be followed by monitoring the iodine value [17], which is a measure for the degree of unsaturation of fatty substances. Crude soybean lecithin and pure soy PC have an iodine value of about 90–100. After completion of the reaction, the metal catalyst is completely removed by means of filtration.

Soybean PC predominantly contains the unsaturated acids oleic, linoleic, and linolenic acid, as well as the saturated acids palmitic and stearic acid. The saturated fatty acids are almost exclusively located in position 1 (Table 7) [18].

Thus, hydrogenation of pure soybean PC with a typical iodine value of about 100, results in a mixture of mainly (ca. 85%) 1,2-distearoylphosphatidylcholine (DSPC) and 1-palmitoyl-2-stearoylphosphatidylcholine (PSPC) (ca. 15%).

2.4 Enzyme modified natural phospholipids

Because of the advent of biotechnology, nowadays alternative biochemical synthesis routes via enzyme catalyzed reactions serve as a viable alternative to organic-chemical synthesis steps. In that respect, the use of enzymes for phospholipid modification has moved quickly in recent years, not only in academic research but also in industry [19]. The fast growing use of enzymes for polar lipid modification arises from factors such as milder reaction conditions, less environmental pollution, better specificity for improved quality, and higher efficiency of reactions. Different enzymes can be used for different modification purposes to modify/synthesize phospholipids. As illustrated in Fig. 5, a number of phospholipid ester bonds can be modified with appropriate enzymes.

For acyl modifications, the natural enzymes will be phospholipase A1 (EC 3.1.1.32) and A2 (EC 3.1.1.4) (PLA1 and PLA2 respectively). However, lipases (EC 3.1.1.3) in general can also be used for such purposes, in particularly for modification at the *sn*-1 position. PLA2 in the phospholipase category has specificity for the *sn*-2 position. Phospholipase D (EC 3.1.4.4) (PLD) is the only potential enzyme for polar group modification. Phospholipase C (EC 3.1.4.3) (PLC) can hydrolyze the bond between the glycerol OH group and the phosphate group but, unfortunately, the enzymes in this category are, at the moment, only active for the hydrolysis reaction.

Table 7. Fatty acid distribution in soybean phosphatidylcholine (w/w %) [18]

Fatty acid	In 1-position	In 2-position	Total
C16:0	24	2	13
C18:0	8	1	4
C18:1	13	10	11
C18:2	50	80	65
C18:3	5	7	6

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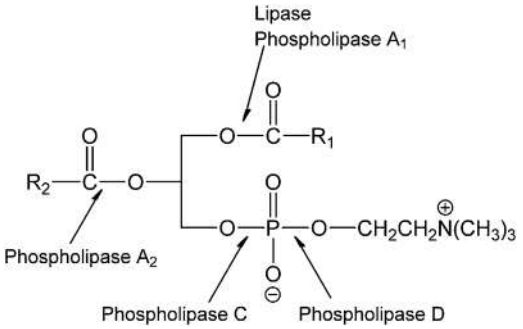

Figure 5. Enzymatic conversion possibilities of phosphatidylcholine [20].

Examples of enzyme-modified natural phospholipids prepared from natural PC are monoacyl-phosphatidylcholine (lyso PC), soy PE, soy PG, egg PG, and saturated analogs.

3 Synthetic phospholipids

In order to study biophysical/biochemical mechanistic aspects of phospholipids at the molecular level in model-membranes, various synthesis routes for phospholipids were developed to get an access to phospholipids, which are homogeneous with respect to the polar head group and fatty acid composition [19, 21–23]

In addition to the need for synthetic analogs of natural phospholipids, further synthetic phospholipids were for instance designed to optimize the drug targeting properties of liposomes. Examples are the PEG-ylated phospholipids [24] and the cationic phospholipid 1,2-diacyl-P-*O*-ethylphosphatidylcholine [25]. Also attempts were made to convert by organic chemical means phospholipids into pharmacological active molecules (for instance ether phospholipids [26] or to make phospholipid pro-drugs (example MTP-PE [27]). These conversions to pharmacological active moieties are outside the scope of this review.

As a result, during the last decades the general demand for synthetic phospholipids has increased, mainly for use in liposomal formulations. Thus, new synthesis routes to produce phospholipids on a larger scale had to be developed. In general, synthetic phospholipids can be produced using organic chemical synthesis steps and/or enzymatic synthesis steps. In the following, the described various syntheses routes are linked to the starting materials.

3.1 Synthesis starting from mannitol

The classical approach to synthesize diacyl-PC's is starting from D-mannitol, which is acetonated in the presence of anhydrous zinc chloride to give 1,2: 5,6-diisopropylidene-D-mannitol. The bis(acetonide) is treated with lead tetra-acetate to give 1,2-diisopropylidene-*sn*-3-glyceraldehyde, which is reduced with sodium borohydride or lithium aluminum hydride to (*S*)-glycerol 1,2-acetonide; the latter is converted to *sn*-glycerol-3-phosphate and then to phosphoglycerides.

Disadvantages of the classical synthesis method are that the method is lengthy, requiring toxic solvents and chemicals in large excess, and 9 steps to convert mannitol into identical fatty acid chain PC's and 14 steps to mixed fatty acid chain PC's. Also reaction intermediates may be unstable and subject to partial racemization [28, 29].

Equally, synthesis methods using acylation of 1-acyl-2-lyso-*sn*-glycerophosphocholine [30–32] requires the availability of the lyso compound and use of disadvantageous chemical reactions. A simpler method to synthesize symmetric chain gycerophospholipids is a method starting from (*R*) or (*S*) glycidyl tosylate [33].The enantiomerically pure glycidyl derivative is, however, expensive, making large scale syntheses of glycerolipids impractical [21].

The method used to synthesize platelet activating factor (PAF = 1-0-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is considered to be the shortest synthesis method of mixed fatty acid chain and identical fatty acid chain phospholipid synthesis [22, 34]. D-Mannitol (12) is reacting with *p*-methoxybenzaldehyde under the formation of two 1,3-dioxane rings (13) (Fig. 6).

The free OH-groups are benzylated with benzylchloride (14), and the 1,3-dioxane rings are opened to keep the *p*-methoxybenzylether specifically only at the primary OH-group (15). The 3,4-diol is split by oxidation and the aldehyde is reduced to (16) (Fig. 7).

Since the differentiation of the three OH-groups is given, other phospholipids can also be synthesized starting from (16) by phosphorylation of the free hydroxyl group, followed by selective removal of the protective –Ar and –Bn group and reaction with the selected fatty acids.

Which synthesis route will be selected is, from industrial perspective, dependent on the (commercial) availability of

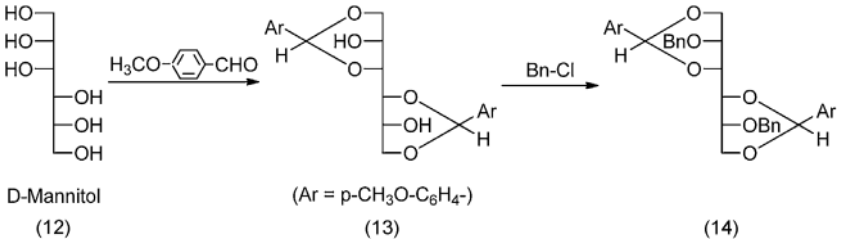

Figure 6. Conversion of D-mannitol to mixed (fatty acid) chain and identical (fatty acid) chain phospholipids (first steps) [22, 34].

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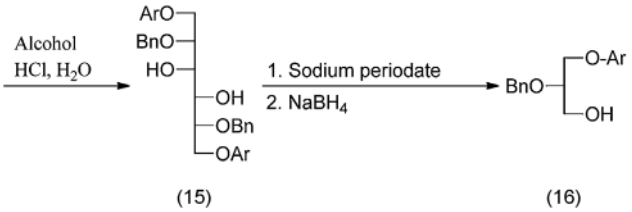

Figure 7. Conversion of D-mannitol to mixed (fatty acid) chain and identical (fatty acid) chain phospholipids (continued).

key intermediates or starting materials. In that respect, synthesis of phospholipids may be started with (*S*)-1, 2-isopropylideneglycerol, which is derivatized to 1,2-diacylglycerol, followed by attachment of the polar head group via chemical synthesis [35].

3.2 Synthesis starting from GPC

Another route to produce phospholipids with defined fatty acids is to start such synthesis from glycerophosphocholine (GPC) (*sn*-glycero-3-phosphocholine: also called: L-alpha glycerylphosphorylcholine, alpha-GPC or choline alfoscerate). This GPC can be synthesized in an enantioselective manner using a biotransformation procedure based on the phosphorylation of glycerol by ATP catalyzed glycerol kinase [36] or, preferably, produced from natural PC. Starting from natural GPC, phospholipids containing two identical acyl moieties can be synthesized with the same *sn*-glycero-3-configuration as naturally occurring glycerophospholipids in a one step process using activated acyl derivatives, e.g., acylimidazolides or anhydrides [23, 37, 38].

For the further synthesis from GPC to mixed fatty acid chain phospholipids, organic chemical methods as well as enzymatic procedures can be applied.

When using organic chemical methods GPC is converted to 1-*O*-trityl GPC, which is then acylated to 1-trityl-2-acyl GPC. In a one-pot reaction, the trityl group is replaced with an acyl group (Fig. 8). For the acylation step of [2] to [3] acyltriazolides can be used instead of fatty acid anhydrides.

In the presence of borontrifluoride-etherate, as a catalyst, the reaction proceeds within a short time (30 min) at low temperature (around 0°C) and the final product obtained in high yield contains less than 2–3% of positional isomers. Pure mixed fatty acid chain PCs are thus accessible in a three-step procedure, which can be carried out on any scale. This reaction is considerably shorter and therefore less expensive than the total synthesis of the corresponding phospholipids described above.

Alternatively, mixed fatty acid chain phospholipids can be synthesized from (natural or synthetic) GPC using an acylation step followed by cleavage of the fatty acid at the second hydroxyl position by means of an enzymatic modification with phospholipase A2, followed by an acylation of the free hydroxyl group with the desired fatty acid.

In addition, the enzymes (phospholipase D) able to convert the choline head group into another head group like, e.g., glycerol or serine can be used in analogy to the conversion of natural phospholipids (see above), to make, e.g., PG or phosphatidylserine from PC with well-defined mixed fatty acid chains, respectively.

Taking these organic chemical and enzymatic synthesis options into consideration, a process to synthesize mixed fatty acid chain phospholipids, optionally with a conversion of the polar head group, can be designed using natural starting materials and enzymatic procedures (Fig. 9).

As a first step, purified natural PC is deacylated to form GPC. Then the GPC is esterified with a selected fatty acid, to yield a diacyl-GPC. The fatty acid at position two of the glycerol backbone can then be selectively removed enzymatically with phospholipase A2 to form 1-monoacyl-

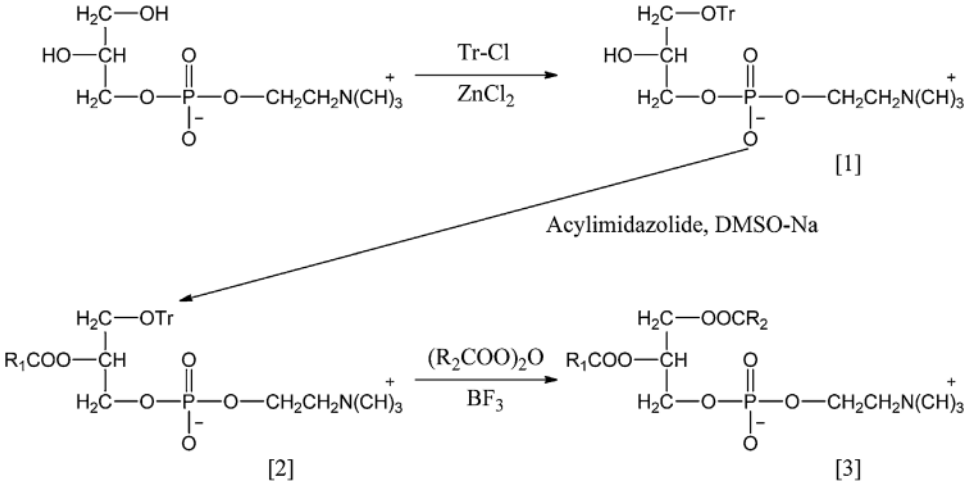

Figure 8. Synthetic preparation of mixed fatty acid chain phosphatidylcholines. Tr = triphenylmethyl [23].

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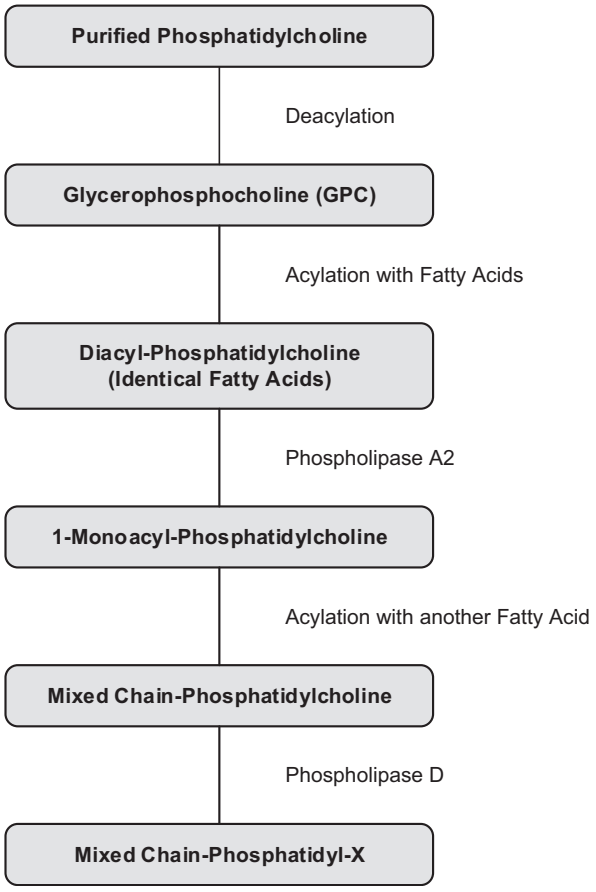

Figure 9. Synthesis of mixed fatty acid chain phospholipids and polar head group modification (X), starting from phosphatidylcholine and using enzymatic procedures.

phosphatidylcholine. The hydroxyl group at the second position of the monoacyl-phosphatidylcholine can then be re-esterified. Finally, when required, the choline polar head group can be replaced via enzyme catalyzed reaction by another polar head group like glycerol, ethanolamine, or serine to make PG, PE, or phosphatidylserine, respectively.

The number of synthesis steps of this synthesis route is lower compared to the synthesis starting from mannitol or synthesis starting from GPC, prepared by using organic chemical synthesis methods, and requires lower amounts of toxic solvents or chemicals. The yield of this alternative synthesis route is higher compared to the other synthetic procedures, but still hazardous chemicals have to be used.

4 Use of natural phospholipids and synthetic phospholipids in pharmaceutical formulations

Phospholipids are used in pharmaceutical technology as wetting agents, emulsifiers, and builder or components of mesophases like liposomes, micelles, mixed micelles, cubosomes, etc. These functional properties are used in many formulation types, like suspensions, various types of emulsions, mixed micelles, solid dispersions, drug–phospholipid complexes, etc. [39, 40]. Due to their physiological role, phospholipids possess a very low toxicity profile and can be used for any route of administration.

Scientific academic literature shows that natural as well as synthetic phospholipids are explored for any route of administration. However, for selection of excipients at the academic research level, the costs of goods, large-scale availability, use of green chemistry to manufacture the excipients and registration status/documentation of the used excipients do not play a role. At industrial level, however, these factors play and should play however a significant role in selection of excipients at the beginning of the development process of pharmaceutical products.

It is therefore relevant to assess the occurrence of natural and synthetic phospholipids in the inactive ingredient (excipient) list of the US FDA for approved products (October 24, 2013) [41]. In this list, lecithin with CAS No. 8002-43-5 covers a broad range of natural lecithin including soybean lecithin, sunflower seed lecithin, and egg lecithin. When sorting the occurrence of natural and synthetic phospholipids (Table 8), it is clear that synthetic phospholipids are only used for parenteral/injectable administration. In contrast, natural phospholipids are used for any route of administration, including parenteral administration.

Since for parenteral administration synthetic as well as natural phospholipids are used and the data provided in Table 8 cover only the products in the USA, the occurrence of natural or synthetic phospholipids in parenteral products in the EU should be considered as well.

The categories of formulations, which are of interest to study the occurrence of either natural or synthetic phospholipids are products used for parenteral administration. These are liposomes, oil-in-water emulsions, mixed micelles for intravenous use and slow release and vaccine vehicles and drug suspensions for intramuscular and subcutaneous administration.

Liposomal products for intravenous administration are formulated with synthetic as well as natural phospholipids (Table 9) [42–52].

Liposomes can also be used as vehicle for slow release after local parenteral administration (at the surgical site, epidural, or intrathecal) (Table 10) [53–57]. In this case, mainly synthetic phospholipids are being used.

Egg phospholipids are used at a concentration of 1.2% in 10–30% oil-in-water emulsions for parenteral nutrition (e.g., Intralipid and Liposyn II) (Table 11) [58]. Derived from a maximal cumulative daily dose of 2.5–3 g triglycerides/kg body weight/day for an adult, maximally 0.30–0.36 g phospholipid/kg body weight/day can be administered [59, 60].

Oil-in-water emulsions can also be used as carrier for oil soluble drug substances. Also, in this case egg phospholipids are exclusively being used as emulsifier (Table 12) [61–63].

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Table 8. Frequency (%) of occurrence of natural and synthetic phospholipids in the US FDA inactive ingredient list of approved drug products dependent on the administration route (status October 24, 2013)

		Administration route			
Excipient	CAS Nr.	Oral	Parenteral	Topical	Inhalation
		Natural phospholipids			
Lecithin	8002-43-5	55	10	25	10
Soybean lecithin	8030-76-0	60	–	20	20
Egg lecithin	93685-90-6	33	66	–	–
Hydrogenated soybean lecithin	92128-87-5		40	40	20
Egg PG	93685906		100		
		Synthetic phospholipids			
DMPC	18194-24-6	–	100	–	–
DOPC	4235-95-4	–	100	–	–
DSPC	816-94-4	–	100	–	–
DPPG	4537-77-3	–	100	–	–
DSPG	217939974	–	100	–	–

In mixed micellar formulations, comprising phospholipids and cholate salts, exclusively soybean phospholipids are being used. These formulations are either used as solubilizer for poorly water soluble compounds, or the soybean PC is used as active principle, through the presence of poly-unsaturated fatty acids for treatment of liver disorders (Table 13) [64].

These products underscore the safe intravenous use of soybean phospholipids. Also the pre-clinical toxicity of mixed micelles comprising soybean PC is well documented. Derived from the soybean PC concentration and the used intravenous dose of the product Essentiale/Lipostabil it can be derived that at least 4 g soybean PC can be administered daily intravenously [65].

Table 9. Characteristics of intravenous liposomal drug products

Product	Drug substance	Lipid Excipients	Indication
Abelcet	Amphotericin B	DMPC DMPG	Invasive fungal infections
AmBisome	Amphotericin B	HSPC DSPG Cholesterol Alpha-tocopherol	*Aspergillus*-, *Candida*- and/or *Cryptococcus* species infections Visceral leishmaniasis
DaunoXome	Daunorubicin citrate	DSPC Cholesterol	Advanced HIV-associated Kaposi's sarcoma
Doxil/Caelyx	Doxorubicin HCl/sulphate	MPEG-DSPE HSPC Cholesterol	AIDS-related Kaposi's sarcoma Ovarian cancer Multiple myeloma
Marqibo	Vincristine sulphate	Egg SM Cholesterol	Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia
Mepact	MTP-PE, Mifartumide	POPC DOPS	Osteosarcoma
Myocet	Doxorubicin HCl/citrate	Egg PC Cholesterol	Metastatic breast cancer
Visudyne, Verteporfin for injection	Benzoporphyrin	DMPC Egg PG Ascorbyl palmitate (Butylated-hydroxytoluene)	Exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) Subfoveal choroidal neovascularisation secondary to pathological myopia.

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Table 10. Liposomal depot vehicles and their (phospho)lipid composition

Product	Drug Substance	Lipid Excipients	Indication
Exparel	Bupivacaine	DEPC DPPG Tricaprylin	Postsurgical analgesia
DepoDur	Morphine sulphate	DOPC DPPG Cholesterol Tricaprylin Triolein	Pain treatment prior to surgery or after clamping the umbilical cord during caesarean section
DepoCyt	Cytarabine	DOPC DPPG Cholesterol Triolein	Lymphomatous meningitis

Considering the products comprising phospholipids for pulmonary administration, natural as well as synthetic phospholipids are being used (Table 14). Most of these products are used for respiratory distress syndrome, a disease in infants characterized by an immature lung epithelium [66]. For treatment of this deficiency, mixtures of phospholipids and extracts from animal origin comprising phospholipid surfactants, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C) are inhaled. In case of the product Tobi Podhaler, DSPC is used as emulsifier during the manufacturing process to generate porous particles [67]. The product is used to treat lung infections with *Pseudomonas aeruginosa* [68].

Table 11. Examples of intravenous oil-in-water emulsions using egg phospholipids as emulsifier

Product	Oil phase
Intralipid	Soybean oil
Liposyn II	Soybean oil/safflower oil
Omegaven	Fish oil
ClinOleic	Soybean oil/olive oil
Lipofundin	Soybean oil/MCT
Structolipid	Interesterified mixture of equimolar amounts of long chain triglycerides (LCT) and medium chain triglycerides (MCT)
SMOFlipid	Soybean oil/MCT/olive oil/fish oil

Table 12. Examples of intravenous drug containing oil-in-water emulsions using egg phospholipids as emulsifier

Product	Drug substance	Indication
Diazemuls	Diazepam	Sedative and muscle relaxant
Limethason	Dexamethasone palmitate	Rheumatoid arthritis
Liple	Alprostadil (prostaglandin E1)	Vasodilator, platelet inhibitor
Diprivan/disoprivan	Propofol	Anesthetic
Etomidat®-Lipuro	Etomidate	Anesthetic
Vitalipid	Vitamin A, D2, E, K1	Parenteral nutrition
Cleviprex	Clevidipine butyrate	Antihypertensive

Table 13. Examples of intravenous mixed micellar products containing soybean phosphatidylcholine as phospholipid component

Product	Drug substance/active	Indication
Valium MM	Diazepam	Anxiolytic
Essentiale	PPC	Liver therapy
Lipostabil	PPC	Lipid regulation
Cernevit	Vitamin blend	Vitamin supplement
Konakion MM	Vitamin K	Vitamin supplement

5 Discussion

As part of an industrial pharmaceutical development process, excipients for the dosage forms have to be selected taking many criteria into consideration. The large-scale availability and related costs of goods and, additionally, sustainability and environmental aspects of the production process play a major role in such selection process in life science industry. The resulting products should have a reproducible composition/quality (and hence functionality).

Compliance with regulatory requirements, the quality of documentation, production under cGMP, the use of validated quality control methods and toxicity/tolerability/biocompatibility profile are also of crucial importance. These aspects are discussed for natural and synthetic phospholipids.

5.1 Production

Natural phospholipids are purified from, e.g., soybeans and egg yolk using non-toxic solvent and chromatography procedures with low consumption of energy and minimum possible waste. When possible, auxiliary materials are continuously recycled. Because of the use of validated purification procedures and sourcing of raw materials with consistent quality, the resulting products differing in PC content possess an excellent batch to batch reproducibility with respect to phospholipid and fatty acid composition. Soybeans and egg yolk as renewable raw materials are abundantly available on the market. The used extraction

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Table 14. Pulmonary products comprising phospholipids

Product	Composition
Alveofact	Phospholipid fraction from bovine lung
Infasurf	Extract of natural surfactant from calf lungs, which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C)
Survanta	Natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, tripalmitin
Surfaxin	DPPC, POPG Na, palmitic acid, sinapultide (KL4 peptide, a 21-amino acid hydrophobic synthetic peptide)
Curosurf	Extract of natural porcine lung surfactant consisting of polar lipids (mainly phospholipids) and hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C)
Tobi Podhaler	Tobramycin/DSPC/$CaCl_2$

procedures and chromatography are amenable to scale-up. This means that natural phospholipids comply with all aspects allowing broad pharmaceutical use.

When starting synthesis from mannitol, synthetic phospholipid intermediates, traces of solvents (other than ICH (International Conference on Harmonisation) class 3) and catalysts used may be present in the final product. Large-scale production of such synthetic lipids requires elaborate synthetic procedures and appropriate chemical synthesis infrastructure to achieve the natural stereochemistry.

The synthesis of phospholipids, which are pure with respect to the polar head group and with high purity fatty acid composition, and of the natural stereochemical configuration, starts preferably from GPC. The desired final purity can only efficiently be obtained by starting the synthesis with a high purity GPC. This GPC is obtained from purified natural PC, which is hydrolyzed to remove the fatty acids. The GPC is then further reacylated and/or treated with specific enzymes to synthesize a specific chemical molecule. This procedure means that synthetic phospholipids are per definition more expensive than natural phospholipids. In addition, due to the additional synthesis steps consequently more solvents and chemicals are needed, more chemical waste is produced, and the overall yield of the final product is considerably decreased. For these reasons, synthetic phospholipids are (irrespective of synthesis route) from sustainability and environmental and ecological point of view clearly inferior compared to natural phospholipids.

5.2 Regulatory and safety aspects

Natural phospholipids are in general well known to regulatory authorities. In addition, their track record as excipient with very high tolerability and biocompatibility is outstanding. From regulatory point of view, the definition of lecithin in the USP is important to note. "Lecithin is a complex mixture of acetone-insoluble phosphatides, which consist chiefly of PC, PE, phosphatidylserine, and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates as separated from the crude vegetable oil source. It contains not less than 50% of acetone-insoluble matter." Also in other pharmacopoeias soybean lecithin is described (Table 15).

Monographs for egg phospholipids have been established in the USP NF31, Chinese Pharmacopeia (2010, Egg lecithin) and in the Japanese Pharmaceutical Excipients (2004, Egg lecithin).

The WHO places no limit on the oral intake of lecithin. Also no limit for the ADI value (acceptable daily intake) for lecithin as a food additive [69] is given. After parenteral administration soybean and egg lecithin (unsaturated and saturated) are well tolerated. The European Commission declares that lecithin is a food additive (E322) "generally permitted for use in foodstuffs" [70, 71]. Also no ADI value has been fixed for lecithin in Europe; the material may be used "quantum satis" [72]. The US FDA assigned the generally recognized as safe (GRAS) affirmation for lecithin [73] and enzyme modified lecithin [74, 75]. The tolerability of natural phospholipids in formulations is further underscored by the use in innumerous products on the market.

Drug products and related formulation technologies show sometimes a remarkable preference for either soybean lecithin or egg lecithin. Oil-in-water emulsions are nowadays exclusively emulsified with egg phospholipids. Mixed micelles are preferably being used with soybean phospholipids. The preference to use egg phospholipids instead of soybean phospholipids was probably related to findings of studies using emulsions, which were not adequately characterized with respect to particle size and chemical composition. For instance, a toxicological study of 1964 wherein in cotton seed oil emulsions emulsified with soybean lecithin was compared with an emulsion using soybean oil and egg lecithin. It was found that dogs treated with the cottonseed oil/soybean lecithin emulsions show serious side effects whereas the soybean oil/egg lecithin emulsion was well tolerated [76]. Since this study was poorly designed (e.g., the control of cotton seed oil/egg lecithin is missing), it is not clear that soybean lecithin is responsible for the observed side effects. In addition, it was known that a toxic component in

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Table 15. Description of soybean lecithin in regulatory directives

Pharmacopeia/directive	Food chemicals codex	231/2012 EC	NF 31	CP 2010	JPE 2004
Monograph number	INS: 322	E 322	–	–	106893
Monograph title	Lecithin	Lecithins	Lecithin	Soya lecithin	Soybean lecithin
Special characteristics	From soybeans and other plant sources	Animal or vegetable origin; additional specifications for hydrolysed lecithins	Origin from the crude vegetable oil source	Extracted and refined from soybean	From soybean, composed mainly of phospholipid
Acetone-insoluble matter	n.l.t. 50.0%	n.l.t. 60.0%	n.l.t. 50.0%	n.l.t. 90.0%	n.l.t. 60%
Toluene-insoluble matter	–	n.m.t. 0.3%	–	–	–
Hexane-insoluble matter	n.m.t. 0.3%	–	n.m.t. 0.3%	n.m.t. 0.3%	–
LPC content/ LPE content	–	–	–	n.m.t. 3.5% /n.m.t. 0.5%	
Water content or loss on drying	n.m.t. 1.5%	n.m.t. 2.0%	n.m.t. 1.5%	n.m.t. 1.5%	n.m.t. 1.5%
Peroxide value	n.m.t. 100	n.m.t. 10	n.m.t. 10	n.m.t. 5	n.m.t. 10
Acid value	n.m.t. 36	n.m.t. 35	n.m.t. 36	n.m.t. 30	n.m.t. 40
Iodine value	–	–	–	n.l.t. 75	–

n.l.t., not less than; n.m.t., not more than.

cotton seed oil, gossypol, was responsible for the observed side effects [77]. Other studies also showed some adverse reactions of soybean lecithin stabilized emulsions [78], whereas others claim that further purification of soybean lecithin may circumvent toxic effects [79]. Because of these uncertainties, egg lecithin has become the preferred emulsifier for parenteral oil-in-water emulsions. Although for this type of emulsion products egg lecithin is preferred, nowadays it is well accepted that soybean phospholipids are acceptable for parenteral administration, because of the use of soybean lecithin (PC) in injectable mixed micellar products (Table 13). The selection of soybean PC for mixed micelles by Hoffmann La Roche for their mixed micelle injectable product diazepam may be related to the presence on the market of the product Essentiale of Nattermann, which comprises mixed micelles of soybean PC and deoxycholate at the time the selection was made.

Saturated PC, prepared from egg yolk or soybeans by means of hydrogenation (HSPC) is not yet mentioned in pharmacopeias. HSPC is, however, listed in the Inactive Ingredient Guide by the FDA Center for Drug Evaluation and, related to the lipid composition of FDA approved drug products, covered in the Draft Guidance on Doxorubicin Hydrochloride (FDA, February 2010) referring to the Draft Guidance for Industry on Liposome Drug Products [80]. In addition, HSPC is covered in a reflection paper on the data requirements for (generic) intravenous liposomal products developed with reference to an innovator liposomal product [81].

The pharmaceutical use of phospholipids isolated from animal sources may sometimes be complicated by the occasional occurrence of animal diseases. Examples are the mad cow disease (bovine spongiform encephalopathy (BSE)/ transmissible spongiform encephalopathy (TSE)) or avian influenza virus. Although it is unlikely that these diseases can be transmitted to man, it is general policy that, even in the very rare event that starting material is contaminated, the applied extraction and purification methods should be able to remove or inactivate the infectious virus. The processes have to be validated in viral safety studies [82]. The raw materials for egg and soy phospholipids are further tested for contaminants possibly originating from the plant or animal origin, e.g., pesticides, aflatoxins, heavy metals, or antibiotic residues and bioburden to ensure the quality and safety of the starting material to obtain pharmaceutical grade phospholipids [83].

Synthetic phospholipids are not mentioned in pharmacopoeias. Just like hydrogenated natural phospholipids they can be found in the Inactive Ingredient Guide by the FDA Center for Drug Evaluation and in the relevant reference documents of FDA and EMA mentioned above. The quality and safety have to be addressed in the application documentation of the drug product. The tolerability of such lipids after parenteral administration can be derived from the doses of the relevant drug products described above. These doses reflect the therapeutic dose of the formulated drugs. The maximal doses of lipids, which can be administered, without drug substance, will be probably significantly higher.

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5.3 Reproducibility/purity/heterogeneity

Although natural phospholipids have a heterogeneous composition (regarding polar head group and fatty acid composition), their over-all quality meets that of synthetic phospholipids. This degree of heterogeneity of natural phospholipids is dependent on the degree of purification. In fact, when the specifications of purified egg PC (≥98%) and synthetic POPC are compared the total content of impurities is nearly the same (Table 16).

Table 16 shows clearly that the risk for presence of unknown impurities and impurities, which are not qualified by means of toxicity testing, is not eliminated by selecting synthetic phospholipids.

As shown above (Tables 5A and 5B) the various phospholipid fractions obtained from soybean lecithin (as an example of a natural phospholipid) by means of solvent extraction and chromatography are indeed heterogeneous with respect to polar head group and fatty acid profile. However, due to a control on the composition of the raw materials and use of validated purification methods, it is also demonstrated that the resulting natural phospholipids, irrespective their heterogeneity, appear to be highly defined and reproducible with respect to the polar head group and fatty acid composition.

When taking reproducibility of composition (irrespective degree of heterogeneity) and hence functionality is taken as quality aspect then natural phospholipids meet at least the quality of synthetic phospholipids.

5.4 Use of natural and synthetic phospholipids in market products

It is remarkable to note that synthetic phospholipids are almost exclusively being used for parenteral drug products. Their use is restricted to liposomal products and slow release vehicles. Simultaneously, in this product class natural phospholipids are used as well. In oral and dermal products, synthetic phospholipids are not used.

Table 16. Comparison of chemical composition (% w/w) of a purified natural phospholipid (egg PC) and a synthetic phospholipid (POPC) [11]

	Specifications	
Test Item	E PC	POPC
PC	≥98%	≥99%
L-PC	≤0.2%	≤0.5%
PE	≤0.1%	–
SM	≤1.0%	–
Triglycerides	≤0.5%	≤0.2%
Cholesterol	≤0.5%	–
Free fatty acids	≤0.2%	≤0.3%
Unidentified concomitant components	n.d.[a)]	≤0.5%
Peroxide value	≤3	≤3

[a)] not detectable, ≤0.1%.

Possible reasons for selecting these synthetic phospholipids instead of natural phospholipids are manifold: First of all, there may not be a natural alternative. An example of such a lipid, with a very specific function to extend the circulation time of intravenously administered liposomes, is a PEGylated phospholipid like MPEG-DSPE, which does not occur in nature.

Most of the liposomal products in question have been developed by small pharmaceutical companies with roots in academic research. The original research interest was mainly in the area of biophysics and membrane biochemistry. These scientific disciplines use well-defined molecular mixtures to study the effect of the components on each other for instance in model membranes. In addition, possibly, the selection of synthetic phospholipids may be related to the unfounded fear for unknown impurities, allergens, etc. present in natural phospholipids. Also, for liposomal dosage intended for active or passive drug targeting, the liposomal phospholipids are considered to make an essential contribution to the targeting properties of the liposomes [80]. Therefore, the phospholipids should meet quality criteria comparable with new drug substances. Without the knowledge that natural phospholipids meet these requirements, synthetic phospholipids are superficially selected to match the quality of the synthetic drug substance (Impurities in New Drug Substances (ICH Q3A R2)). For all these reasons, there is some preference for using synthetic phospholipids to formulate liposomes.

At this research stage, only relatively small amounts of phospholipids are needed. Scale-up considerations are most of the time at that stage not sufficiently considered. Since cancer is the indication for which such formulations are developed, and therapy improvement for this disease will be rewarded by health insurances, irrespective the costs, consequently relative expensive excipients are being and can be used. These small amounts of phospholipids are also sufficient in the stage of preclinical efficacy testing in mice and rats. In case indeed an improvement of the therapeutic index of the phospholipid based formulations is observed in preclinical models, then most of the time the same formulations will be tested in Phase I clinical trials.

Unfortunately, such products may experience, at a later development stage, severe scale up problems due to lack of availability of the synthetic phospholipids used. This may give rise to delays in development and decrease of return in investment. Also, since the synthetic phospholipids are expensive, the profit margin on the product may be smaller as compared to the product when developed with natural phospholipids. It is therefore advisable to consider, at a very early pharmaceutical development stage, to use natural phospholipids whenever possible.

Considering the discussion above on suitability of the various phospholipid classes for development of dosage forms

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and scale up, natural phospholipids including hydrogenated natural phospholipids are, irrespective the intended administration route, preferred compared to synthetic phospholipids. When synthetic phospholipids are selected then the synthesis starting from GPC is preferred to syntheses starting from mannitol or (*S*)-1,2-isopropylideneglycerol to produce the synthetic phospholipids.

Argumentations that natural phospholipids are disadvantageous, because they are heterogeneous and have a high degree of instability due to multiple unsaturation in the fatty acyl chains and are possibly contaminated by trace amounts of proteins, nucleic acids, and other lipids [84, 85] do not apply.

This so-called heterogeneity in composition, which can better be described as "presence of well defined other molecular species besides the main lipid component" should not be interpreted as lack of reproducibility. On the contrary, natural phospholipids can be manufactured highly reproducibly with respect to phospholipid and fatty acid composition and their composition is well defined. The presence of well defined other molecular species besides the main lipid component may be even advantageous, compared to mono-component compounds regarding, e.g., emulsifier and solubilizer properties.

The concerns regarding increased instability of natural phospholipids are eliminated by the demonstrated broad use of this class of phospholipids in many products for any route of administration in marketed products for many years.

Contamination risks by traces of proteins, etc. of natural phospholipids are because of the applied extraction solvents and chromatography procedures virtually eliminated.

This selection/preference sequence is of particular interest in technology areas, like liposomes, wherein all classes can be considered. Table 17 shows exemplary some synthetic phospholipids and their natural alternatives, which are more suitable for scale-up.

As illustrated in Table 17, alternative natural phospholipids, which have the same head group purity and a similar fatty acid composition may be considered as alternative to synthetic phospholipids. HSPC is preferred compared to DSPC because it is easier to hydrogenate soybean PC than to produce the lipid synthetically. Likewise, it is easier to manufacture hydrogenated soybean phosphatidylglycerol (HSPG) from hydrogenated soy bean PC followed by phospholipase D treatment to convert HSPC to HSPG, than to produce it synthetically.

Since, the fatty acid composition of the alternative lipids is not exactly the same, the liquid crystalline to gel state phase temperature will not be identical. Production processes at which this may play a role need to be rechecked, when the synthetic phospholipid shall be replaced. As mostly mixtures of phospholipids and other ingredients (e.g., cholesterol, which suppresses the phase transition) are used, this should be negligible.

These details point to the importance of selecting the most suitable phospholipid at the beginning of a dosage form development process. In addition to selection of alternative phospholipids based on similarity of chemical composition, alternative natural phospholipids may be selected when considering their functionality and role in the formulation.

For instance, emulsions are known to be more stable when using mixtures of emulsifiers compared to mono-component emulsifier. Purified egg or soybean phospholipids consist of well-defined mixtures of phospholipids, which possess better emulsifier properties for oil-in-water emulsion (see above). For these reasons, they offer an even better alternative to, e.g., POPC. A further example to demonstrate the beneficial alternative use of natural phospholipids is the demonstration that, as part of the design and selection of the phospholipid composition of Doxil liposomes, HSPC could be used instead of DPPC or DSPC to make plasma stable liposomes [86].

6 Conclusions

Natural phospholipids are derived from renewable sources and produced with more ecologically friendly processes and are available in larger scale at relatively low costs compared to synthetic phospholipids. They comply with all requirements of the regulatory authorities and are safe in use for any administration route and any dosage form. Synthetic phospholipids contain chemically specific, defined polar head groups and fatty acids but are synthesized with various chemicals and solvents. Dependent on the synthesis route selected, they may contain intermediates or by-products and unnatural enantiomers may be formed. Synthetic phospholipids are only available in relatively small amounts at high prices.

In the overall phospholipid excipient market, synthetic phospholipids play, compared to natural phospholipid

Table 17. Natural phospholipids as alternatives to synthetic phospholipids

Synthetic phospholipid	Alternative natural phospholipid	Main components of alternative phospholipid
POPC	E PC	POPC 38%, PLPC 26%, SLPC 13%, SOPC 11%
POPG (Na)	E PG (Na)	POPG 38%, PLPG 26%, SLPG 13%, SOPG 11%
DSPC	HSPC	DSPC 85%, PSPC 15%
DSPG (Na)	HSPG (Na)	DSPG 85%, PSPG 15%

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(including hydrogenated and enzyme modified phospholipids), from number of drug products comprising these phospholipids, a minor role. Their use is restricted to some pharmaceutical products. If the use of synthetic phospholipids is unavoidable, synthetic phospholipids using the synthesis route starting from GPC, obtained from natural PC, should be used. At this way, the natural stereochemical configuration is guaranteed and the extra production steps compared to natural phospholipids can be performed with minimal additional usage of solvents and chemicals.

In order to avoid scale up problems during pharmaceutical development and production, natural phospholipid excipients instead of synthetic phospholipids should be selected for formulations whenever possible.

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Anonymous	
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Basis and contents of observation

1. The observation is made on the basis of the claims in the international application as filed.
2. The observation comprises:
   References to documents: 4
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3. Further explanations:
   Uploaded copies of documents: 1

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Patent Applicant/Patent Owner:	Title of invention:
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Most relevant passages or drawings:	Relevant to Claims:
pp.11–12, 29–30, 34–35, 38–40, 47–48, 51–56, 68, Figs.4–6, 10, Claims 17–22, 35–38, 42–45, 51–57, 60–65, 69–72, 77–81, 84–86	1-68

Brief explanation of relevance:

WO2018035359 (WO'359) relates to HIV capsid inhibitors and its pharmaceutical compositions. The pharmaceutical compositions contain pharmaceutically acceptable excipients, in parenteral (injectable) form (pp.11–12). WO'359 discloses pharmaceutical compositions of capsid inhibitors, their method and use:
1. Excipients such as those set forth in Rowe, et al. Handbook of Pharmaceutical Excipients, 5th edition (p.47), and may be prepared using techniques and formulations found in Remington: The Science and Practice of Pharmacy, 21st edition, (p.48); for parenteral administration, suitable excipients are well known to a person skilled in the art and may be found in the Handbook of Pharmaceutical Excipients (Ed. Rowe, Sheskey and Quinn), 6th edition 2009 (p.51).

2. Examples of solubilizing excipients in parenteral formulation include, but not limited to: poloxamers (such as poloxamer 338, 188 or 207), in particular poloxamer 338 (p.51), and wherein poloxamer 188 ranges in molecular weight from about 7860 to 9510 Daltons (Da), and poloxamer 338 has a range in molecular weight from 12700 to about 17400 Da (p.52);

3. In some embodiments, excipients include polyethylene glycol (PEG) (p.51); the PEG has an average molecular weight approx. 100 to 1000, whereas average is about 200 to approx. 600, including PEG 200, 300, 400 (p.52)

4. In some embodiments, the suspension comprises saline and poloxamer (P188 or P338), where concentration of poloxamer 188 in saline is 1–10% (2%) (Figs. 4 to 6); or poloxamer and mannitol with concentration of poloxamer in mannitol from 0.1% to 20% (pp.53–54, Claims 63–65, 69–72);

5. In some embodiments that parenteral formulation comprises the compound or a pharmaceutical salt thereof and water (p.54, Claim 77); and in some embodiments it further comprises an alcohol, where the alcohol is ethanol (id. Claims 78–79); and it further comprises PEG200 (id., Claims 80–81) (p.55);

6. In some embodiments the formulation comprises of 5–20% ethanol, 5–20% water, about 60–90% PEG200 (p.55, Fig.10, Claims 84–86).

7. In some embodiments, the oral form, includes excipients including acceptable oils such as sesame oil (p.56)

8. Routes of administration include intravenous, subcutaneous or intramuscular (pp.29–30, 68; Claims 60–62)

9. Combination therapy with one to four additional therapeutic agents (pp.24–29), including HIV integrase inhibitors like dolutegravir, bictegravir, etc. and entry inhibitors like CCR5 inhibitors, etc. and others like lamivudine, and various combinations, etc. (pp.34–35, 38–40; Claims 17–22, 35–38, 42–45, 51–57).

Another application, by Gilead, WO2019035904 (WO'904), similar to WO'359, claims solid forms of capsid inhibitors, that also discloses injectables, such as sterile injectable aqueous and non-aqueous, that use wetting agents, sterile fixed oils, water, fatty acids, buffers, and suitable excipients such as polysorbates, poloxamers (338, 188, 207) – poloxamer 338 [pp.60-62]. WO'904 exemplifies intravenous administration of a capsid inhibitor formulated in 5% ethanol, 20%PG, 45% PEG300, 30% pH2 water at 0.5 mg/ml, and of other capsid inhibitors with 5% ethanol, 45% PEG400, and 50% water at 0.5 mg/ml [p.101]. WO'904 also provides formulation examples – example A that contains 2% poloxamer 188 in saline, and Example C that contains ethanol, water and PEG200 [pp.105–106]; the pharmacokinetic data for Example C at day 28 demonstrates extended release pharmacokinetics.

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, the excipients used in the formulations of WO'559 are known to be used for preparing parenteral long-acting formulations, are commonly and routinely used—as shown in WO'359 (Citation 1) and WO'904 (Citation 1A) (with extended release pharmacokinetic data for capsid inhibitor, PEG, ethanol and water formulation), and also include those that are known in the art and/or set forth in text books.

Thus, all the claims of WO'559 lack inventive step.

Citation # 2 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2020/018459	A1

Patent Applicant/Patent Owner:	Title of invention:
Gilead Sciences, Inc.	Capsid Inhibitors for the treatment of HIV

Link to document:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020018459

Publication Date:	Filing Date:	Priority Date:
23 Jan 2020 (23/01/2020)	15 Jul 2019 (15/07/2019)	16 Jul 2018 (16/07/2018)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
pp. 4, 27–28, 30, 32–34, 36–37, 40–41, 56, 58–59, 61, 113, 129–150; Figs. 4–10; Claims 88 to 94	1-68

Brief explanation of relevance:

WO2020018459 (WO'459) relates to HIV capsid inhibitor compounds and its salts, useful in the treatment of an HIV (Abstract).

WO'459 discloses the formulations of these compounds that can be administered parenterally – subcutaneously, intravenously, etc. (p. 4) and also specifically claims compositions in the form of a solution (Claims 88 to 94).

With respect to liquid, parenteral formulations, WO'459 discloses the following relating to compounds of formula Ia and Ib and its pharmaceutically acceptable salts:
1. Pharmaceutical compositions contain the active ingredient together with or more pharmaceutically acceptable excipients and optionally other therapeutic agent, in ordinary practice — any form suitable for the intended method of administration (p.27);

2. Composition can be in the form of formulations suitable for parenteral administration including aqueous or non-aqueous sterile injectable solution or suspension (p.33)

3. Solution formulation comprising N-methyl-2-pyrrolidone (NMP), polyethylene glycol (PEG- PEG 200, 300), water, glycofurol, ethanol, dimethyl sulfoxide (DMSO) (pp .33, 59).

4. In one embodiment, the formulation has 10% ethanol, 13% water, and 77% PEG200 – for subcutaneous administration (pp.33–34, 36, Fig. 3). There are similar compositions with PEG300 too — The solution comprising PEG 300 and water comprises PEG 300 (about 50–85% w/w) and water (about 5–25% w/w or about 10–12% w/w); this solution may further comprise an inorganic base (e.g., sodium hydroxide; 0.5–3% w/w) (pp.34, 40–41, 56, 61, Figs. 4–10).

5. Solubilizing excipients in a parenteral formulation (e.g., subcutaneous) include, but are not limited to polysorbates (e.g., Polysorbate 20 and 80) and poloxamers (e.g., Poloxamer 338, 188, 207; pp.34, 35, Figs. 12). In some embodiments, a suspension comprising of the compound or salt thereof, in poloxamer and mannitol where the concentration of poloxamer 188 in mannitol is 0.1 to 20% (pp.58–59)

6. In certain embodiments the alcohol is ethanol, and PEG 200 is used, the formulation comprises of ethanol, water, and PEG200 (pp.60–61)

7. Administration of the disclosed compounds or its pharmaceutically acceptable salt with one or more therapeutic agents, either intravenously, subcutaneously, intramuscularly (p. 113) either simultaneously or sequentially (pp.132–150).

8. All compositions can further contain excipients such as antioxidants, chelating agents (e.g., EDTA), etc – that are disclosed in textbooks on pharmaceutical excipients – and that suitable excipients for parenteral formulation are known in the art (pp. 28, 32). It also discloses that compositions can be formulated using techniques and formulations known in the art. (p. 30).

9. Combination therapy with one to four additional therapeutic agents, including HIV combination therapy, such as lamivudine, bictegravir, etc. (pp.129–150)

 The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, WO'459 already discloses the excipients commonly used for preparing parenteral formulations of HIV capsid inhibitors, and the use of the formulated compounds in combination with other agents.< br/>
Thus, all claims of WO'559 lack inventive step.

Citation # 3 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2021/116872	A1

Patent Applicant/Patent Owner:	Title of invention:
ViiV Healthcare Company	Pharmaceutical compositions comprising cabotegravir

Link to document:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021116872

Publication Date:	Filing Date:	Priority Date:
17 Jun 2021 (17/06/2021)	07 Dec 2020 (07/12/2020)	09 Dec 2019 (09/12/2019)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Abstract, pp.1–11, 14–18.23, 28, 32; Examples 3, 7 and 9; Table 2a, 7, 8, 15, 19; Fig. 2	33–68

Brief explanation of relevance:

WO2021116872 (WO872) discloses pharmaceutical compositions (compositions) comprising cabotegravir, an HIV integrase inhibitor, poloxamer and optionally polyethylene glycol (PEG) (as it may be 0), useful as a long-acting HIV treatment (Abstract, p.1; Table 2a).

WO872 discloses – (a) the need for long-acting injectable for HIV that can be dosed at fewer intervals and overcoming known difficulties with high concentration suspensions; (b) compositions that overcomes these difficulties and exhibit particle size stability (pp.1–2).

WO872 discloses and/or claims:
1. Compositions comprising cabotegravir or its salt (350–600 mg/mL), poloxamer (4–50 mg/mL), mannitol (20 mg/mL) and optionally PEG (0 to 75 mg/mL) (pp.3, 5–6; Table 2a)
2. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (PEG), and may be P237, P338 or P407 (p.4).
3. The use of poloxamer allows a high concentration of cabotegravir to be present in the composition; it is thought that (a) the hydrophobic polyoxypropylene chains adsorb onto the surface of the cabotegravir particles and thus provide steric hindrance between particles and provides stabilization against particle aggregation or flocculation; (b) PEG chains provide stabilisation through steric hindrance, thus allowing a higher concentration of cabotegravir in the composition and minimising particle to particle interactions usually associated with high particle concentrations (pp.4–5).
4. Use of poloxamer P237, P407 or P338 gives enhanced physical stability to the compositions, possibly as they contain more PEG chains p.5).
5. The composition may not comprise PEG3350 (0 mg/mL), which otherwise acts as a stabilizer, as the PEG chains in poloxamer itself provide stabilisation by steric hindrance (pp.5–6).
6. The median particle diameter (MPD) of cabotegravir in the composition is 0.1 to 10.0 microm; compositions with MPD of 0.15 to 0.25 microm (about 0.2 microm) have improved resuspension over those with larger particle sizes (p.7).
7. Mannitol (present at a concentration of 15–40 mg/mL) is used as a tonicity adjuster (pp.7–8).
8. Composition may be administered parenterally (subcutaneous, intravenous, etc.) (p.3)
9. Composition for treatment or prevention of HIV; suitable for use as an injectable composition; use and method thereof (pp.8, 14–15).
10. Composition may be administered in combination with other anti-HIV agents, including capsid inhibitors (p.9).
11. Capsid inhibitors used in combination may include Compounds 1 and 2 or lenacapavir (pp.9–11, 15–18). It may be noted that Compounds 1 and 2 are Formula Ia and Ib of the present Application WO2023062559.
12. Exemplified compositions include those of 400 mg/mL and 500 mg/mL cabotegravir with P338 or P407 and mannitol; the lack of change in particle size after 1 month indicated stability of the suspensions (p.23, Ex. 3, Tables 7 and 8; p.32, Ex. 9, Table 19).
13. Pharmacokinetic profile for suspension of cabotegravir (400 mg/mL) with P338 and mannitol showed it to be similar to those with PEG3350; long-acting profile is maintained (p.28, Ex. 7; Table 15, Fig. 2).

The present Application, WO2023062559 (WO559), claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt (previously disclosed HIV capsid inhibitors) particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B).
In Set B, the claimed compositions (heterogeneous; Claim 45) comprise: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38); 3. with described MPD for compounds of Formula Ia and Ib of less than or equal to 0.2 microm (Claims 39–42). It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use (Claims 66–68). It may be noted that that Claims 46 to 58 appear to be identical to Claims 33 to 45.

However, WO872 already discloses the use of P338 and mannitol to make stable, long-acting formulations of cabotegravir, an anti-HIV drug, in a suspension form, with desired particle size of the compound, for treating HIV. WO872 also discloses the use of cabotegravir in combination with capsid inhibitors of compounds 1 and 2 (identical to compounds of formula Ia and Ib of WO559).

The applicant of WO559 has merely applied the strategy disclosed in WO872 to make long-acting formulations for the admittedly known HIV capsid inhibitors of formula Ia and Ib.

Thus, Claims 33 to 68 of the present Application, WO559, lack inventive step

Citation # 4 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2021/209900	A1

Patent Applicant/Patent Owner:	Title of invention:
ViiV Healthcare UK (No.5) Limited	Inhibitors of human immunodeficiency virus replication

Link to document:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021209900

Publication Date:	Filing Date:	Priority Date:
21 Oct 2021 (21/10/2021)	13 Apr 2021 (13/04/2021)	15 Apr 2020 (15/04/2020)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Abstract, pp. 3–6, 8–12, 57–58; Claims 1–18	1-68

Brief explanation of relevance:

Though WO2021209900 (WO900) was published on (21/10/2021), after the priority date of the present Application, WO2023062559 (WO559) (13/10/2021), it claims an earlier priority date (15/04/2020). It is therefore relevant in those countries whose patent law consider such documents as relevant.

Both WO900 and WO559 are applications by ViiV Healthcare and relate to specific HIV capsid inhibitors (p. 12 of WO900; p. 1 of WO559).

WO900 claims pharmaceutical compositions comprising compounds of Formula Ia and Id, which are identical to compounds Ia and Ib respectively of the present Application, WO559 (Abstract).

WO900 discloses and/or claims
1. Pharmaceutical compositions of Formula Ia or Id or a salt thereof, and a solvent or diluent "selected" from the group consisting of water, an alcohol (ethanol), polyethylene glycol (PEG) – PEG 200, PEG300, PEG400; N-methyl-2-pyrrolidone (NMP), ethyl lactate, propylene glycol, glycofurol, and dimethylsulfoxide (DMSO) (pp.3–5, 9–10; Claims 1, 5–8)
2. The composition further comprises a solubilizing excipient selected from polysorbate 20, polysorbate 80, poloxamer 188 (P188) (at least 90% by weight), poloxamer 207 (P207), poloxamer 338 (P338), a fatty acid (with poloxamer), sodium chloride, and sodium hydroxide, (pp.3–4, 6; Claims 2, 9 (poloxamer188), 10)
3. The composition which specifically comprises (a) specifically water and PEG200 (p.6); (b) at least 90% by weight of solvents/diluents are water and PEG300 (Claims 11, 13–14); (c) at least 90% by weight of excipient is P188 (Claim 12).
4. The composition also comprises a buffer, such as acetate buffer (pH 4.8–5.2) (pp.8–9)
5. The compound or salt is present in the composition at a concentration of 50 to 500 mg/ml or 225 to 275, 275 to 350, 350 to 425 mg/ml based on weight of the free compound (p.4, 8–9; Claims 15–18)
6. The composition is a solution or suspension (p.3; Claims 3–4)
7. Method of treating HIV infection by administering the claimed composition (p.3)
8. Pharmaceutical composition for use in therapy and for use in treating HIV infection (p.3)
9. The use of the pharmaceutical composition in the manufacture of a medicament for the treatment of HIV infection (p.3)
10. Composition may be employed alone or in combination with other anti-HIV agents (p.11).
11. The exemplified formulation that was tested for pharmacokinetic parameters via subcutaneous injection comprised compound of Formula Ia, PEG300 and water (pp.57–58).

The present Application, WO559, claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt , particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B). The claimed compositions comprise:

Set A: 1. PEG (particularly PEG200, PEG300, PEG400; 40–50% by weight) and ethanol (5–25% by weight) (Claims 1–2, 8–13); 2. further comprises one or more of water, lecithin (soy), propylene glycol , benzyl alcohol, or sesame oil (Claim 3–7); 3. Composition is homogenous solution (Claim 14). It specifically claims formulations comprising PEG200, ethanol and lecithin (Claims 15–16).

Set B: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38), 3. with described mean particle diameters for compounds of Formula Ia and Ib (Claims 39–42). 3. It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44). 4. The composition is a heterogenous suspension (Claim 45).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use in therapy and use in treating HIV infection and in the manufacture of a medicament for the treatment of HIV infection in a human (Claims 66–68).

It may be noted that that Claims 17 to 31 and Claims 46 to 58 appear to be identical to Claims 1 to 16 and Claims 33 to 45, respectively.

Thus, WO900 already discloses the claimed compounds and pharmaceutical compositions thereof, specifically with PEG200, PEG300 or PEG400, ethanol and water as well as with P338 or P188 and other excipients (water, sodium chloride, acetate buffer), for treating HIV.

The applicant of WO559 has merely used routine experimentation to prepare and determine the characteristics of the formulations prepared using excipients already known in the art for HIV capsid inhibitors (WO900 as well as WO2018035359, WO2019035904 and WO2020018459 (Citations 1, 1A and 2.).

In light of the above, Claims 1 to 68 of the present Application, WO559, lack inventive step.

ADDITIONAL COMMENTS FOR WO2023062559

The Third-Party Observation (TPO) accompanying this Additional Comment for WO2023062559 (WO'559) brings out the following through various prior art. The details of the TPO are as follows:-

Prior art: Citation 1: WO2018035359 and Citation 1A: WO2019035904

<table>
<tr><td>Country Code: WO</td><td colspan="2">Publication Number: 2018/035359</td><td>Document Kind Code: A1</td></tr>
<tr><td colspan="2">Patent Applicant/ Owner: Gilead Sciences Inc.</td><td colspan="2">Title of Invention: Therapeutic compounds useful for the prophylactic or therapeutic treatment of and HIV virus infection</td></tr>
<tr><td colspan="4">Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018035359</td></tr>
<tr><td colspan="2">Publication Date: 22.02.2018</td><td>Filing Date: 17.08.2017</td><td>Priority Date: 19.08.2016</td></tr>
<tr><td>Source of Abstract:</td><td>Accession Number:</td><td>Publication date of Abstract:</td><td>Retrieval date of Abstract:</td></tr>
<tr><td colspan="2">Most relevant passages or drawings:
pp.11–12, 29–30, 34–35, 38–40, 47–48, 51–56, 68, Figs.4–6, 10, Claims 17–22, 35–38, 42–45, 51–57, 60–65, 69–72, 77–81, 84–86</td><td colspan="2">Relevant to Claims:
1–68</td></tr>
<tr><td colspan="4">Brief Explanation of Relevance:

WO2018035359 (WO'359) relates to HIV capsid inhibitors and its pharmaceutical compositions. The pharmaceutical compositions contain pharmaceutically acceptable excipients, in parenteral (injectable) form (pp.11–12). WO'359 discloses pharmaceutical compositions of capsid inhibitors, their method and use:
1. Excipients such as those set forth in Rowe, et al. Handbook of Pharmaceutical Excipients, 5th edition (p.47), and may be prepared using techniques and formulations found in Remington: The Science and Practice of Pharmacy, 21st edition, (p.48); for parenteral administration, suitable excipients are well known to a person skilled in the art and may be found in the Handbook of Pharmaceutical Excipients (Ed. Rowe, Sheskey and Quinn), 6th edition 2009 (p.51).

2. Examples of solubilizing excipients in parenteral formulation include, but not limited to: poloxamers (such as poloxamer 338, 188 or 207), in particular poloxamer 338 (p.51), and wherein poloxamer 188 ranges in molecular weight from about 7860 to 9510 Daltons (Da), and poloxamer 338 has a range in molecular weight from 12700 to about 17400 Da (p.52);

3. In some embodiments, excipients include polyethylene glycol (PEG) (p.51); the PEG has an average molecular weight approx. 100 to 1000, whereas average is about 200 to approx. 600, including PEG 200, 300, 400 (p.52)</td></tr>
</table>

4. In some embodiments, the suspension comprises saline and poloxamer (P188 or P338), where concentration of poloxamer 188 in saline is 1–10% (2%) (Figs. 4 to 6); or poloxamer and mannitol with concentration of poloxamer in mannitol from 0.1% to 20% (pp.53–54, Claims 63–65, 69–72);

5. In some embodiments that parenteral formulation comprises the compound or a pharmaceutical salt thereof and water (p.54, Claim 77); and in some embodiments it further comprises an alcohol, where the alcohol is ethanol (id. Claims 78–79); and it further comprises PEG200 (id., Claims 80–81) (p.55);

6. In some embodiments the formulation comprises of 5–20% ethanol, 5–20% water, about 60–90% PEG200 (p.55, Fig.10, Claims 84–86).

7. In some embodiments, the oral form, includes excipients including acceptable oils such as sesame oil (p.56)

8. Routes of administration include intravenous, subcutaneous or intramuscular (pp.29–30, 68; Claims 60–62)

9. Combination therapy with one to four additional therapeutic agents (pp.24–29), including HIV integrase inhibitors like dolutegravir, bictegravir, etc. and entry inhibitors like CCR5 inhibitors, etc. and others like lamivudine, and various combinations, etc. (pp.34–35, 38–40; Claims 17–22, 35–38, 42–45, 51–57).

Another application, by Gilead, WO2019035904 (WO'904), similar to WO'359, claims solid forms of capsid inhibitors, that also discloses injectables, such as sterile injectable aqueous and non-aqueous, that use wetting agents, sterile fixed oils, water, fatty acids, buffers, and suitable excipients such as polysorbates, poloxamers (338, 188, 207) – poloxamer 338 [pp.60-62]. WO'904 exemplifies intravenous administration of a capsid inhibitor formulated in 5% ethanol, 20%PG, 45% PEG300, 30% pH2 water at 0.5 mg/ml, and of other capsid inhibitors with 5% ethanol, 45% PEG400, and 50% water at 0.5 mg/ml [p.101]. WO'904 also provides formulation examples – example A that contains 2% poloxamer 188 in saline, and Example C that contains ethanol, water and PEG200 [pp.105–106]; the pharmacokinetic data for Example C at day 28 demonstrates extended release pharmacokinetics.

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, the excipients used in the formulations of WO'559 are known to be used for preparing parenteral long-acting formulations, are commonly and routinely used—as shown in WO'359 (Citation 1) and WO'904 (Citation 1A) (with extended release pharmacokinetic data for capsid inhibitor, PEG, ethanol and water formulation), and also include those that are known in the art and/or set forth in text books.

Thus, all the claims of WO'559 lack inventive step.

Prior art: Citation 2: WO2020018459

Country Code: WO	Publication Number: 2020/018459		Document Kind Code: A1
Patent Applicant/ Owner: Gilead Sciences, Inc.		Title of Invention: Capsid Inhibitors for the treatment of HIV	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020018459			
Publication Date: 23/01/2020		Filing Date: 15/07/2019	Priority Date: 16/07/2018
Source of Abstract:	Accession Number:	Publication date of Abstract:	Retrieval date of Abstract:
Most relevant passages or drawings: pp. 4, 27–28, 30, 32–34, 36–37, 40–41, 56, 58–59, 61, 113, 129–150; Figs. 4–10; Claims 88 to 94		Relevant to Claims: 1 to 68	

Brief Explanation of Relevance:

WO2020018459 (WO'459) relates to HIV capsid inhibitor compounds and its salts, useful in the treatment of an HIV (Abstract).

WO'459 discloses the formulations of these compounds that can be administered parenterally – subcutaneously, intravenously, etc. (p. 4) and also specifically claims compositions in the form of a solution (Claims 88 to 94).

With respect to liquid, parenteral formulations, WO'459 discloses the following relating to compounds of formula Ia and Ib and its pharmaceutically acceptable salts:
1. Pharmaceutical compositions contain the active ingredient together with or more pharmaceutically acceptable excipients and optionally other therapeutic agent, in ordinary practice — any form suitable for the intended method of administration (p.27);

2. Composition can be in the form of formulations suitable for parenteral administration including aqueous or non-aqueous sterile injectable solution or suspension (p.33)

3. Solution formulation comprising N-methyl-2-pyrrolidone (NMP), polyethylene glycol (PEG-PEG 200, 300), water, glycofurol, ethanol, dimethyl sulfoxide (DMSO) (pp.33, 59).

4. In one embodiment, the formulation has 10% ethanol, 13% water, and 77% PEG200 – for subcutaneous administration (pp.33–34, 36, Fig. 3). There are similar compositions with PEG300 too — The solution comprising PEG 300 and water comprises PEG 300 (about 50–85% w/w) and water (about 5–25% w/w or about 10–12% w/w); this solution may further

comprise an inorganic base (e.g., sodium hydroxide; 0.5–3% w/w) (pp.34, 40–41, 56, 61, Figs. 4–10).

5. Solubilizing excipients in a parenteral formulation (e.g., subcutaneous) include, but are not limited to polysorbates (e.g., Polysorbate 20 and 80) and poloxamers (e.g., Poloxamer 338, 188, 207; pp.34, 35, Figs. 12). In some embodiments, a suspension comprising of the compound or salt thereof, in poloxamer and mannitol where the concentration of poloxamer 188 in mannitol is 0.1 to 20% (pp.58–59)

6. In certain embodiments the alcohol is ethanol, and PEG 200 is used, the formulation comprises of ethanol, water, and PEG200 (pp.60–61)

7. Administration of the disclosed compounds or its pharmaceutically acceptable salt with one or more therapeutic agents, either intravenously, subcutaneously, intramuscularly (p. 113) either simultaneously or sequentially (pp.132–150).

8. All compositions can further contain excipients such as antioxidants, chelating agents (e.g., EDTA), etc – that are disclosed in textbooks on pharmaceutical excipients – and that suitable excipients for parenteral formulation are known in the art (pp. 28, 32). It also discloses that compositions can be formulated using techniques and formulations known in the art. (p. 30).

9. Combination therapy with one to four additional therapeutic agents, including HIV combination therapy, such as lamivudine, bictegravir, etc. (pp.129–150)

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, WO'459 already discloses the excipients commonly used for preparing parenteral formulations of HIV capsid inhibitors, and the use of the formulated compounds in combination with other agents.

Thus, all claims of WO'559 lack inventive step.

Prior art: Citation 3: WO2021116872

Country Code: WO	Publication Number: 2021/116872		Document Kind Code: A1
Patent Applicant/ Owner: ViiV Healthcare Company		Title of Invention: Pharmaceutical compositions comprising cabotegravir	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021116872			
Publication Date: 17.06.2021		Filing Date: 07.12.2020	Priority Date: 09.12.2019
Source of Abstract:	Accession Number:	Publication date of Abstract:	Retrieval date of Abstract:
Most relevant passages or drawings: Abstract, pp.1–11, 14–18.23, 28, 32; Examples 3, 7 and 9; Table 2a, 7, 8, 15, 19; Fig. 2		Relevant to Claims: 1–68	

Brief Explanation of Relevance:

WO2021116872 (WO872) discloses pharmaceutical compositions (compositions) comprising cabotegravir, an HIV integrase inhibitor, poloxamer and optionally polyethylene glycol (PEG) (as it may be 0), useful as a long-acting HIV treatment (Abstract, p.1; Table 2a).

WO872 discloses – (a) the need for long-acting injectable for HIV that can be dosed at fewer intervals and overcoming known difficulties with high concentration suspensions; (b) compositions that overcomes these difficulties and exhibit particle size stability (pp.1–2).

WO872 discloses and/or claims:

1. Compositions comprising cabotegravir or its salt (350–600 mg/mL), poloxamer (4–50 mg/mL), mannitol (20 mg/mL) and optionally PEG (0 to 75 mg/mL) (pp.3, 5–6; Table 2a)
2. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (PEG), and may be P237, P338 or P407 (p.4).
3. The use of poloxamer allows a high concentration of cabotegravir to be present in the composition; it is thought that (a) the hydrophobic polyoxypropylene chains adsorb onto the surface of the cabotegravir particles and thus provide steric hindrance between particles and provides stabilization against particle aggregation or flocculation; (b) PEG chains provide stabilisation through steric hindrance, thus allowing a higher concentration of cabotegravir in the composition and minimising particle to particle interactions usually associated with high particle concentrations (pp.4–5).
4. Use of poloxamer P237, P407 or P338 gives enhanced physical stability to the compositions, possibly as they contain more PEG chains p.5).

5. The composition may not comprise PEG3350 (0 mg/mL), which otherwise acts as a stabilizer, as the PEG chains in poloxamer itself provide stabilisation by steric hindrance (pp.5–6).
6. The median particle diameter (MPD) of cabotegravir in the composition is 0.1 to 10.0 microm; compositions with MPD of 0.15 to 0.25 microm (about 0.2 microm) have improved resuspension over those with larger particle sizes (p.7).
7. Mannitol (present at a concentration of 15–40 mg/mL) is used as a tonicity adjuster (pp.7–8).
8. Composition may be administered parenterally (subcutaneous, intravenous, etc.) (p.3)
9. Composition for treatment or prevention of HIV; suitable for use as an injectable composition; use and method thereof (pp.8, 14–15).
10. Composition may be administered in combination with other anti-HIV agents, including capsid inhibitors (p.9).
11. Capsid inhibitors used in combination may include Compounds 1 and 2 or lenacapavir (pp.9–11, 15–18). It may be noted that Compounds 1 and 2 are Formula Ia and Ib of the present Application WO2023062559.
12. Exemplified compositions include those of 400 mg/mL and 500 mg/mL cabotegravir with P338 or P407 and mannitol; the lack of change in particle size after 1 month indicated stability of the suspensions (p.23, Ex. 3, Tables 7 and 8; p.32, Ex. 9, Table 19).
13. Pharmacokinetic profile for suspension of cabotegravir (400 mg/mL) with P338 and mannitol showed it to be similar to those with PEG3350; long-acting profile is maintained (p.28, Ex. 7; Table 15, Fig. 2).

The present Application, WO2023062559 (WO559), claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt (previously disclosed HIV capsid inhibitors) particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B).
In Set B, the claimed compositions (heterogeneous; Claim 45) comprise: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38); 3. with described MPD for compounds of Formula Ia and Ib of less than or equal to 0.2 microm (Claims 39–42). It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use (Claims 66–68). It may be noted that that Claims 46 to 58 appear to be identical to Claims 33 to 45.

However, WO872 already discloses the use of P338 and mannitol to make stable, long-acting formulations of cabotegravir, an anti-HIV drug, in a suspension form, with desired particle size of the compound, for treating HIV. WO872 also discloses the use of cabotegravir in combination with capsid inhibitors of compounds 1 and 2 (identical to compounds of formula Ia and Ib of WO559).

The applicant of WO559 has merely applied the strategy disclosed in WO872 to make long-acting formulations for the admittedly known HIV capsid inhibitors of formula Ia and Ib. Thus, Claims 33 to 68 of the present Application, WO559, lack inventive step.

Prior art: Citation 4: WO2021209900

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Brief Explanation of Relevance:
Though WO2021209900 (WO900) was published on (21/10/2021), after the priority date of the present Application, WO2023062559 (WO559) (13/10/2021), it claims an earlier priority date (15/04/2020). It is therefore relevant in those countries whose patent law consider such documents as relevant.

Both WO900 and WO559 are applications by ViiV Healthcare and relate to specific HIV capsid inhibitors (p. 12 of WO900; p. 1 of WO559).

WO900 claims pharmaceutical compositions comprising compounds of Formula Ia and Id, which are identical to compounds Ia and Ib respectively of the present Application, WO559 (Abstract).

WO900 discloses and/or claims

1. Pharmaceutical compositions of Formula Ia or Id or a salt thereof, and a solvent or diluent "selected" from the group consisting of water, an alcohol (ethanol), polyethylene glycol (PEG) – PEG 200, PEG300, PEG400; N-methyl-2-pyrrolidone (NMP), ethyl lactate, propylene glycol, glycofurol, and dimethylsulfoxide (DMSO) (pp.3–5, 9–10; Claims 1, 5–8)
2. The composition further comprises a solubilizing excipient selected from polysorbate 20, polysorbate 80, poloxamer 188 (P188) (at least 90% by weight), poloxamer 207 (P207), poloxamer 338 (P338), a fatty acid (with poloxamer), sodium chloride, and sodium hydroxide, (pp.3–4, 6; Claims 2, 9 (poloxamer188), 10)

3. The composition which specifically comprises (a) specifically water and PEG200 (p.6); (b) at least 90% by weight of solvents/diluents are water and PEG300 (Claims 11, 13–14); (c) at least 90% by weight of excipient is P188 (Claim 12).
4. The composition also comprises a buffer, such as acetate buffer (pH 4.8–5.2) (pp.8–9)
5. The compound or salt is present in the composition at a concentration of 50 to 500 mg/ml or 225 to 275, 275 to 350, 350 to 425 mg/ml based on weight of the free compound (p.4, 8–9; Claims 15–18)
6. The composition is a solution or suspension (p.3; Claims 3–4)
7. Method of treating HIV infection by administering the claimed composition (p.3)
8. Pharmaceutical composition for use in therapy and for use in treating HIV infection (p.3)
9. The use of the pharmaceutical composition in the manufacture of a medicament for the treatment of HIV infection (p.3)
10. Composition may be employed alone or in combination with other anti-HIV agents (p.11).
11. The exemplified formulation that was tested for pharmacokinetic parameters via subcutaneous injection comprised compound of Formula Ia, PEG300 and water (pp.57–58).

The present Application, WO559, claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt, particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B). The claimed compositions comprise:

- Set A: 1. PEG (particularly PEG200, PEG300, PEG400; 40–50% by weight) and ethanol (5–25% by weight) (Claims 1–2, 8–13); 2. further comprises one or more of water, lecithin (soy), propylene glycol , benzyl alcohol, or sesame oil (Claim 3–7); 3. Composition is homogenous solution (Claim 14). It specifically claims formulations comprising PEG200, ethanol and lecithin (Claims 15–16).

- Set B: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38), 3. with described mean particle diameters for compounds of Formula Ia and Ib (Claims 39–42). 3. It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44). 4. The composition is a heterogenous suspension (Claim 45).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use in therapy and use in treating HIV infection and in the manufacture of a medicament for the treatment of HIV infection in a human (Claims 66–68).

It may be noted that that Claims 17 to 31 and Claims 46 to 58 appear to be identical to Claims 1 to 16 and Claims 33 to 45, respectively.

Thus, WO900 already discloses the claimed compounds and pharmaceutical compositions thereof, specifically with PEG200, PEG300 or PEG400, ethanol and water as well as with

P338 or P188 and other excipients (water, sodium chloride, acetate buffer), for treating HIV.

The applicant of WO559 has merely used routine experimentation to prepare and determine the characteristics of the formulations prepared using excipients already known in the art for HIV capsid inhibitors (WO900 as well as WO2018035359, WO2019035904 and WO2020018459 (Citations 1, 1A and 2.).

In light of the above, Claims 1 to 68 of the present Application, WO559, lack inventive step.