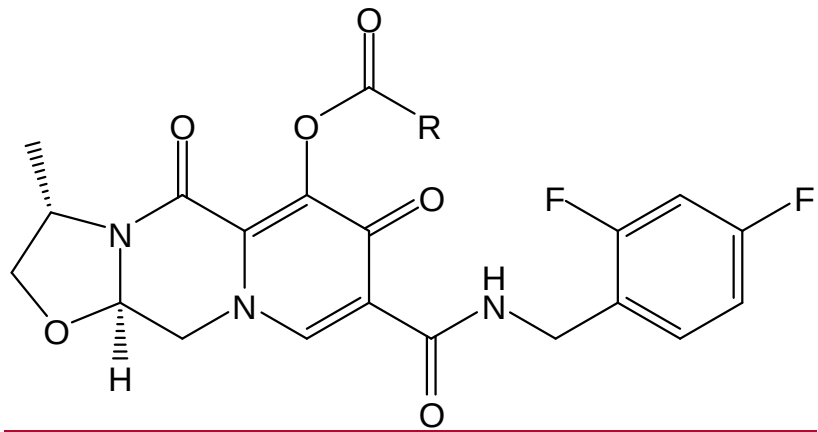
(Margolis, et al. (2017) Lancet 390(10101):1499-510; Markowitz, et al. (2017) Lancet HIV 4(8):331-340). Moreover, the maximal dosing interval is only 8 weeks. Recently, the administration of CAB LAP every 12 weeks has been tested with the aim of maintaining plasma CAB concentrations above 4 times protein-binding-adjusted 90% inhibitory concentration (4 × PA-IC_{90}, 660 ng/mL), a concentration demonstrated to be protective against new infections in macaques (Spreen, W.W. (2014) J. Acquir. Immune Defic. Syndr., 67(5):481-486; Andrews, et al. (2014) Science 343(6175):1151-1154; Andrews, et al. (2015) Sci. Transl. Med., 7(270) 270ra4; Radzio, et al. (2015) Sci. Transl. Med., 7(270) 270ra5-270ra5; Andrews, et al. (2016) AIDS 2016:461-467; Markowitz, et al. (2017) Lancet HIV 4(8):331-340; Spreen, et al. (2014) J. Acquir. Immune Defic. Syndr., 67(5):487-492). However, two-thirds of participants had faster than anticipated drug absorption leading to plasma drug concentrations below the targeted effective concentration of 4 × PA-IC_{90} at 12 weeks. Thus, ways to extend the dose interval beyond 8 weeks and reduce injection volumes to improve regimen adherence are greatly needed (Boyd, et al. (2017) Lancet 390(10101):1468-1470).

SUMMARY ~~OF THE INVENTION~~

In one aspect of the present disclosure, there is provided a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein R is a saturated linear aliphatic chain of a length of 17 carbons.

In another aspect of the present disclosure, there is provided a nanoparticle comprising a compound disclosed herein and a polymer or surfactant.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating an HIV infection in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use in therapy.

In accordance with the instant ~~invention~~disclosure, prodrugs of integrase inhibitors are provided. In a particular ~~embodiment~~example, the prodrug comprises an integrase inhibitor modified with an ester comprising an aliphatic or alkyl group (e.g., an aliphatic or alkyl comprising about 3 to about 30 carbons). In a particular ~~embodiment~~example, the aliphatic or alkyl group is the alkyl chain of a fatty acid or a saturated linear aliphatic chain, optionally substituted with at least one heteroatom. In a particular ~~embodiment~~example, the integrase inhibitor is selected from the group consisting of cabotegravir (CAB), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and bictegravir (BIC). Compositions comprising at least one prodrug of the instant ~~invention~~disclosure and at least one pharmaceutically acceptable carrier are also encompassed by the present ~~invention~~disclosure.

In accordance with another aspect of the instant ~~invention~~disclosure, nanoparticles comprising at least one prodrug of the instant ~~invention~~disclosure and at least one polymer or surfactant are provided. In a particular ~~embodiment~~example, the prodrug is crystalline. In a particular ~~embodiment~~example, the polymer or surfactant is an amphiphilic block copolymer such as an amphiphilic block copolymer comprising at least one block of

poly(oxyethylene) and at least one block of poly(oxypropylene) (e.g., poloxamer 407). The nanoparticle may comprise a polymer or surfactant linked to at least one targeting ligand. An individual nanoparticle may comprise targeted and non-targeted surfactants. In a particular ~~embodiment~~example, the nanoparticles have a diameter of about 100 nm to 1 μm. Compositions comprising at least one nanoparticle of the instant ~~invention~~disclosure and at least one pharmaceutically acceptable carrier are also encompassed by the present ~~invention~~disclosure.

In accordance with another aspect of the instant ~~invention~~disclosure, methods for treating, inhibiting, and/or preventing a disease or disorder in a subject in need thereof are provided. The methods comprise administering to the subject at least one prodrug or nanoparticle of the instant ~~invention~~disclosure, optionally within a composition comprising a pharmaceutically acceptable carrier. In a particular ~~embodiment~~example, the disease or disorder is a viral infection (e.g., a retroviral infection). In a particular ~~embodiment~~example, the method further comprises administering at least one further therapeutic agent or therapy for the disease or disorder, e.g., at least one additional anti-HIV compound.

BRIEF DESCRIPTIONS OF THE DRAWING

Figure 1A provides images of NM2CAB (top) and NCAB (bottom) nanoparticles as determined by scanning electron microscopy. Figure 1B provides graphs of NM2CAB nanoparticle stability at 25°C over the indicated periods of time. Particularly, nanoparticle zeta potential (top), polydispersity index (middle), and particle diameter (bottom) were determined by dynamic light scattering

Figure 2A provides a graph (top) of the drug uptake as measured by UPLC-UV/Vis by human monocyte derived macrophages (MDM) and a graph (bottom) of drug retention by MDM and collected at the indicated timepoints for intracellular drug analysis. Figure 2B provides a graph (top) of HIV-1 reverse transcriptase activity at the indicated concentration of drug and a graph (bottom) of HIV-1 reverse transcriptase activity in MDM treated with drug and challenged with HIV-1_{ADA} and measured at the indicated timepoints post-treatment. Figure 2C provides images of p24 stained MDM cells post-challenge.

Figure 3A provides a graph of plasma CAB levels after a single intramuscular (IM) dose of NCAB, NMCAB or NM2CAB in female NSG (NOD scid gamma mouse) mice. Administered dose was 45 mg CAB equivalents (eq) /

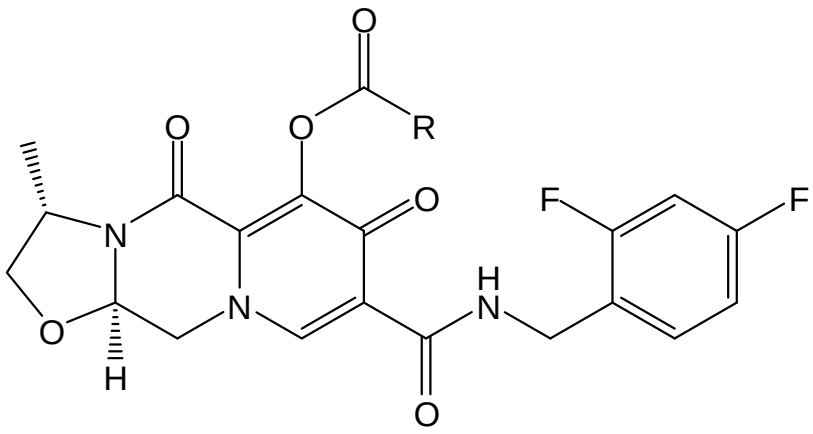
What is claimed is:

~~1. A prodrug of an integrase inhibitor, wherein said prodrug comprises an ester comprising an aliphatic or alkyl group conjugated to said integrase inhibitor, or a pharmaceutically acceptable salt thereof.~~

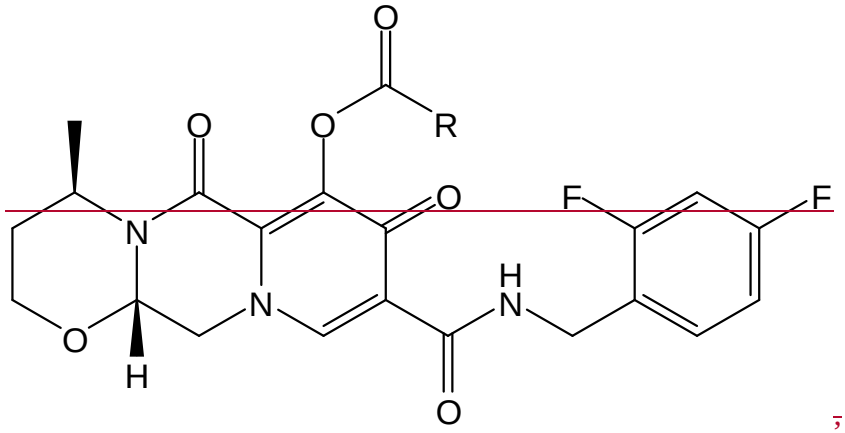
~~2. The prodrug of claim 1, wherein said integrase inhibitor is selected from the group consisting of cabotegravir (CAB), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), bictegravir (BIC), BI 224436, and MK-2048.~~

~~3. The prodrug of claim 1, wherein said integrase inhibitor is selected from the group consisting of cabotegravir (CAB), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), and bictegravir (BIC)~~

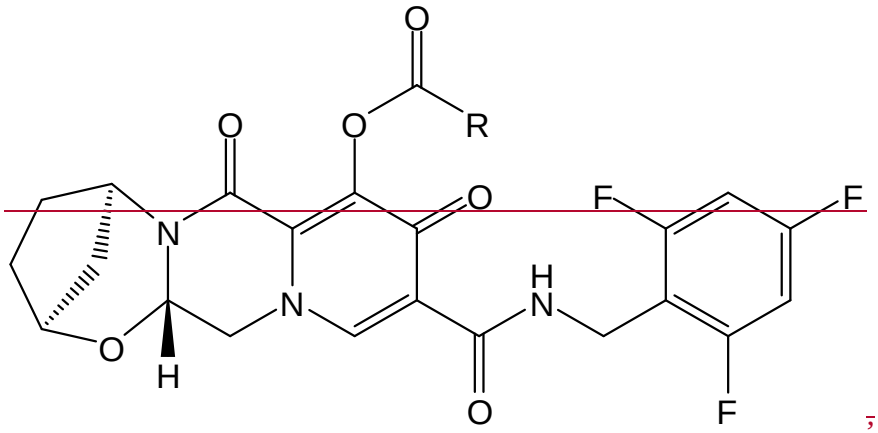
1~~4~~. A compound of formula (I)~~The prodrug of claim 1, wherein the prodrug is selected from the group consisting of~~:



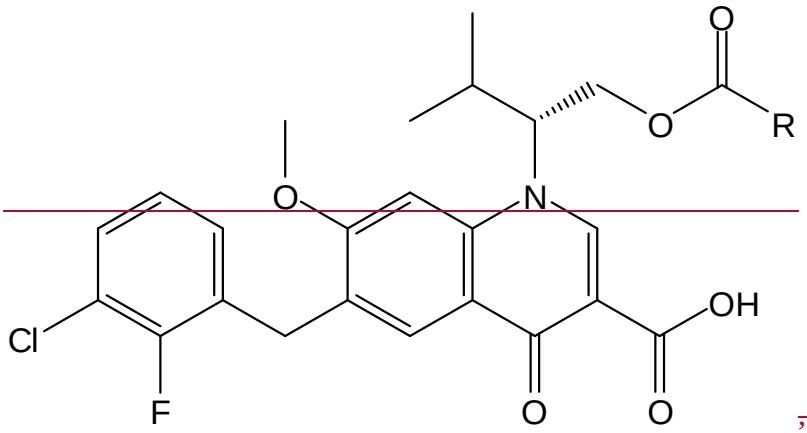
(I),



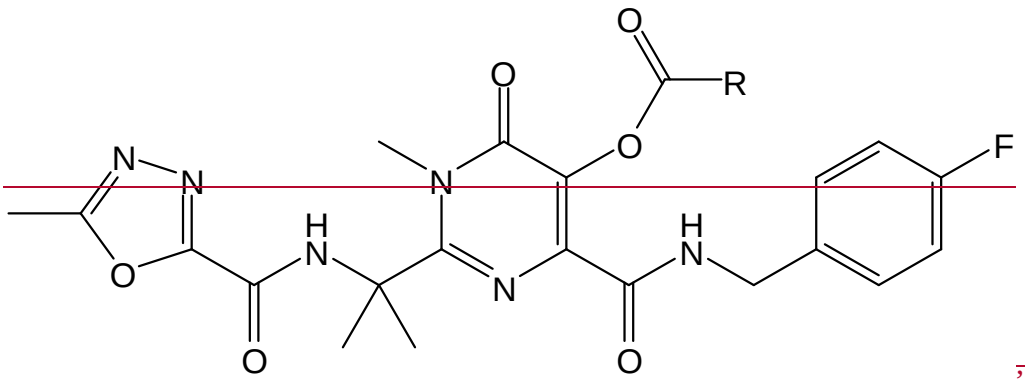
;



;



, and



;

~~wherein R is an optionally substituted aliphatic or alkyl,~~ or

~~———~~a pharmaceutically acceptable salt thereof,

wherein R is a saturated linear aliphatic chain of a length of 17 carbons.

~~5. The prodrug of claim 4, wherein R is the alkyl chain of a fatty acid.~~

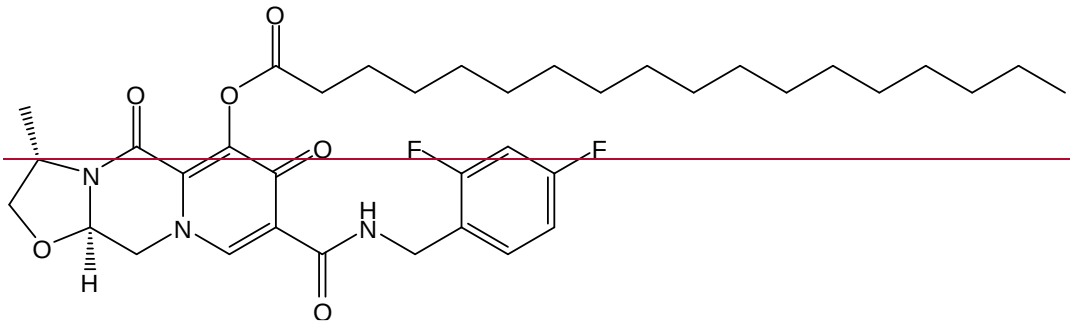
~~6. The prodrug of claim 4, wherein R has a main chain of at least 15 carbons.~~

~~7. The prodrug of claim 4, wherein R is a saturated linear aliphatic chain of a length of 15 to 19 carbons.~~

~~8. The prodrug of claim 4, wherein R is a saturated linear aliphatic chain of a length of 15 to 17 carbons.~~

~~9. The prodrug of claim 4, wherein R is a saturated linear aliphatic chain of a length of 17 carbons.~~

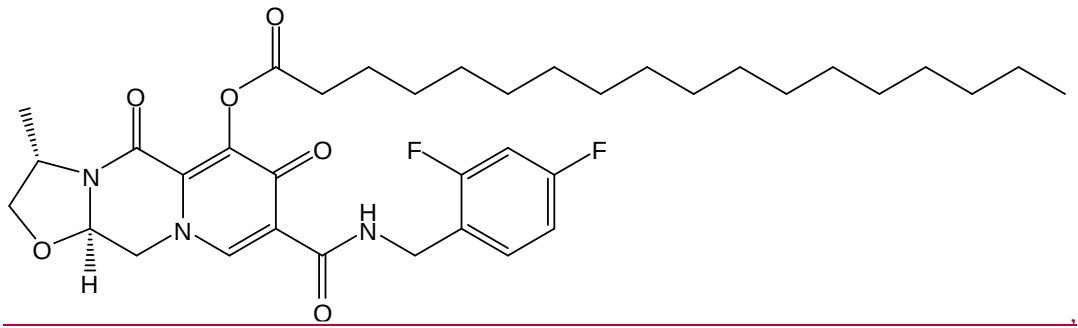
~~10. The prodrug of claim 1, wherein said prodrug is~~



~~or a pharmaceutically acceptable salt thereof.~~

2~~11~~. A nanoparticle comprising ~~at least one prodrug of any one~~a compound of claim~~s~~ 1~~-10~~ and a~~at least one~~ polymer or surfactant.

3~~12~~. The nanoparticle of claim 2~~11~~, wherein the compound~~said prodrug~~ is ~~crystalline~~



, or a pharmaceutically acceptable salt thereof, and the polymer or surfactant is P407.

~~13. The nanoparticle of claim 11, wherein said polymer or surfactant is an amphiphilic block copolymer.~~

~~14. The nanoparticle of claim 13, wherein said amphiphilic block copolymer comprises at least one block of poly(oxyethylene) and at least one block of poly(oxypropylene).~~

~~15. The nanoparticle of claim 11, wherein the polymer or surfactant is P407.~~

~~16. The nanoparticle of claim 11, wherein said nanoparticle further comprises a polymer or surfactant linked to at least one targeting ligand.~~

~~17. The nanoparticle of claim 11, wherein the diameter of the nanoparticle is about 100 nm to 1 μm.~~

4~~18~~. A pharmaceutical composition comprising a compound of claim 1 and a~~at least one nanoparticle of claim 11 and at least one~~ pharmaceutically acceptable carrier.

~~19. A composition comprising at least one prodrug of any one of claims 1-10 and at least one pharmaceutically acceptable carrier.~~

5~~20~~. Use of a pharmaceutical composition of claim 4 in the manufacture of a medicament~~A method~~ for treating an HIV infection~~, inhibiting, and/or preventing a disease or disorder~~ in a subject in need thereof~~, said method comprising administering to said subject a prodrug of claim 1 or a nanoparticle of claim 11~~.

6~~21~~. The use~~method~~ of claim 5~~20~~, wherein the pharmaceutical composition is to be administered via injection~~disease or disorder is a viral infection~~.

7~~22~~. The use~~method~~ of claim 5~~21~~, wherein the pharmaceutical composition is to be administered one time in a 3, 6, 9, 12, 18, or 24 month period~~disease or disorder is a retroviral infection~~.

~~23. The method of claim 21, wherein the viral infection is an HIV infection.~~

~~24. The prodrug of claim 1 or a nanoparticle of claim 11 for use in treating a disease or disorder.~~

8. The pharmaceutical composition of claim 4 for use in therapy.