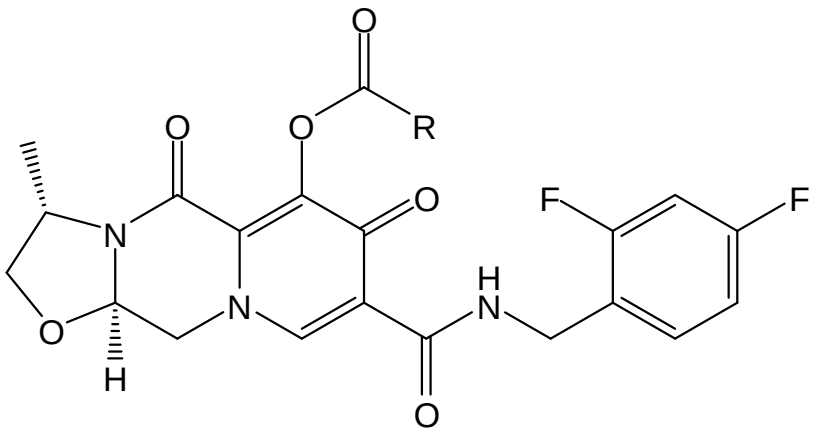
(Margolis, et al. (2017) Lancet 390(10101):1499-510; Markowitz, et al. (2017) Lancet HIV 4(8):331-340). Moreover, the maximal dosing interval is only 8 weeks. Recently, the administration of CAB LAP every 12 weeks has been tested with the aim of maintaining plasma CAB concentrations above 4 times protein-binding-adjusted 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

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 disclosure, prodrugs of integrase inhibitors are provided. In a particular 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 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 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 disclosure and at least one pharmaceutically acceptable carrier are also encompassed by the present disclosure.

In accordance with another aspect of the instant disclosure, nanoparticles comprising at least one prodrug of the instant disclosure and at least one polymer or surfactant are provided. In a particular example, the prodrug is crystalline. In a particular 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 example, the nanoparticles have a diameter of about 100 nm to 1 μm. Compositions comprising at least one nanoparticle of the instant disclosure and at least one pharmaceutically acceptable carrier are also encompassed by the present disclosure.

In accordance with another aspect of the instant 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 disclosure, optionally within a composition comprising a pharmaceutically acceptable carrier. In a particular example, the disease or disorder is a viral infection (e.g., a retroviral infection). In a particular 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

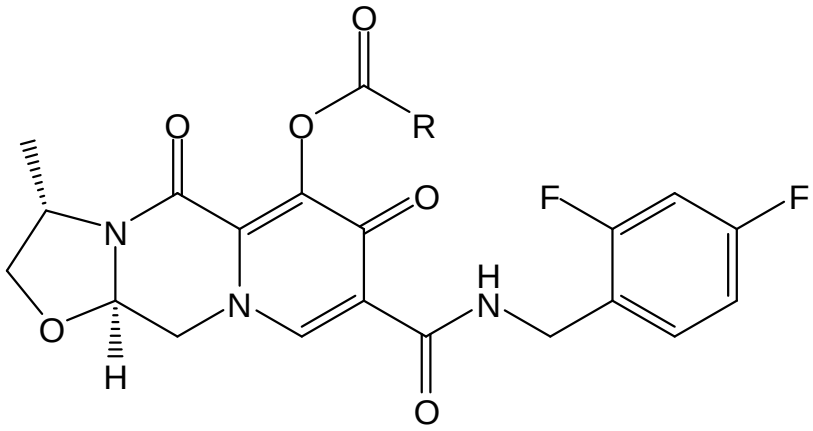
Figure 1A provides images of NM2CAB (top) and NCAB (bottom) nanoparticles as determined by scanning electron microscopy. Figure 1B provides graphs of NM2CAB nanoparticle stability at 25°C over the indicated periods of time. Particularly, nanoparticle zeta potential (top), polydispersity index (middle),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



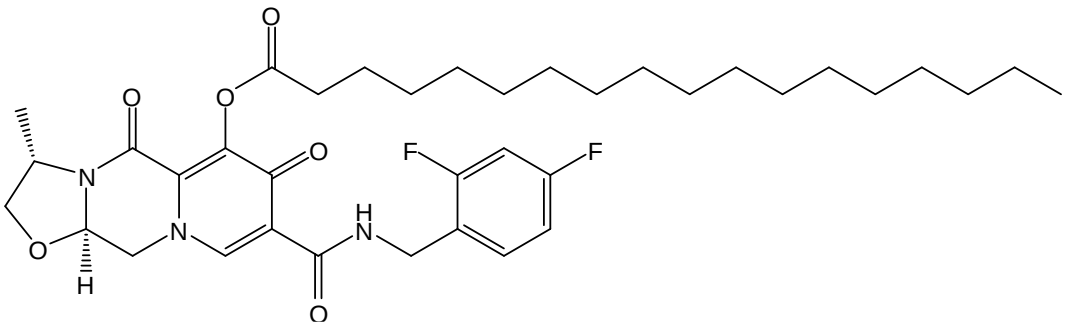
(I),

or a pharmaceutically acceptable salt thereof,

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

2. A nanoparticle comprising a compound of claim 1 and a polymer or surfactant.

3. The nanoparticle of claim 2, wherein the compound is



,

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

4. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

5. Use of a pharmaceutical composition of claim 4 in the manufacture of a medicament for treating an HIV infection in a subject in need thereof.

6. The use of claim 5, wherein the pharmaceutical composition is to be administered via injection.

7. The use of claim 5, wherein the pharmaceutical composition is to be administered one time in a 3, 6, 9, 12, 18, or 24 month period.

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