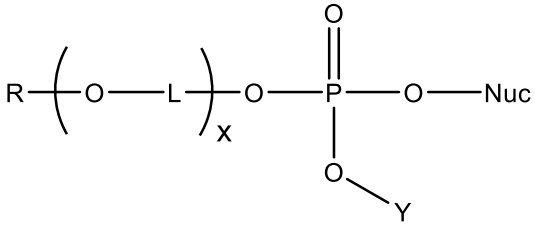
classes if long-acting ART is to be of widespread use in patient populations vulnerable to different toxicities and with viruses of differing drug susceptibility.

There remains a need for pharmaceutical formulations that can be delivered in various ways, such as intramuscularly. There also remains a need for pharmaceutical formulations that are long-acting, such as formulations that can provide effective plasma levels for extended periods after infrequent administration, such as once monthly.

Summary

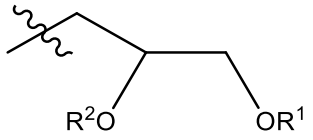
Provided herein are compounds, such as antiviral prodrugs, and pharmaceutical formulations that overcome one or more of the disadvantages of currently used drugs and/or formulations. For example, examples of the compounds and pharmaceutical formulations provided herein include orally useful antiviral prodrugs that may specifically target organs where viral replication is maximal and be conveniently administered at scale in any disease stage. For oral use and enhanced lung exposure, some examples of the prodrugs of RVn or formulations provided herein can accomplish one or more of the following: 1) kinase bypass of the first nucleoside phosphorylation, 2) provide increased oral bioavailability, 3) deliver antivirally significant concentrations to lung and gastrointestinal tract and formulations which may provide for sustained levels in plasma for 5 to 30 days following a single injection. Also provided herein are methods for the synthesis and antiviral evaluation of the compounds, including novel lipophilic prodrugs of RVn-monophosphate that are substantially more active than remdesivir in Vero E6 cells infected with SARS-CoV-2. Not wishing to be bound by any particular theory, examples of the compounds herein are prodrugs that may allow earlier and/or more effective treatment at the time of diagnosis of SARS-CoV-2 infection. The prodrugs herein may represent an approach that may be able to target the antiviral to the lung and away from the liver where remdesivir's major dose limiting is directed.

Compounds, including antiviral prodrugs, are provided herein. The compounds have a structure according to formula (I):



formula (I);

wherein Nuc is selected from the group consisting of an antiviral nucleoside and an antiviral nucleoside analog; Y is independently selected from the group consisting of hydrogen, a C_1-C_{30} hydrocarbyl, a pharmaceutically acceptable cation, and a covalent bond to a carbon atom of a five-carbon sugar moiety of the antiviral nucleoside or the antiviral nucleoside analog; x is 0 or 1; L is independently a C_1-C_{30} hydrocarbyl (such as a C_1-C_6 hydrocarbyl); and R is independently selected from the group consisting of a C_{10}-C_{30} hydrocarbyl and a substituent of formula (A);



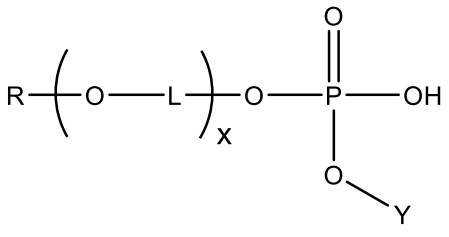
formula (A),

wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1-C_{30} hydrocarbyl.

Pharmaceutical formulations are provided. The pharmaceutical formulations include an oil and one or more compounds described herein. The pharmaceutical formulations may be formulated for injection, such as intramuscular injection or subcutaneous injection. The pharmaceutical formulations may be orally bioavailable.

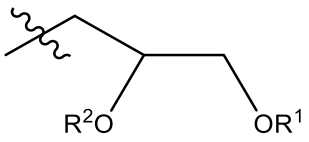
Methods of treatment are provided, such as methods for treating a virus (e.g., coronavirus), including virus infections in mammals. The methods include administering an effective amount of a compound described herein, or a pharmaceutical formulation described herein.

Methods of producing a compound, such as a prodrug, are provided. The methods include (i) providing a compound of formula (a) –



formula (a);

(ii) providing a compound of formula (b) –

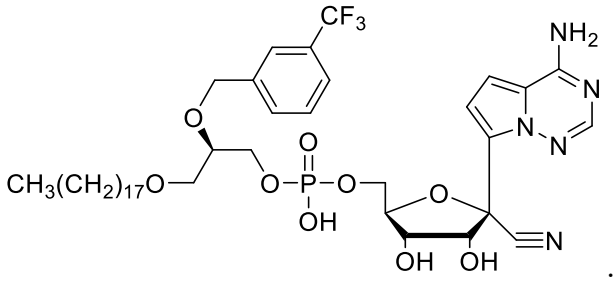


formula (A),

wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1-C_{30} hydrocarbyl. The methods may include performing an intramolecular esterification reaction of a product, such as a phosphodiester, to form a cyclic phosphate, such as a 3′,5′-cyclic phosphate.

Methods of producing a drug triphosphate also are provided. The methods include providing a plurality of cells, contacting the plurality of cells with an amount of a drug, incubating the plurality of cells and the amount of the drug for period effective to form the drug triphosphate.

In one aspect, the present disclosure provides a compound of the following formula or a pharmaceutically acceptable salt thereof:



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Additional aspects will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the aspects described herein. The advantages described herein may be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

Brief Description of the Drawings

FIG. 1A—FIG. 1F depict concentration-response curves for ODBG-P-RVn, ODE-P-RVn, and HDP-P-RVn (**4b**), remdesivir (RDV), and remdesivir nucleoside (RVn) for SARS-CoV-2 infection in Vero E6 cells in two separate experiments performed in duplicate.

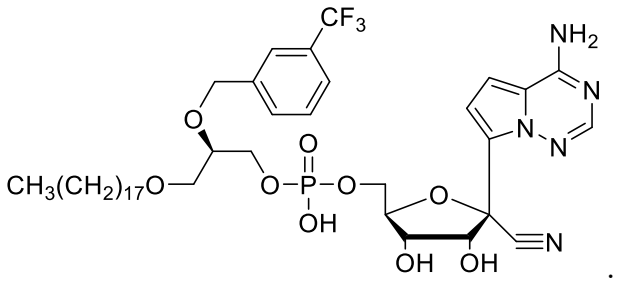
FIG. 2 depicts relative viabilities of embodiments of treated Vero E6 cells, as measured by CellTiter-Glo luminescent cell viability assay.

FIG. 3 depicts LC/MS/MS analysis of cells that were centrifuged at 1200 rpm for 10 minutes, diluent aspirated, and resuspended in 250 μL of methanol/distilled water (70/30).

FIG. 4A and **FIG. 4B** depict plasma levels of ODBG-P-RVn (**FIG. 4A**) and RVn (**FIG. 4B**) in a seven day oral pharmacokinetic study in Syrian hamsters.

Claims:

1. A compound of the following formula or a pharmaceutically acceptable salt thereof:



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