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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 September 2023 (07.09.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/167938 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *C07F 9/38* (2006.01)
A61P 31/14 (2006.01) *A61K 31/53* (2006.01)

(21) International Application Number:
PCT/US2023/014293

(22) International Filing Date:
01 March 2023 (01.03.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/315,919 02 March 2022 (02.03.2022) US
63/413,748 06 October 2022 (06.10.2022) US

(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) Inventors: **CHUN, Byoung-Kwon**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **KALLA, Rao V.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US). **MACKMAN, Richard L.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(74) Agent: **KING, Annie J.** et al.; FISH & RICHARDSON P.C., P. O. Box 1022, Minneapolis, Minnesota 55440-1033 (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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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).

Published:
— *with international search report (Art. 21(3))*

(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF VIRAL INFECTIONS

(57) Abstract: Compounds and methods of using said compounds, singly or in combination with additional agents, and salts or pharmaceutical compositions of said compounds for the treatment of viral infections are disclosed.

WO 2023/167938 A1

COMPOUNDS AND METHODS FOR TREATMENT OF VIRAL INFECTIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 63/315,919, filed on March 2, 2022, and U.S. Provisional Application No. 63/413,748, filed on October 6, 2022. The entire contents of these applications are incorporated herein by reference in their entirety.

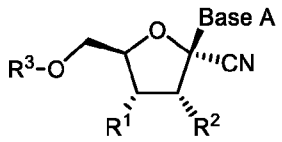
BACKGROUND

[0002] There is a need for compounds and methods for treating viral infections, for example *paramyxoviridae*, *pneumoviridae*, *picornaviridae*, *flaviviridae*, *filoviridae*, *arenaviridae*, *orthomyxovirus*, and *coronaviridae* infections. The present disclosure addresses these and other needs.

[0003] The oral route is a preferred route for daily drug administration, due to its advantages, such as non-invasiveness, patient compliance, and convenience of drug administration. Nevertheless, oral administration can be limited due to poor physicochemical properties of the drug molecule, including low aqueous solubility between pH2 and pH7, instability, low permeability, and rapid metabolism, all of which can combine to result in low and irregular oral bioavailability. Oral bioavailability (F%) is the fraction of an oral administered drug that reaches systemic circulation relative to the same dose delivery by intravenous administration. After intravenous administration, a drug is directly and fully available in the bloodstream and can be distributed via systemic circulation to the point where a pharmacological effect takes place. If a drug is administered orally, it has to survive the intestinal fluid, cross further barriers such as the gastero-intestinal (GI) cell layer and then the liver in order to reach the systemic circulation, which can significantly reduce the amount of administered drug that reaches the bloodstream. Oral bioavailability is therefore an important property in drug design and development. A high oral bioavailability reduces the required amount of an administered drug that would be necessary to achieve a desired pharmacological effect and therefore could reduce the risk of side-effects and toxicity during the absorption process. The present disclosure also provides compounds with combined solubility, stability and permeability properties leading to improved oral bioavailabilty.

SUMMARY

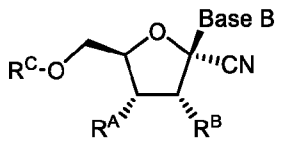
[0004] The instant disclosure provides a compound of Formula A:



Formula A

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and Base A are defined herein.

[0005] Also provided herein is a compound of Formula B:



Formula B

or a pharmaceutically acceptable salt thereof, wherein R^A, R^B, R^C, and Base B are defined herein.

[0006] Also provided herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula A or Formula B), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0007] Also provided herein is a method of treating or preventing a viral infection in a human in need thereof, wherein the method comprises administering to the human a compound disclosed herein (e.g., a compound of Formula A or Formula B), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

[0008] Also provided herein is a use of a compound disclosed herein (e.g., a compound of Formula A or Formula B), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a viral infection in a human in need thereof.

[0009] Also provided herein is a composition comprising a compound described herein (e.g., a compound of Formula A or Formula B), or a pharmaceutically acceptable salt thereof, for use in treatment or prevention of a viral infection in a human in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0010] The invention relates generally to methods and compounds for treating or preventing viral infections, for example *paramyxoviridae*, *pneumoviridae*, *picornaviridae*, *flaviviridae*, *filoviridae*, *arenaviridae*, *orthomyxovirus*, and *coronaviridae* infections.

II. Definitions

[0011] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0012] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} alkyl), 1 to 8 carbon atoms (*i.e.*, C_1-C_8 alkyl), 1 to 6 carbon atoms (*i.e.*, C_1-C_6 alkyl), or 1 to 3 carbon atoms (*i.e.*, C_1-C_3 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (*n*-Pr, *n*-propyl, -$CH_2CH_2CH_3$), 2-propyl (*i*-Pr, *i*-propyl, -$CH(CH_3)_2$), 1-butyl (*n*-Bu, *n*-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (*s*-Bu, *s*-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -$C(CH_3)_3$), 1-pentyl (*n*-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), and 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$.

[0013] "Alkenyl" refers to an aliphatic group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (*i.e.*, C_{2-20} alkenyl), 2 to 8 carbon atoms (*i.e.*, C_{2-8} alkenyl), 2 to 6 carbon atoms (*i.e.*, C_{2-6} alkenyl), or 2 to 4 carbon atoms (*i.e.*, C_{2-4} alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0014] "Alkynyl" refers to an aliphatic group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (*i.e.*, C_{2-20} alkynyl), 2 to 8 carbon atoms (*i.e.*, C_{2-8} alkynyl), 2 to 6 carbon atoms (*i.e.*, C_{2-6} alkynyl), or 2 to 4 carbon atoms (*i.e.*, C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0015] "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} haloalkyl), 1 to 12 carbon atoms (*i.e.*, C_1-C_{12} haloalkyl), 1 to 8 carbon atoms (*i.e.*, C_1-C_8 haloalkyl), 1 to 6 carbon atoms (*i.e.*, C_1-C_6 alkyl) or 1 to 3 carbon atoms (*i.e.*, C_1-C_3 alkyl). Examples of suitable haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, and the like.

[0016] "Alkoxy" refers to a group of formula -O-alkyl. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), butoxy (e.g., *n*-butoxy and *tert*-butoxy), and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0017] "Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

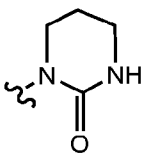
[0018] "Aryloxy" refers to a group of formula -O-aryl. Example alkoxy groups include, but are not limited to, phenoxy and naphthyloxy, and the like. In some embodiments, the aryl group has 6 or 10 carbon atoms.

[0019] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring atoms (*i.e.*, 1 to 20 membered heteroaryl), 3 to 12 ring atoms (*i.e.*, 3 to 12 membered heteroaryl) or 3 to 8 carbon ring atoms (3 to 8 membered heteroaryl) or 5 to 6 ring atoms (5 to 6 membered heteroaryl). Examples of heteroaryl groups include pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Heteroaryl does not encompass or overlap with aryl as defined above.

[0020] "Carbocyclyl" or "carbocyclic ring" refers to a non-aromatic hydrocarbon ring consisting of carbon and hydrogen atoms, having from three to twenty carbon atoms, in certain embodiments having from three to fifteen carbon atoms, in certain embodiments having from three to ten carbon atoms, from three to eight carbon atoms, from three to seven carbon atoms, or from 3 to 6 carbon atoms and which is saturated or partially unsaturated and attached to the rest of the molecule by a single bond. Carbocyclic rings include, for example, cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, 1,3-cyclohexadiene, 1,4-cyclohexadiene, cycloheptane, cycloheptene, and cyclooctane. Carbocyclic rings include cycloalkyl groups.

[0021] "Cycloalkyl" refers to a saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[0022] "Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; *Principles of Modern Heterocyclic Chemistry* (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "*The Chemistry of Heterocyclic Compounds, A Series of Monographs*" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. For example, "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). As used herein, a heterocycle or heterocyclyl has from 3 to 20 ring atoms, 3 to 12 ring atoms, 3 to 10 ring atoms, 3 to 8 ring atoms, or 3 to 6 ring atoms. The terms "heterocycle" or "heterocyclyl" includes saturated rings and partially unsaturated rings. Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



. Example heterocycles include, but are not limited to, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, and piperidinyl.

[0023] The term "optionally substituted" in reference to a particular moiety of the compound described herein such as the compound of Formula A or Formula B(e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by the listed substituents.

[0024] Unless otherwise specified, the carbon atoms of the compounds described herein (e.g., the compounds of Formula A or Formula B) are intended to have a valence of four. If in some chemical structure representations, carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen.

[0025] The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, or inhibiting the progress of the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0026] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. The compounds and compositions disclosed herein may, in some embodiments, be administered to a subject (including a human) who is at risk of having the disease or condition. As used herein, the terms "preventing" and "prevention" encompass the administration of a compound, composition, or pharmaceutically acceptable salt according to the embodiments disclosed herein pre- or post-exposure of the individual to a virus, but before the appearance of symptoms of the viral infection, and/or prior to the detection of the virus in the blood. The terms also refer to prevention of the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood. The terms include both pre-exposure prophylaxis (PrEP), as well as post-exposure prophylaxis (PEP) and event driven or "on demand" prophylaxis. The terms also refer to prevention of perinatal transmission of a virus from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. The terms also refer to prevention of transmission of a virus through blood transfusion.

[0027] The term "therapeutically effective amount", as used herein, is the amount of compound of Formula A or Formula B present in a composition described herein that is needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated

physiological response or desired biological effect when such a composition is administered by the chosen route of administration. The precise amount will depend upon numerous factors, for example the particular compound of Formula A or Formula B, the specific activity of the composition, the delivery device employed, the physical characteristics of the composition, its intended use, as well as patient considerations such as severity of the disease state, patient cooperation, etc., and can readily be determined by one skilled in the art based upon the information provided herein.

III. Compounds

[0028] Any reference to the compounds of the invention described herein also includes a reference to a pharmaceutically acceptable salt thereof. Examples of pharmaceutically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+.

[0029] In some embodiments, R is H, (C_1-C_8) alkyl, (C_2-C_8)alkenyl, (C_2-C_8) alkynyl, C_6–C_{20} aryl, or C_2–C_{20} heterocyclyl.

[0030] For therapeutic use, salts of active ingredients of the compounds of the invention will be pharmaceutically acceptable, i.e., they will be salts derived from a pharmaceutically

acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether or not derived form a pharmaceutically acceptable acid or base, are within the scope of the present invention.

[0031] It is also to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

[0032] It is to be noted that all enantiomers, diastereomers, racemic mixtures, tautomers, polymorphs, and pseudopolymorphs of compounds within the scope of Formula A and Formula B, and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

[0033] The compounds of the invention, exemplified by Formula A and Formula B may have chiral centers, e.g., chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through appropriate techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0034] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds* (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of

the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

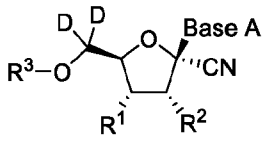
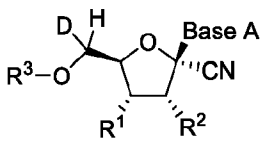
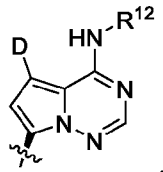
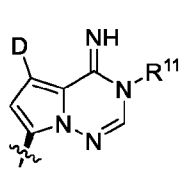
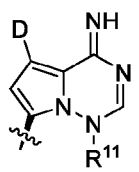
[0035] The compounds of the invention may also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

[0036] Any formula or structure given herein, including Formula A and Formula B compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

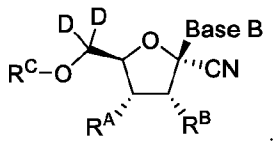
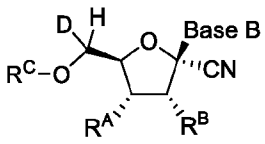
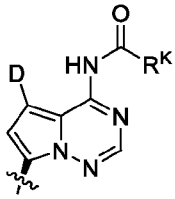
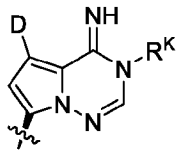
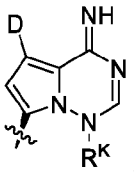
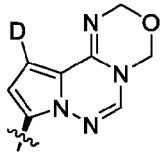
[0037] The disclosure also includes compounds described herein (e.g., compounds of Formula A and Formula B) in which from 1 to x hydrogens attached to a carbon atom is/are replaced by deuterium, in which x is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the

half-life of any compound described herein (e.g., compounds of Formula A and Formula B) when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). In view of the present disclosure, such compounds are synthesized by means known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0038] Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula A or Formula B.

[0039] In some embodiments, the carbon bonded to the 5 position on the tetrahydrofuranyl ring of Formula A is substituted with one or two deuterium atoms. In some embodiments, the compound of Formula A is . In some embodiments, the compound of Formula A is . In some embodiments, a carbon of the Base A of Formula A is substituted with one or more deuterium atoms. In some embodiments, Base A is , , or . In some embodiments, a carbon on R^{12} of the Base of Formula A is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^{11} of the Base of Formula A is substituted with one or more deuterium atoms. In

some embodiments, a carbon on R^1 of Formula A is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^2 of Formula A is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^3 of Formula A is substituted with one or more deuterium atoms.

[0040] In some embodiments, the carbon bonded to the 5 position on the tetrahydrofuranyl ring of Formula B is substituted with one or two deuterium atoms. In some embodiments, the compound of Formula B is . In some embodiments, the compound of Formula B is . In some embodiments, a carbon of the Base B of Formula B is substituted with one or more deuterium atoms. In some embodiments, Base B is , , , or . In some embodiments, a carbon on R^K of the Base of Formula B is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^A of Formula B is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^B of Formula B is substituted with one or more deuterium atoms. In some embodiments, a carbon on R^C of Formula B is substituted with one or more deuterium atoms.

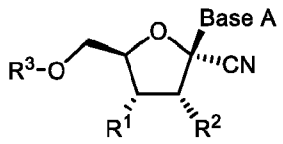
[0041] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0042] Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

[0043] Wavy lines, ~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

IV. Compounds

[0044] In certain embodiments, provided herein is a compound of Formula A:



Formula A

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are taken together to form -OC(=O)O-, -OCHR^{6}O-, or -OP(=O)(OR^{14})O-;

R^6 is H, C_1-C_6 alkyl, C_6-C_{10} aryloxy, or C_1-C_6 alkoxy;

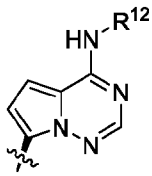
R^3 is -C(=O)R^7;

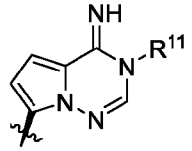
R^7 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein each C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^7 is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^8, -NR^{9}R^{10}, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

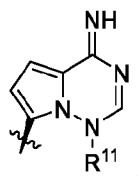
each R^8 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^9 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^{10} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

Base A is 

, 

, or 

;

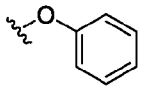
R^{11} is C_1-C_6 alkyl optionally substituted with -OP(=O)(OH)$_2$;

R^{12} is H, C_1-C_6 alkyl, -C(=O)R^{13} or -C(=O)OR^{13};

each R^{13} is independently H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{13} is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl, wherein phenyl is optionally substituted with -OP(=O)(OH)(OR^{14}); and

each R^{14} is independently H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

[0045] In some embodiments, R^1 and R^2 are taken together to form -OC(=O)O- or -$OCHR^6$O-. In some embodiments, R^1 and R^2 are taken together to form -OC(=O)O-. In some embodiments, R^1 and R^2 are taken together to form -$OCHR^6$O-. In some embodiments, R^1 and R^2 are taken together to form -$OCH(OCH_3)$O-. In some embodiments, R^1 and R^2 are taken together to form -OP(=O)(OR^{14})O-. In some embodiments, R^1 and R^2 are taken together to form -OP(=O)(OH)O-. In some embodiments, R^1 and R^2 are taken together to form -OC(=O)O-, -$OCH(OCH_3)$O-, or -OP(=O)(OH)O-. In some embodiments, R^1 and R^2 are taken together to form -OC(=O)O- or -$OCH(OCH_3)$O-.

[0046] In some embodiments, R^6 is H. In some embodiments, R^6 is C_1-C_6 alkyl. In some embodiments, R^6 is C_1-C_3 alkyl. In some embodiments, R^6 is -CH_3. In some embodiments, R^6 is C_6-C_{10} aryloxy. In some embodiments, R^6 is . In some embodiments, R^6 is C_1-C_6 alkoxy. In some embodiments, R^6 is C_1-C_3 alkoxy. In some embodiments, R^6 is -OCH_2CH_3, -$OCH(CH_3)_2$, or -OCH_3.In some embodiments, R^6 is -OCH_3.

[0047] In some embodiments, R^7 is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein each C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^7 is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^8, -NR^9R^{10}, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

[0048] In some embodiments, R^7 is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^8, -NR^9R^{10}, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

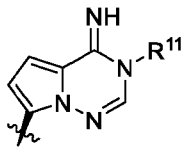
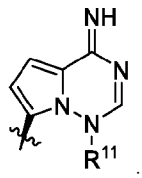
[0049] In some embodiments, R^7 is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^8$, $-NR^9R^{10}$, and phenyl.

[0050] In some embodiments, R^8 is H. In some embodiments, R^8 is C_1-C_6 alkyl. In some embodiments, R^8 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^8 is $-CH_3$. In some embodiments, R^8 is C_1-C_6 haloalkyl. In some embodiments, R^8 is C_3-C_6 cycloalkyl.

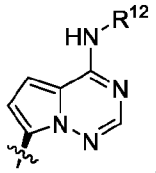
[0051] In some embodiments, R^9 is H. In some embodiments, R^9 is C_1-C_6 alkyl. In some embodiments, R^9 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^9 is $-CH_3$. In some embodiments, R^9 is C_1-C_6 haloalkyl. In some embodiments, R^9 is C_3-C_6 cycloalkyl.

[0052] In some embodiments, R^{10} is H. In some embodiments, R^{10} is C_1-C_6 alkyl. In some embodiments, R^{10} is $-CH_3$. In some embodiments, R^{10} is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^{10} is C_1-C_6 haloalkyl. In some embodiments, R^{10} is C_3-C_6 cycloalkyl.

[0053] In some embodiments, R^7 is C_1-C_8 alkyl. In some embodiments, R^7 is C_1-C_6 alkyl. In some embodiments, R^7 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$. In some embodiments, R^7 is $-CH(CH_3)_2$.

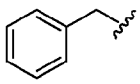
[0054] In some embodiments, Base A is . In some embodiments, Base A is .

[0055] In some embodiments, R^{11} is C_1-C_3 alkyl substituted with $-OP(=O)(OH)_2$. In some embodiments, R^{11} is $-(CH_2)OP(=O)(OH)_2$.

[0056] In some embodiments, Base A is .

[0057] In some embodiments, R^{12} is $-C(=O)R^{13}$. In some embodiments, R^{12} is $-C(=O)OR^{13}$.

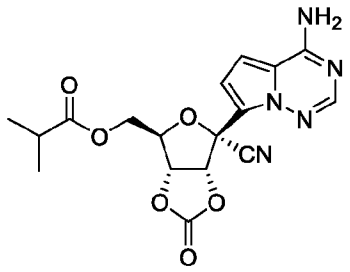
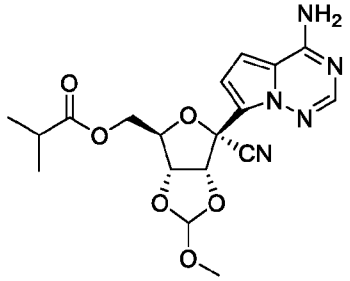
[0058] In some embodiments, R^{13} is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl; wherein phenyl is optionally substituted with $-OP(=O)(OH)(OR^{14})$.

[0059] In some embodiments, R^{14} is H. In some embodiments, R^{14} is H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some embodiments, R^{14} is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some embodiments, R^{14} is C_1-C_3 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some embodiments, R^{14} is C_1-C_3 alkyl substituted with one phenyl. In some embodiments, R^{14} is .

[0060] In some embodiments, R^{13} is H. In some embodiments, R^{13} is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl. In some embodiments, R^{13} is C_1-C_8 alkyl. In some embodiments, R^{13} is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$. In some embodiments, R^{13} is $-CH_2CH(CH_3)_2$ or $-(CH_2)_2CH_3$.

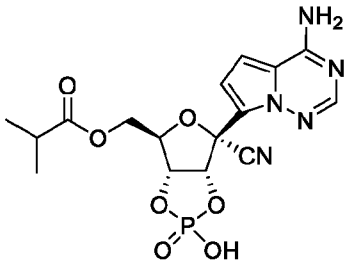
[0061] In some embodiments, R^{12} is H. In some embodiments, R^{12} is C_1-C_6 alkyl. In some embodiments, R^{12} is $-C(=O)(CH_2)_2CH_3$. In some embodiments, R^{12} is $-C(=O)OCH_2CH(CH_3)_2$. In some embodiments, R^{12} is $-C(=O)OCH_2CH(CH_3)_2$ or $-C(=O)(CH_2)_2CH_3$.

[0062] In some embodiments, the compound of Formula A is

Compound 3	
Compound 4	

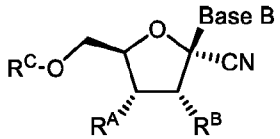
or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the compound of Formula A is

Compound 12	

or a pharmaceutically acceptable salt thereof.

[0064] Also provided herein is a compound of Formula B:



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^A is -OH, -OC(=O)R^D, or -OC(=O)OR^D;

R^B is -OH, -OC(=O)R^E, or -OC(=O)OR^E; or

R^A and R^B are taken together to form -OC(=O)O- or –OCHR^FO-;

R^F is H, C_1-C_6 alkyl or C_6-C_{10} aryl;

R^C is -C(=O)R^G;

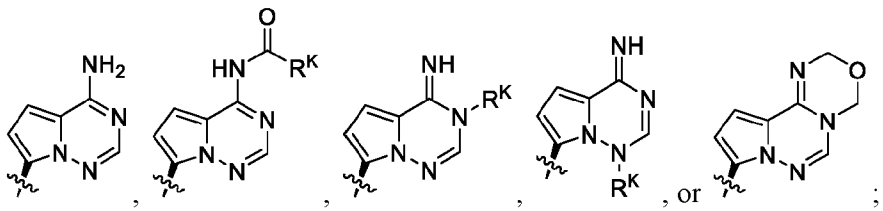
R^D and R^E are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^D and R^E are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

R^G is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)(OH)(OR^L), and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

each R^H is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

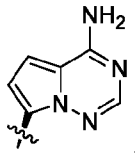
each R^I is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^J is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

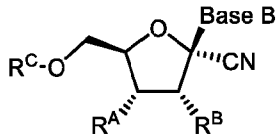
Base B is , , , , or ;

R^K is C_6-C_{10} aryl, -O-C_6-C_{10} aryl, -O-C_1-C_{10} alkyl, or C_1-C_{10} alkyl optionally substituted with -OP(=O)(OH)(OR^L); and

R^L is H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl of R^L is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl;

provided when Base B is , R^G is C_1-C_8 alkyl substituted with one, two or three -OP(=O)(OH)(OR^L).

[0065] Also provided herein is a compound of Formula B:



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^A is -OH, -OC(=O)R^D, or -OC(=O)OR^D;

R^B is -OH, -OC(=O)R^E, or -OC(=O)OR^E; or

R^A and R^B are taken together to form -OC(=O)O- or –OCHR^FO-;

R^F is H, C_1-C_6 alkyl or C_6-C_{10} aryl;

R^C is -C(=O)R^G;

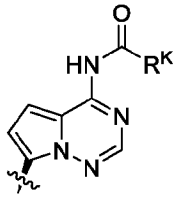
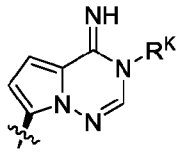
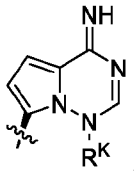
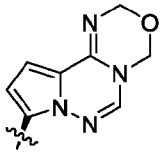
R^D and R^E are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^D and R^E are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

R^G is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)(OH)(OR^L), and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

each R^H is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^I is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^J is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

Base B is  ,  ,  , or  ;

R^K is C_6-C_{10} aryl, -O-C_6-C_{10} aryl, -O-C_1-C_{10} alkyl, or C_1-C_{10} alkyl optionally substituted with -OP(=O)(OH)(OR^L); and

R^L is H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl of R^L is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

[0066] In some embodiments, R^A is -OC(=O)R^D. In some embodiments, R^A is -OC(=O)OR^D.

[0067] In some embodiments, R^B is -OC(=O)R^E. In some embodiments, R^B is -OC(=O)OR^E.

[0068] In some embodiments, R^A is -OC(=O)R^D and R^B is -OC(=O)R^E. In some embodiments, R^A is -OH, and R^B is -OC(=O)R^E or -OC(=O)OR^E. In some embodiments, R^A is -OC(=O)R^D or -OC(=O)OR^D, and R^B is -OH.

[0069] In some embodiments, R^D is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^4 are each, independently, optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)$(OH)_2$, C_3-C_8 carbocyclyl and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl. In some embodiments, R^D is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)$(OH)_2$, C_3-C_8 carbocyclyl and phenyl. In some embodiments, R^D is C_1-C_8 alkyl. In some embodiments, R^D is C_1-C_6 alkyl. In some embodiments, R^D is C_1-C_3 alkyl. In some embodiments, R^D is -CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, -$CH(CH_3)_2$, -$(CH_2)_3CH_3$, or -$C(CH_3)_3$. In some embodiments, R^D is -CH_3 or -$CH(CH_3)_2$.

[0070] In some embodiments, R^E is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^4 are each, independently, optionally substituted with one, two, or three substituents independently selected from the group

consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)_2$, C_3-C_8 carbocyclyl and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl. In some embodiments, R^E is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)_2$, C_3-C_8 carbocyclyl and phenyl. In some embodiments, R^E is C_1-C_8 alkyl. In some embodiments, R^E is C_1-C_6 alkyl. In some embodiments, R^E is C_1-C_3 alkyl. In some embodiments, R^E is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$. In some embodiments, R^E is $-CH_3$ or $-CH(CH_3)_2$.

[0071] In some embodiments, R^A is -OH. In some embodiments, R^B is -OH. In some embodiments, R^A and R^B are both -OH. In some embodiments, R^A is OH, $OC(O)CH(CH_3)_2$, or $OC(O)CH_3$, and R^B is OH, $OC(O)CH(CH_3)_2$, or $OC(O)CH_3$. In some embodiments, both R^A and R^B are $OC(O)CH_3$.

[0072] In some embodiments, R^A and R^B are taken together to form -OC(=O)O-. In some embodiments, R^A and R^B are taken together to form $-OCHR^FO$-.

[0073] In some embodiments, R^F is H. In some embodiments, R^F is C_1-C_6 alkyl. In some embodiments, R^F is C_6-C_{10} aryl.

[0074] In some embodiments, R^G are each independently C_3-C_8 carbocyclyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

[0075] In some embodiments, R^G are each independently C_6-C_{10} aryl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

[0076] In some embodiments, R^G are each independently 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano,

$-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

[0077] In some embodiments, R^G are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

[0078] In some embodiments, R^G are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl.

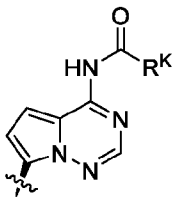
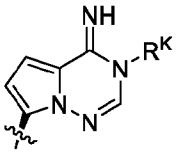
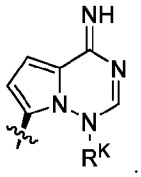
[0079] In some embodiments, R^G is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

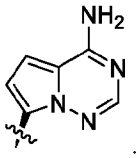
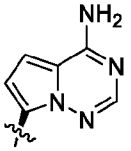
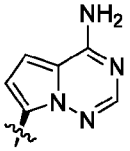
[0080] In some embodiments, R^G is C_1-C_8 alkyl. In some embodiments, R^G is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$. In some embodiments, R^G is C_1-C_4 alkyl. In some embodiments, R^G is $-(CH_2)_2CH_3$ and $-CH(CH_3)_2$. In some embodiments, R^G is $-CH(CH_3)_2$. In some embodiments, R^G is H. In some embodiments, R^G is $-(CH_2)OP(=O)(OH)_2$.

[0081] In some embodiments, R^H is H. In some embodiments, R^H is C_1-C_6 alkyl. In some embodiments, R^H is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^H is $-CH_3$. In some embodiments, R^H is C_1-C_6 haloalkyl. In some embodiments, R^H is C_3-C_6 cycloalkyl.

[0082] In some embodiments, R^I is H. In some embodiments, R^I is C_1-C_6 alkyl. In some embodiments, R^I is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^I is $-CH_3$. In some embodiments, R^I is C_1-C_6 haloalkyl. In some embodiments, R^I is C_3-C_6 cycloalkyl.

[0083] In some embodiments, R^J is H. In some embodiments, R^J is C_1-C_6 alkyl. In some embodiments, R^J is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, R^J is $-CH_3$. In some embodiments, R^J is C_1-C_6 haloalkyl. In some embodiments, R^J is C_3-C_6 cycloalkyl.

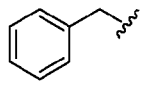
[0084] In some embodiments, Base B is . In some embodiments, Base B is . In some embodiments, Base B is .

[0085] In some embodiments, Base B is . In some embodiments, Base B is  and R^G is $-(CH_2)OP(=O)(OH)(OR^L)$. In some embodiments, Base B is  and R^G is $-(CH_2)OP(=O)(OH_2)$.

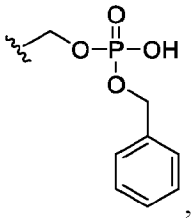
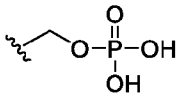
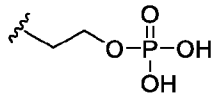
[0086] In some embodiments, R^K is C_1-C_6 alkyl substituted with $-OP(=O)(OH)(OR^L)$. In some embodiments, R^K is $-(CH_2)OP(=O)(OH)(OR^L)$ or is $-(CH_2)_2OP(=O)(OH)(OR^L)$.

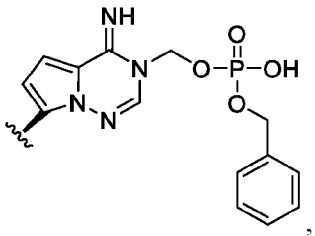
[0087] In some embodiments, R^L is H. In some embodiments, R^L is H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some embodiments, R^L is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some embodiments, R^L is C_1-C_3 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl. In some

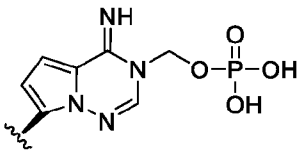
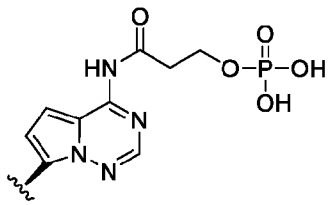
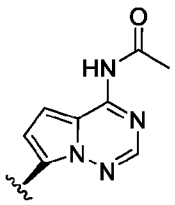
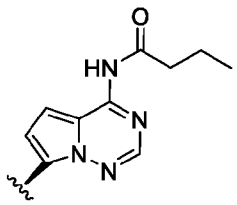
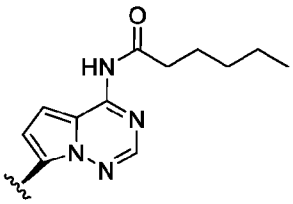
embodiments, R^L is C_1-C_3 alkyl substituted with one phenyl. In some embodiments, R^L is

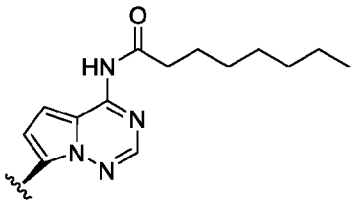


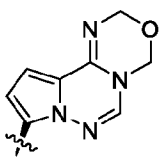
.

[0088] In some embodiments, R^K is , , or . In some embodiments, R^K is C_1-C_{10} alkyl. In some embodiments, R^K is C_1-C_7 alkyl. In some embodiments, R^K is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_4CH_3$, or $-(CH_2)_6CH_3$. In some embodiments, R^K is C_6-C_{10} aryl. In some embodiments, R^K is phenyl. In some embodiments, R^K is $-O-C_6$-C_{10} aryl. In some embodiments, R^K is -O-phenyl. In some embodiments, R^K is $-O-C_1$-C_{10} alkyl. In some embodiments, R^K is $-O-CH_3$, $-O-CH_2CH_3$, $-O-(CH_2)_2CH_3$, $-O-(CH_2)_4CH_3$, or $-O-(CH_2)_6CH_3$.

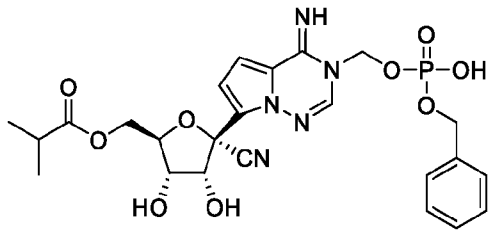
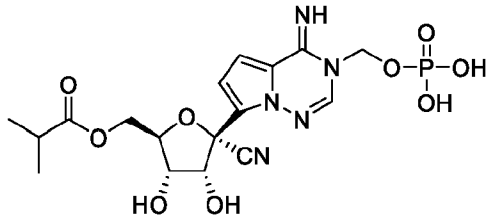
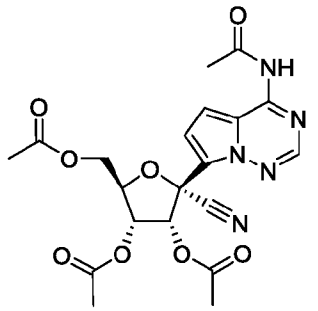
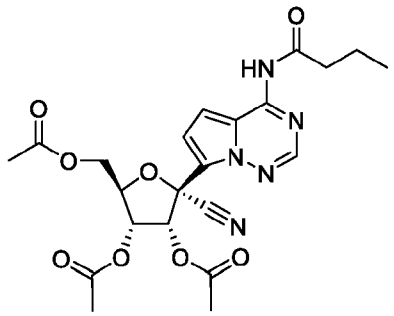
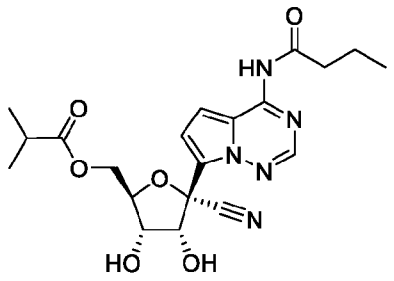
[0089] In some embodiments, Base B is ,

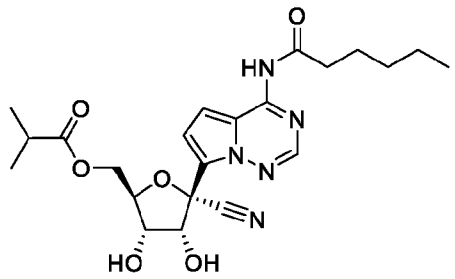
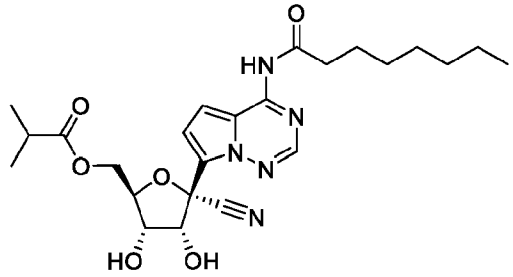
, , , , 

or .

[0090] In some embodiments, Base B is .

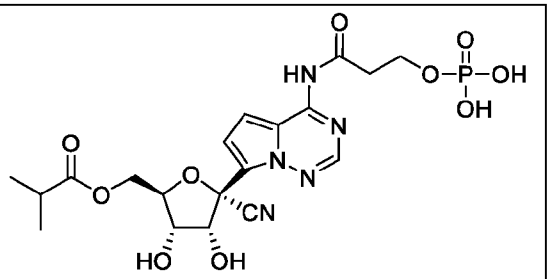
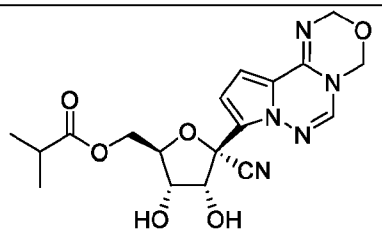
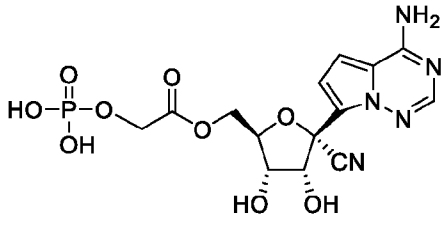
[0091] In some embodiments, the compound of Formula B is

Compound 5	
Compound 6	
Compound 7	
Compound 8	
Compound 9	

Compound 10	
Compound 11	

or a pharmaceutically acceptable salt thereof.

[0092] In some embodiments, the compound of Formula B is

Compound 13	
Compound 14	
Compound 15	

or a pharmaceutically acceptable salt thereof.

V. Pharmaceutical Formulations

[0093] The compounds disclosed herein may be formulated with conventional carriers and excipients. For example, tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations may optionally comprise excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Pharmaceutically acceptable excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. In some embodiments, the formulations comprise one or more pharmaceutically acceptable excipients. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10. In some embodiments, the pH of the formulations ranges from about 2 to about 5, but is ordinarily about 3 to 4.

[0094] While it is possible for the compounds of the disclosure ("the active ingredients") to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients, particularly those additional therapeutic ingredients as discussed herein. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0095] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any appropriate method known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are 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.

[0096] In some embodiments, the pharmaceutical formulation is for subcutaneous, intramuscular, intravenous, oral, or inhalation administration.

[0097] In some embodiments, the compound described herein, e.g., compounds of Formula A or Formula B, or the pharmaceutically acceptable salt thereof, described herein have optimized/improved pharmacokinetic properties and are amenable to oral administration. For example, the compounds of Formula A or Formula B have improved bioavailability and can therefore be administered by oral administration.

[0098] In some embodiments, the formulations of the present invention are suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[0099] In some embodiments, the tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0100] For infections of the eye or other external tissues, e.g., mouth and skin, the formulations are applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[0101] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin

or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0102] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0103] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate. Further emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 80.

[0104] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0105] Pharmaceutical formulations according to the present invention comprise a compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. 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, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as 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.

[0106] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0107] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin. Further non-limiting examples of suspending agents include Cyclodextrin. In some examples, the suspending agent is Sulfobutyl ether beta-cyclodextrin (SEB-beta-CD), for example Captisol®.

[0108] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0109] Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0110] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0111] The pharmaceutical compositions of the invention 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 above. 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. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution isotonic sodium chloride solution, and hypertonic sodium chloride solution.

[0112] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 mg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0113] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

[0114] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0115] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0116] In some embodiments, the compounds disclosed herein are administered by inhalation. In some embodiments, formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry

powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents. In some embodiments, the compounds used herein are formulated and dosed as dry powder. In some embodiments, the compounds used herein are formulated and dosed as a nebulized formulation. In some embodiments, the compounds used herein are formulated for delivery by a face mask. In some embodiments, the compounds used herein are formulated for delivery by a face tent.

[0117] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0118] 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.

[0119] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0120] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0121] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

[0122] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These

veterinary compositions may be administered orally, parenterally or by any other desired route.

[0123] Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

VI. Kits

[0124] Also provided herein are kits that includes a compound disclosed herein, a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof. In some embodiments the kits described herein may comprise a label and/or instructions for use of the compound in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In some embodiments, the disease or condition is viral infection.

[0125] In some embodiments, the kit may also comprise one or more additional therapeutic agents and/or instructions for use of additional therapeutic agents in combination with the compound described herein, e.g., the compound of Formula A or Formula B in the treatment of the disease or condition in a subject (e.g., human) in need thereof.

[0126] In some embodiments, the kits provided herein comprises individual dose units of a compound as described herein, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. Examples of individual dosage units may include pills, tablets, capsules, prefilled syringes or syringe cartridges, IV bags, inhalers, nebulizers etc., each comprising a therapeutically effective amount of the compound in question, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. In some embodiments, the kit may contain a single dosage unit and in others, multiple dosage units are present, such as the number of dosage units required for a specified regimen or period.

[0127] Also provided are articles of manufacture that include a compound described herein, e.g., a compound of Formula A or Formula B, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, and a container. In some

embodiments, the container of the article of manufacture is a vial, jar, ampoule, preloaded syringe, blister package, tin, can, bottle, box, an intravenous bag, an inhaler, or a nebulizer.

VII. Administration

[0128] One or more compounds of the invention are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, inhalation, pulmonary, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. In some embodiments, the compounds disclosed herein are administered by inhalation or intravenously. In some embodiments, the compounds disclosed herein are administered orally. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

[0129] In the methods of the present invention for the treatment of a viral infection, the compounds of the present invention can be administered at any time to a human who may come into contact with the virus or is already suffering from the viral infection. In some embodiments, the compounds of the present invention can be administered prophylactically to humans coming into contact with humans suffering from the viral infection or at risk of coming into contact with humans suffering from the viral infection, e.g., healthcare providers. In some embodiments, administration of the compounds of the present invention can be to humans testing positive for the viral infection but not yet showing symptoms of the viral infection. In some embodiments, administration of the compounds of the present invention can be to humans upon commencement of symptoms of the viral infection.

[0130] In some embodiments, the methods disclosed herein comprise event driven administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, to the subject.

[0131] As used herein, the terms "event driven" or "event driven administration" refer to administration of the compound described herein, e.g., the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, (1) prior to an event (e.g., 2 hours, 1 day, 2 days, 5 day, or 7 or more days prior to the event) that would expose the individual to the virus (or that would otherwise increase the individual's risk of acquiring the viral infection); and/or (2) during an event (or more than one recurring event) that would expose the individual to the virus (or that would otherwise increase the individual's risk of acquiring

the viral infection); and/or (3) after an event (or after the final event in a series of recurring events) that would expose the individual to the virus (or that would otherwise increase the individual's risk of acquiring the viral infection). In some embodiments, the event driven administration is performed pre-exposure of the subject to the virus. In some embodiments, the event driven administration is performed post-exposure of the subject to the virus. In some embodiments, the event driven administration is performed pre-exposure of the subject to the virus and post-exposure of the subject to the virus.

[0132] In certain embodiments, the methods disclosed herein involve administration prior to and/or after an event that would expose the individual to the virus or that would otherwise increase the individual's risk of acquiring the viral infection, e.g., as pre-exposure prophylaxis (PrEP) and/or as post-exposure prophylaxis (PEP). In some embodiments, the methods disclosed herein comprise pre-exposure prophylaxis (PrEP). In some embodiments, methods disclosed herein comprise post-exposure prophylaxis (PEP).

[0133] In some embodiments, the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, is administered before exposure of the subject to the virus.

[0134] In some embodiments, the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, is administered before and after exposure of the subject to the virus.

[0135] In some embodiments, the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, is administered after exposure of the subject to the virus.

[0136] An example of event driven dosing regimen includes administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, within 24 to 2 hours prior to the virus, followed by administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt, every 24 hours during the period of exposure, followed by a further administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, after the last exposure, and one last administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, 24 hours later.

[0137] A further example of an event driven dosing regimen includes administration of the compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, within 24 hours before the viral exposure, then daily administration during the period of exposure, followed by a last administration approximately 24 hours later after the last exposure (which may be an increased dose, such as a double dose).

[0138] The specific dose level of a compound of the present disclosure for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

[0139] The daily dosage may also be described as a total amount of a compound described herein administered per dose or per day. Daily dosage of a compound of Formula A or Formula B, or a pharmaceutically acceptable salt thereof, may be between about 1 mg and 4,000 mg, between about 2,000 to 4,000 mg/day, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 10 to 500 mg/day, between about 20 to 500 mg/day, between about 50 to 300 mg/day, between about 75 to 200 mg/day, or between about 15 to 150 mg/day.

[0140] The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[0141] The compounds of the present disclosure may be administered to an individual (*e.g.*, a human) in a therapeutically effective amount. In some embodiments, the compound is administered once daily.

[0142] The compounds provided herein can be administered by any useful route and means, such as by oral or parenteral (e.g., intravenous) administration. Therapeutically effective amounts of the compound may include from about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as from about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.05 mg/kg body weight per day to about 0.5 mg/kg body weight per day. In some embodiments, a therapeutically effective amount of the compounds provided herein include from about 0.3 mg to about 30 mg per day, or from about 30 mg to about 300 mg per day, or from about 0.3 mg to about 30 mg per day, or from about 30 mg to about 300 mg per day.

[0143] A compound of the present disclosure may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (e.g., from 1 mg to 1000 mg of compound). Therapeutically effective amounts may include from about 0.1 mg per dose to about 1000 mg per dose, such as from about 50 mg per dose to about 500 mg per dose, or such as from about 100 mg per dose to about 400 mg per dose, or such as from about 150 mg per dose to about 350 mg per dose, or such as from about 200 mg per dose to about 300 mg per dose, or such as from about 0.01 mg per dose to about 1000 mg per dose, or such as from about 0.01 mg per dose to about 100 mg per dose, or such as from about 0.1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to about 10 mg per dose, or such as from about 1 mg per dose to about 1000 mg per dose. Other therapeutically effective amounts of the compound of Formula A or Formula B are about 1 mg per dose, or about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or about 100 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, or about 1000 mg per dose.

[0144] In some embodiments, the methods described herein comprise administering to the subject an initial daily dose of about 1 to 500 mg of a compound provided herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50, or 100 mg can be used to increase the dose. The dosage can be increased daily,

every other day, twice per week, once per week, once every two weeks, once every three weeks, or once a month.

[0145] When administered orally, the total daily dosage for a human subject may be between about 1-4,000 mg/day, between about 1-3,000 mg/day, between 1-2,000 mg/day, about 1-1,000 mg/day, between about 10-500 mg/day, between about 50-300 mg/day, between about 75-200 mg/day, or between about 100-150 mg/day. In some embodiments, the total daily dosage for a human subject may be about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, or 3000 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 200, 300, 400, 500, 600, 700, or 800 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 300, 400, 500, or 600 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, or 4000 mg/day. In some embodiments, the total daily dosage for a human subject may be about 100-200, 100-300, 100-400, 100-500, 100-600, 100-700, 100-800, 100-900, 100-1000, 500-1100, 500-1200, 500-1300, 500-1400, 500-1500, 500-1600, 500-1700, 500-1800, 500-1900, 500-2000, 1500-2100, 1500-2200, 1500-2300, 1500-2400, 1500-2500, 2000-2600, 2000-2700, 2000-2800, 2000-2900, 2000-3000, 2500-3100, 2500-3200, 2500-3300, 2500-3400, 2500-3500, 3000-3600, 3000-3700, 3000-3800, 3000-3900, or 3000-4000 mg/day.

[0146] In some embodiments, the total daily dosage for a human subject may be about 100 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 150 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 200 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 250 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 300 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 350 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 400 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 450 mg/day

administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 500 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 550 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 600 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 650 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 700 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 750 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 800 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 850 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 900 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 950 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 1000 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 1500 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 2000 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 2500 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 3000 mg/day administered in a single dose. In some embodiments, the total daily dosage for a human subject may be about 4000 mg/day administered in a single dose.

[0147] A single dose can be administered hourly, daily, weekly, or monthly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In certain embodiments, a single dose can be administered once every week. A single dose can also be administered once every month. In some embodiments, a compound disclosed herein is administered once daily in a method disclosed herein. In some embodiments, a compound disclosed herein is administered twice daily in a method disclosed herein. In some embodiments, a compound disclosed herein is administered three times daily in a method disclosed herein.

[0148] In some embodiments, a compound disclosed herein is administered once daily in the total daily dose of 100-4000 mg/day. In some embodiments, a compound disclosed herein is administered twice daily in the total daily dose of 100-4000 mg/day. In some embodiments, a compound disclosed herein is administered three times daily in the total daily dose of 100-4000 mg/day.

[0149] The frequency of dosage of the compound of the present disclosure will be determined by the needs of the individual patient and can be, for example, once per day or twice, or more times, per day. Administration of the compound continues for as long as necessary to treat the viral infection. For example, a compound can be administered to a human being infected with the virus for a period of from 20 days to 180 days or, for example, for a period of from 20 days to 90 days or, for example, for a period of from 30 days to 60 days.

[0150] Administration can be intermittent, with a period of several or more days during which a patient receives a daily dose of the compound of the present disclosure followed by a period of several or more days during which a patient does not receive a daily dose of the compound. For example, a patient can receive a dose of the compound every other day, or three times per week. Again by way of example, a patient can receive a dose of the compound each day for a period of from 1 to 14 days, followed by a period of 7 to 21 days during which the patient does not receive a dose of the compound, followed by a subsequent period (e.g., from 1 to 14 days) during which the patient again receives a daily dose of the compound. Alternating periods of administration of the compound, followed by non-administration of the compound, can be repeated as clinically required to treat the patient.

[0151] The compounds of the present disclosure or the pharmaceutical compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are well known in cancer chemotherapy, and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

VIII. Methods of Use

[0152] The present disclosure also provides a method of treating or preventing a viral infection in a subject (e.g., human) in need thereof, the method comprising administering to the subject a compound described herein.

[0153] In some embodiments, the present disclosure provides a method of treating a viral infection in a subject (e.g., human) in need thereof, the method comprising administering to a subject in need thereof a compound described herein.

[0154] In some embodiments, the compound described herein is administered to the human via oral, intramuscular, intravenous, subcutaneous, or inhalation administration.

[0155] In some embodiments, the present disclosure provides for methods of treating or preventing a viral infection in a subject (e.g., human) in need thereof, the method comprising administering to the subject a compound disclosed herein and at least one additional active therapeutic or prophylactic agent.

[0156] In some embodiments, the present disclosure provides for methods of treating a viral infection in a subject (e.g., human) in need thereof, the method comprising administering to the subject a compound disclosed herein, and at least one additional active therapeutic or prophylactic agent.

[0157] In one embodiment, the present disclosure provides for methods of inhibiting a viral polymerase in a cell, the methods comprising contacting the cell infected a virus with a compound disclosed herein, whereby the viral polymerase is inhibited.

[0158] In one embodiment, the present disclosure provides for methods of inhibiting a viral polymerase in a cell, the methods comprising contacting the cell infected a virus with a compound disclosed herein, and at least one additional active therapeutic agent, whereby the viral polymerase is inhibited.

[0159] Also provided here are the uses of the compounds disclosed herein for use in treating or preventing a viral infection in a subject in need thereof. For example, provided herein are uses of the compounds disclosed herein for use in treating a viral infection in a subject in need thereof.

[0160] In some embodiments, the viral infection is a paramyxoviridae virus infection. As such, in some embodiments, the present disclosure provides methods for treating a

paramyxoviridae infection in a subject (e.g., a human) in need thereof, the method comprising administering to the subject a compound disclosed herein. Paramyxoviridae viruses include, but are not limited to Nipah virus, Hendra virus, measles, mumps, and parainfluenze virus.

[0161] In some embodiments, the viral infection is a human parainfluenza virus, Nipah virus, Hendra virus, measles, or mumps infection.

[0162] In some embodiments, the viral infection is a pneumoviridae virus infection. As such, in some embodiments, the present disclosure provides a method of treating a pneumoviridae virus infection in a human in need thereof, the method comprising administering to the human a compound provided herein. Pneumoviridae viruses include, but are not limited to, respiratory snycytial virus and human metapneumovirus. In some embodiments, the pneumoviridae virus infection is a respiratory syncytial virus infection. In some embodiments, the pneumoviridae virus infection is human metapneumovirus infection.

[0163] In some embodiments, the present disclosure provides a compound disclosed herein, for use in the treatment of a pneumoviridae virus infection in a human in need thereof. In some embodiments, the pneumoviridae virus infection is a respiratory syncytial virus infection. In some embodiments, the pneumoviridae virus infection is human *metapneumovirus* infection.

[0164] In some embodiments, the present disclosure provides methods for treating a RSV infection in a human in need thereof, the method comprising administering to the human a compound provided herein. In some embodiments, the human is suffering from a chronic respiratory syncytial viral infection. In some embodiments, the human is acutely infected with RSV.

[0165] In some embodiments, a method of inhibiting RSV replication is provided, wherein the method comprises administering to a human in need thereof, a compound disclosed herein, wherein the administration is by inhalation.

[0166] In some embodiments, the present disclosure provides a method for reducing the viral load associated with RSV infection, wherein the method comprises administering to a human infected with RSV a compound disclosed herein.

[0167] In some embodiments, the viral infection is a picornaviridae virus infection. As such, in some embodiments, the present disclosure provides a method of treating a picornaviridae

virus infection in a human in need thereof, the method comprising administering to the human a compound of the present disclosure. Picornaviridae viruses are eneteroviruses causing a heterogeneous group of infections including herpangina, aseptic meningitis, a common-cold-like syndrome (human rhinovirus infection), a non-paralytic poliomyelitis-like syndrome, epidemic pleurodynia (an acute, febrile, infectious disease generally occurring in epidemics), hand-foot-mouth syndrome, pediatric and adult pancreatitis and serious myocarditis. In some embodiments, the *Picornaviridae* virus infection is human rhinovirus infection (HRV). In some embodiments, the *Picornaviridae* virus infection is HRV-A, HRV-B, or HRV-C infection.

[0168] In some embodiments, the viral infection is selected from the group consisting of Coxsackie A virus infection, Coxsackie A virus infection, enterovirus D68 infection, enterovirus B69 infection, enterovirus D70 infection, enterovirus A71 infection, and poliovirus infection.

[0169] In some embodiments, the present disclosure provides a compound, for use in the treatment of a picornaviridae virus infection in a human in need thereof. In some embodiments, the picornaviridae virus infection is human rhinovirus infection.

[0170] In some embodiments, the viral infection is a flaviviridae virus infection. As such, in some embodiments, the present disclosure provides a method of treating a flaviviridae virus infection in a human in need thereof, the method comprising administering to the human a compound described herein. Representative flaviviridae viruses include, but are not limited to, dengue, Yellow fever, West Nile, Zika, Japanese encephalitis virus, and Hepatitis C (HCV). In some embodiments, the flaviviridae virus infection is a dengue virus infection. In some embodiments, the flaviviridae virus infection is a yellow fever virus infection. In some embodiments, the flaviviridae virus infection is a West Nile virus infection. In some embodiments, the flaviviridae virus infection is a zika virus infection. In some embodiments, the flaviviridae virus infection is a Japanese ensephalitis virus infection. In some embodiments, the flaviviridae virus infection is a hepatitis C virus infection.

[0171] In some embodiments, the flaviviridae virus infection is a dengue virus infection, yellow fever virus infection, West Nile virus infection, tick borne encephalitis, Kunjin Japanese encephalitis, St. Louis encephalitis, Murray valley encephalitis, Omsk hemorrhagic fever, bovine viral diarrhea, zika virus infection, or a HCV infection.

[0172] In some embodiments, the present disclosure provides use of a compound disclosed herein for treatment of a flaviviridae virus infection in a human in need thereof. In some embodiments, the flaviviridae virus infection is a dengue virus infection. In some embodiments, the flaviviridae virus infection is a yellow fever virus infection. In some embodiments, the flaviviridae virus infection is a West Nile virus infection. In some embodiments, the flaviviridae virus infection is a zika virus infection. In some embodiments, the flaviviridae virus infection is a hepatitis C virus infection.

[0173] In some embodiments, the viral infection is a filoviridae virus infection. As such, in some embodiments, provided herein is a method of treating a filoviridae virus infection in a human in need thereof, the method comprising administering to the human a compound disclosed herein. Representative filoviridae viruses include, but are not limited to, ebola (variants Zaire, Bundibugio, Sudan, Tai forest, or Reston) and marburg. In some embodiments, the filoviridae virus infection is an ebola virus infection. In some embodiments, the filoviridae virus infection is a marburg virus infection.

[0174] In some embodiments, the present disclosure provides a compound for use in the treatment of a filoviridae virus infection in a human in need thereof. In some embodiments, the filoviridae virus infection is an ebola virus infection. In some embodiments, the filoviridae virus infection is a marburg virus infection.

[0175] In some embodiments, the viral infection is a coronavirus infection. As such, in some embodiments, provided herein is a method of treating a coronavirus infection in a human in need thereof, wherein the method comprises administering to the human a compound provided herein. In some embodiments, the coronavirus infection is a Severe Acute Respiratory Syndrome (SARS-CoV) infection, Middle Eastern Respiratory Syndrome (MERS) infection, SARS-CoV-2 infection, other human coronavirus (229E, NL63, OC43, HKU1, or WIV1) infections, zoonotic coronavirus (PEDV or HKU CoV isolates such as HKU3, HKU5, or HKU9) infections. In some embodiments, the viral infection is a Severe Acute Respiratory Syndrome (SARS) infection. In some embodiments, the viral infection is a Middle Eastern Respiratory Syndrome (MERS) infection. In some embodiments, the viral infection is SARS-CoV-2 infection. In some embodiments, the viral infection is a zoonotic coronavirus infection, In some embodiments, the viral infection is caused by a virus having at least 70% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2. In some embodiments,

the viral infection is caused by a virus having at least 80% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2. In some embodiments, the viral infection is caused by a virus having at least 90% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2. In some embodiments, the viral infection is caused by a virus having at least 95% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2.

[0176] In some embodiments, the viral infection is caused by a variant of SARS-CoV-2, for example by the B.1.1.7 variant (the UK variant), B.1.351 variant (the South African variant), P.1 variant (the Brazil variant), B.1.1.7 with E484K variant, B.1.1.207 variant, B.1.1.317 variant, B.1.1.318 variant, B.1.429 variant, B.1.525 variant, or P.3 variant. In some embodiments, the viral infection is caused by the B.1.1.7 variant of SARS-CoV-2. In some embodiments, the viral infection is caused by the B.1.351 variant of SARS-CoV-2. In some embodiments, the viral infection is caused by the P.1 variant of SARS-CoV-2.

[0177] In some embodiments, the present disclosure provides a compound for use in the treatment of a coronavirus virus infection in a human in need thereof. In some embodiments, the coronavirus infection is a Severe Acute Respiratory Syndrome (SARS) infection, Middle Eastern Respiratory Syndrome (MERS) infection, SARS-CoV-2 infection, other human coronavirus (229E, NL63, OC43, HKU1, or WIV1) infections, and zoonotic coronavirus (PEDV or HKU CoV isolates such as HKU3, HKU5, or HKU9) infections. In some embodiments, the viral infection is a Severe Acute Respiratory Syndrome (SARS) infection. In some embodiments, the viral infection is a Middle Eastern Respiratory Syndrome (MERS) infection. In some embodiments, the viral infection is SARS-CoV-2 infection (COVID19).

[0178] In some embodiments, the viral infection is an arenaviridae virus infection. As such, in some embodiments, the disclosure provides a method of treating an arenaviridae virus infection in a human in need thereof, the method comprising administering to the human a compound disclosed herein. In some embodiments, the arenaviridae virus infection is a Lassa infection or a Junin infection.

[0179] In some embodiments, the present disclosure provides a compound for use in the treatment of an arenaviridae virus infection in a human in need thereof. In some embodiments, the arenaviridae virus infection is a Lassa infection or a Junin infection.

[0180] In some embodiments, the viral infection is an orthomyxovirus infection, for example, an influenza virus infection. In some embodiments, the viral infection is an influenza virus A, influenza virus B, or influenza virus C infection.

[0181] As described more fully herein, the compounds described herein can be administered with one or more additional therapeutic agent(s) to an individual (*e.g.*, a human) infected with a viral infection. The additional therapeutic agent(s) can be administered to the infected individual at the same time as the compound of the present disclosure or before or after administration of the compound of the present disclosure.

IX. Combination Therapy

[0182] The compounds described herein can also be used in combination with one or more additional therapeutic agents. As such, also provided herein are methods of treatment of a viral infection in a subject in need thereof, wherein the methods comprise administering to the subject a compound disclosed therein and a therapeutically effective amount of one or more additional therapeutic or prophylactic agents.

[0183] In some embodiments, the additional therapeutic agent is an antiviral agent. Any suitable antiviral agent can be used in the methods described herein. In some embodiments, the antiviral agent is selected from the group consisting of 5-substituted 2'-deoxyuridine analogues, nucleoside analogues, pyrophosphate analogues, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, entry inhibitors, acyclic guanosine analogues, acyclic nucleoside phosphonate analogues, HCV NS5A/NS5B inhibitors, influenza virus inhibitors, interferons, immunostimulators, oligonucleotides, antimitotic inhibitors, and combinations thereof.

[0184] In some embodiments, the additional therapeutic agent is a 5-substituted 2'-deoxyuridine analogue. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of idoxuridine, trifluridine, brivudine [BVDU], and combinations thereof.

[0185] In some embodiments, the additional therapeutic agent is a nucleoside analogue. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of vidarabine, entecavir (ETV), telbivudine, lamivudine, adefovir dipivoxil, tenofovir disoproxil fumarate (TDF) and combinations thereof. In some embodiments, the

additional therapeutic agent is favipiravir, ribavirin, galidesivir, β-D-N4-hydroxycytidine or a combination thereof.

[0186] In some embodiments, the additional therapeutic agent is a pyrophosphate analogue. For example, in some embodiments, the additional therapeutic agent is foscarnet or phosphonoacetic acid. In some embodiments, the additional therapeutic agent is foscarnet.

[0187] In some embodiments, the additional therapeutic agent is nucleoside reverse transcriptase inhibitor. In some embodiments, the antiviral agent is zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, and combinations thereof.

[0188] In some embodiments, the additional therapeutic agent is a non-nucleoside reverse transcriptase inhibitor. In some embodiments, the antiviral agent is selected from the group consisting of nevirapine, delavirdine, efavirenz, etravirine, rilpivirine, and combinations thereof.

[0189] In some embodiments, the additional therapeutic agent is a protease inhibitor. In some embodiments, the protease inhibitor is a HIV protease inhibitor. For example, in some embodiments, the antiviral agent is selected from the group consisting of saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, cobicistat, and combinations thereof. In some embodiments, the antiviral agent is selected from the group consisting of saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, and combinations thereof. In some embodiments, the protease inhibitor is a HCV NS3/4A protease inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of voxilaprevir, asunaprevir, boceprevir, paritaprevir, simeprevir, telaprevir, vaniprevir, grazoprevir, ribavirin, danoprevir, faldaprevir, vedroprevir, sovaprevir, deldeprevir, narlaprevir and combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of voxilaprevir, asunaprevir, boceprevir, paritaprevir, simeprevir, telaprevir, vaniprevir, grazoprevir, and combinations thereof.

[0190] In some embodiments, the additional therapeutic agent is an integrase inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of raltegravir, dolutegravir, elvitegravir, abacavir, lamivudine, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of bictegravir, raltegravir, dolutegravir, cabotegravir, elvitegravir, and

combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of bictegravir, dolutegravir, and cabotegravir, and combinations thereof. In some embodiments, the additional therapeutic agent is bictegravir.

[0191] In some embodiments, the additional therapeutic agent is an entry inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of docosanol, enfuvirtide, maraviroc, ibalizumab, fostemsavir, leronlimab, ibalizumab, fostemsavir, leronlimab, palivizumab, respiratory syncytial virus immune globulin, intravenous [RSV-IGIV], varicella-zoster immunoglobulin [VariZIG], varicella-zoster immune globulin [VZIG]), and combinations thereof.

[0192] In some embodiments, the additional therapeutic agent is an acyclic guanosine analogue. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of acyclovir, ganciclovir, valacyclovir (also known as valaciclovir), valganciclovir, penciclovir, famciclovir, and combinations thereof.

[0193] In some embodiments, the additional therapeutic agent is an acyclic nucleoside phosphonate analogue. For example, in some embodiments, the additional therapeutic agent is selected from a group consisting of cidofovir, adefovir, adefovir dipivoxil, tenofovir, TDF, emtricitabine, efavirenz, rilpivirine, elvitegravir, and combinations thereof. In some embodiment, the additional therapeutic agent is selected from the group consisting of cidofovir, adefovir, adefovir dipivoxil, tenofovir, TDF, and combinations thereof. In some embodiment, the additional therapeutic agent is selected from the group consisting of cidofovir, adefovir dipivoxil, TDF, and combinations thereof.

[0194] In some embodiments, the additional therapeutic agent is a HCV NS5A/NS5B inhibitor. In some embodiments, the additional therapeutic agent is a NS3/4A protease inhibitor. In some embodiments, the additional therapeutic agent is a NS5A protein inhibitor. In some embodiments, the additional therapeutic agent is a NS5B polymerase inhibitor of the nucleoside/nucleotide type. In some embodiments, the additional therapeutic agent is a NS5B polymerase inhibitor of the nonnucleoside type. In some embodiments, the additional therapeutic agent is selected from the group consisting of daclatasvir, ledipasvir, velpatasvir, ombitasvir, elbasvir, sofosbuvir, dasabuvir, ribavirin, asunaprevir, simeprevir, paritaprevir, ritonavir, elbasvir, grazoprevir, AT-527, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of daclatasvir, ledipasvir, velpatasvir, ombitasvir, elbasvir, sofosbuvir, dasabuvir, and combinations thereof.

[0195] In some embodiments, the additional therapeutic agent is an influenza virus inhibitor. In some embodiments, the additional therapeutic agent is a matrix 2 inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of amantadine, rimantadine, and combinations thereof. In some embodiments, the additional therapeutic agent is a neuraminidase inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of zanamivir, oseltamivir, peramivir, laninamivir octanoate, and combinations thereof. In some embodiments, the additional therapeutic agent is a polymerase inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of ribavirin, favipiravir, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of amantadine, rimantadine, arbidol (umifenovir), baloxavir marboxil, oseltamivir, peramivir, ingavirin, laninamivir octanoate, zanamivir, favipiravir, ribavirin, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from the group consisting of amantadine, rimantadine, zanamivir, oseltamivir, peramivir, laninamivir octanoate, ribavirin, favipiravir, and combinations thereof.

[0196] In some embodiments, the additional therapeutic agent is an interferon. In some embodiments, the additional therapeutic agent is selected from the group consisting of interferon alfacon 1, interferon alfa 1b, interferon alfa 2a, interferon alfa 2b, pegylated interferon alfacon 1, pegylated interferon alfa 1b, pegylated interferon alfa 2a (PegIFNα-2a), and PegIFNα-2b. e embodiments, the additional therapeutic agent is selected from the group consisting of interferon alfacon 1, interferon alfa 1b, interferon alfa 2a, interferon alfa 2b, pegylated interferon alfa 2a (PegIFNα-2a), and PegIFNα-2b. In some embodiments, the additional therapeutic agent is selected from the group consisting of interferon alfacon 1, pegylated interferon alfa 2a (PegIFNα-2a), PegIFNα-2b, and ribavirin. In some embodiments, the additional therapeutic agent is pegylated interferon alfa-2a, pegylated interferon alfa-2b, or a combination thereof.

[0197] In some embodiments, the additional therapeutic agent is an immunostimulatory agent. In some embodiments, the additional therapeutic agent is an oligonucleotide. In some embodiments, the additional therapeutic agent is an antimitotic inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of fomivirsen, podofilox, imiquimod, sinecatechins, and combinations thereof.

[0198] In some embodiments, the additional therapeutic agent is selected from the group consisting of besifovir, nitazoxanide, REGN2222, doravirine, sofosbuvir, velpatasvir, daclatasvir, asunaprevir, beclabuvir, FV100, and letermovir, and combinations thereof.

[0199] In some embodiments, the additional therapeutic agent is an agent for treatment of RSV. For example, in some embodiments, the antiviral agent is ribavirin, ALS-8112 or presatovir. For example, in some embodiments, the antiviral agent is ALS-8112 or presatovir.

[0200] In some embodiments, the additional therapeutic agent is an agent for treatment of picornavirus. In some embodiments, the additional therapeutic agent is selected from the group consisting of hydantoin, guanidine hydrochloride, L-buthionine sulfoximine, Py-11, and combinations thereof. In some embodiments, the additional therapeutic agent is a picornavirus polymerase inhibitor. In some embodiments, the additional therapeutic agent is rupintrivir.

[0201] In some embodiments, the additional therapeutic agent is an agent for treatment of malaria. In some embodiments, the additional therapeutic agent is chloroquine.

[0202] In some embodiments, the additional therapeutic agent is selected from the group consisting of hydroxychloroquine, chloroquine, artemether, lumefantrine, atovaquone, proguanil, tafenoquine, pyronaridine, artesunate, artenimol, piperaquine, artesunate, amodiaquine, pyronaridine, artesunate, halofantrine, quinine sulfate, mefloquine, solithromycin, pyrimethamine, MMV-390048, ferroquine, artefenomel mesylate, ganaplacide, DSM-265, cipargamin, artemisone, and combinations thereof.

[0203] In some embodiments, the additional therapeutic agent is an agent for treatment of coronavirus. In some embodiments, the additional therapeutic agent is selected from a group consisting of IFX-1, FM-201, CYNK-001, DPP4-Fc, ranpirnase, nafamostat, LB-2, AM-1, anti-viroporins, and combinations thereof.

[0204] In some embodiments, the additional therapeutic agent is an agent for treatment of ebola virus. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444, MDT-637, BMS-433771, amiodarone, dronedarone, verapamil, Ebola Convalescent Plasma (ECP), TKM-100201, BCX4430 ((2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol), favipiravir (also known as T-705 or Avigan),T-705 monophosphate, T-705 diphosphate, T-705 triphosphate,

FGI-106 (1-N,7-N-bis[3-(dimethylamino)propyl]-3,9-dimethylquinolino[8,7-h]quinolone-1,7-diamine), JK-05, TKM-Ebola, ZMapp, rNAPc2, VRC-EBOADC076-00-VP, OS-2966, MVA-BN filo, brincidofovir, Vaxart adenovirus vector 5-based ebola vaccine, Ad26-ZEBOV, FiloVax vaccine, GOVX-E301, GOVX-E302, ebola virus entry inhibitors (NPC1 inhibitors), rVSV-EBOV, and combinations thereof. In some embodiments, the additional therapeutic agent is ZMapp, mAB114, REGEN-EB3, and combinations thereof.

[0205] In some embodiments, the additional therapeutic agent is an agent for treatment of HCV. In some embodiments, the additional therapeutic agent is a HCV polymerase inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of sofosbuvir, GS-6620, PSI-938, ribavirin, tegobuvir, radalbuvir, MK-0608, and combinations thereof. In some embodiments, the additional therapeutic agent is a HCV protease inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of such as GS-9256, vedroprevir, voxilaprevir, and combinations thereof.

[0206] In some embodiments, the additional therapeutic agent is a NS5A inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of ledipasvir, velpatasvir, and combinations thereof.

[0207] In some embodiments, the additional therapeutic agent is an anti HBV agent. For example, in some embodiments, the additional therapeutic agent is tenofovir disoproxil fumarate and emtricitabine, or a combination thereof. Examples of additional anti HBV agents include but are not limited to alpha-hydroxytropolones, amdoxovir, antroquinonol, beta-hydroxycytosine nucleosides, ARB-199, CCC-0975, ccc-R08, elvucitabine, ezetimibe, cyclosporin A, gentiopicrin (gentiopicroside), HH-003, hepalatide, JNJ-56136379, nitazoxanide, birinapant, NJK14047, NOV-205 (molixan, BAM-205), oligotide, mivotilate, feron, GST-HG-131, levamisole, Ka Shu Ning, alloferon, WS-007, Y-101 (Ti Fen Tai), rSIFN-co, PEG-IIFNm, KW-3, BP-Inter-014, oleanolic acid, HepB-nRNA, cTP-5 (rTP-5), HSK-II-2, HEISCO-106-1, HEISCO-106, Hepbarna, IBPB-006IA, Hepuyinfen, DasKloster 0014-01, ISA-204, Jiangantai (Ganxikang), MIV-210, OB-AI-004, PF-06, picroside, DasKloster-0039, hepulantai, IMB-2613, TCM-800B, reduced glutathione, RO-6864018, RG-7834, QL-007sofosbuvir, ledipasvir, UB-551, and ZH-2N, and the compounds disclosed in US20150210682, (Roche), US 2016/0122344 (Roche), WO2015173164, WO2016023877, US2015252057A (Roche), WO16128335A1 (Roche), WO16120186A1 (Roche),

US2016237090A (Roche), WO16107833A1 (Roche), WO16107832A1 (Roche), US2016176899A (Roche), WO16102438A1 (Roche), WO16012470A1 (Roche), US2016220586A (Roche), and US2015031687A (Roche). In some embodiments, the additional therapeutic agent is a HBV polymerase inhibitor. Examples of HBV DNA polymerase inhibitors include, but are not limited to, adefovir (HEPSERA®), emtricitabine (EMTRIVA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir dipivoxil, tenofovir dipivoxil fumarate, tenofovir octadecyloxyethyl ester, CMX-157, tenofovir exalidex, besifovir, entecavir (BARACLUDE®), entecavir maleate, telbivudine (TYZEKA®), filocilovir, pradefovir, clevudine, ribavirin, lamivudine (EPIVIR-HBV®), phosphazide, famciclovir, fusolin, metacavir, SNC-019754, FMCA, AGX-1009, AR-II-04-26, HIP-1302, tenofovir disoproxil aspartate, tenofovir disoproxil orotate, and HS-10234. In some embodiments, the additional therapeutic agent is a HBV capsid inhibitor.

[0208] In some embodiments, the additional therapeutic agent is an agent for treatment of HIV. In some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, entry inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV nonnucleoside reverse transcriptase inhibitors, acyclic nucleoside phosphonate analogues, and combinations thereof.

[0209] In some embodiments, the additional therapeutic agent is selected from the group consisting of 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, 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, and engineered T cell receptors, TCR-T, autologous T cell therapies).

[0210] 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.

[0211] In some embodiments, the additional therapeutic agent is a HIV combination drug. Examples of the HIV combination drugs include, but are not limited to ATRIPLA® (efavirenz, tenofovir disoproxil fumarate, and emtricitabine); BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide); 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); SYMTUZA® (darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat); SYMFI™ (efavirenz, lamivudine, and tenofovir disoproxil fumarate); CIMDU™ (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; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dapivirine + levonorgestrel, dolutegravir + lamivudine, dolutegravir + emtricitabine + tenofovir alafenamide, elsulfavirine + emtricitabine + tenofovir disoproxil, 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.

[0212] In some embodiments, the additional therapeutic agent is a HIV protease inhibitor. For example, in some embodiments the additional therapeutic agent is selected from the

group consisting of saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, cobicistat, ASC-09, AEBL-2, MK-8718, GS-9500, GS-1156, and combinations thereof. For example, in some embodiments the additional therapeutic agent is selected from the group consisting of saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, cobicistat. In some embodiments, the additional therapeutic agent is selected from the group consisting of 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, MK-8122, TMB-607, TMC-310911, and combinations thereof.

[0213] In some embodiments, the additional therapeutic agent is a HIV integrase inhibitor. For example, in some embodiment, the additional therapeutic agent is selected from the group consisting of raltegravir, elvitegravir, dolutegravir, abacavir, lamivudine, bictegravir and combinations thereof. In some embodiment, the additional therapeutic agent is bictegravir. In some embodiments, the additional therapeutic agent is selected from a group consisting of bictegravir, 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, BMS-986197, cabotegravir (long-acting injectable), 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, VM-3500, cabotegravir, and combinations thereof.

[0214] In some embodiments, the additional therapeutic agent is a HIV entry inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of enfuvirtide, maraviroc, and combinations thereof. Further examples of HIV entry inhibitors include, but are not limited to, cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, DS-003 (BMS-599793), gp120 inhibitors, and CXCR4 inhibitors. Examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, leronlimab (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 CXCR4 inhibitors include plerixafor, ALT-1188, N15 peptide, and vMIP (Haimipu).

[0215] In some embodiments, the additional therapeutic agent is a HIV nucleoside reverse transcriptase inhibitors. In some embodiments, the additional therapeutic agent is a HIV nonnucleoside reverse transcriptase inhibitors. In some embodiments, the additional therapeutic agent is an acyclic nucleoside phosphonate analogue. In some embodiments, the additional therapeutic agent is a HIV capsid inhibitor.

[0216] In some embodiments, the additional therapeutic agent is a HIV nucleoside or nucleotide inhibitor of reverse transcriptase. For example, the additional therapeutic agent is selected from the group consisting of 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, islatravir, lamivudine, phosphazid, stavudine, zalcitabine, zidovudine, rovafovir etalafenamide (GS-9131), GS-9148, MK-8504, MK-8591, MK-858, VM-2500, KP-1461, and combinations thereof.

[0217] In some embodiments, the additional therapeutic agent is a HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase. For example, the additional agent is selected from the group consisting of dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, MK-8583, nevirapine, rilpivirine, TMC-278LA, ACC-007, AIC-292, KM-023, PC-1005, elsulfavirine rilp (VM-1500), combinations thereof.

[0218] In some embodiments, the additional therapeutic agents are 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.

[0219] In some embodiments, the additional therapeutic agent is selected from the group consisting of colistin, valrubicin, icatibant, bepotastine, epirubicin, epoprosetnol, vapreotide, aprepitant, caspofungin, perphenazine, atazanavir, efavirenz, ritonavir, acyclovir, ganciclovir, penciclovir, prulifloxacin, bictegravir, nelfinavir, tegobuvi, nelfinavir, praziquantel, pitavastatin, perampanel, eszopiclone, and zopiclone.

[0220] In some embodiments, the additional therapeutic agent is an inhibitor of Bruton tyrosine kinase (BTK, AGMX1, AT, ATK, BPK, IGHD3, IMD1, PSCTK1, XLA; NCBI Gene ID: 695). For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one, acalabrutinib (ACP-196), BGB-3111, CB988, HM71224, ibrutinib (Imbruvica), M-2951 (evobrutinib), M7583, tirabrutinib (ONO-4059), PRN-1008, spebrutinib (CC-292), TAK-020, vecabrutinib, ARQ-531, SHR-1459, DTRMWXHS-12, TAS-5315, AZD6738, calquence, danvatirsen, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from a group consisting of tirabrutinib, ibrutinib, acalabrutinib, and combinations thereof. In some embodiments, the additional therapeutic agent is selected from a group consisting of tirabrutinib, ibrutinib, and combinations thereof. In some embodiments, the additional therapeutic agent is tyrphostin A9 (A9).

[0221] In some embodiments, the additional therapeutic agent is a KRAS inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of AMG-510, COTI-219, MRTX-1257, ARS-3248, ARS-853, WDB-178, BI-3406, BI-1701963, ARS-1620 (G12C), SML-8-73-1 (G12C), Compound 3144 (G12D), Kobe0065/2602 (Ras GTP), RT11, MRTX-849 (G12C) and K-Ras(G12D)-selective inhibitory peptides, including KRpep-2 (Ac-RRCPLYISYDPVCRR-NH2), KRpep-2d (Ac-RRRRCPLYISYDPVCRRRR-NH2), and combinations thereof.

[0222] In some embodiments, the additional therapeutic agent is a proteasome inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from a group consisting of ixazomib, carfilzomib, marizomib, bortezomib, and combinations thereof. In some embodiments, the additional therapeutic agent is carfilzomib.

[0223] In some embodiments, the additional therapeutic agent is a vaccine. For example, in some embodiments, the additional therapeutic agent is a DNA vaccine, RNA vaccine, live-attenuated vaccine, therapeutic vaccine, prophylactic vaccine, protein based vaccine, or a combination thereof. In some embodiments, the additional therapeutic agent is mRNA-1273. In some embodiments, the additional therapeutic agent is INO-4800 or INO-4700. In some embodiments, the additional therapeutic agent is live-attenuated RSV vaccine MEDI-559, human monoclonal antibody REGN2222 against RSV, palivizumab, respiratory syncytial virus immune globulin, intravenous [RSV-IGIV], and combinations thereof. In some embodiments, the additional therapeutic agent is a HBV vaccine, for example pediarix, engerix-B, and recombivax HB. In some embodiments, the additional therapeutic agent is a VZV vaccine, for example zostavax and varivax. In some embodiments, the additional therapeutic agent is a HPV vaccine, for example cervarix, gardasil 9, and gardasil. In some embodiments, the additional therapeutic agent is an influenza virus vaccine. For example, a (i) monovalent vaccine for influenza A (e.g., influenza A [H5N1] virus monovalent vaccine and influenza A [H1N1] 2009 virus monovalent vaccines), (ii) trivalent vaccine for influenza A and B viruses (e.g., Afluria, Agriflu, Fluad, Fluarix, Flublok, Flucelvax, FluLaval, Fluvirin, and Fluzone), and (iii) quadrivalent vaccine for influenza A and B viruses (FluMist, Fluarix, Fluzone, and FluLaval). In some embodiments, the additional therapeutic agent is a human adenovirus vaccine (e.g., Adenovirus Type 4 and Type 7 Vaccine, Live, Oral). In some embodiments, the additional therapeutic agent is a rotavirus vaccine (e.g., Rotarix for rotavirus serotype G1, G3, G4, or G9 and RotaTeq for rotavirus serotype G1, G2, G3, or G4). In some embodiments, the additional therapeutic agent is a hepatitis A virus vaccine (e.g.,

Havrix and Vaqta). In some embodiments, the additional therapeutic agent is poliovirus vaccines (e.g., Kinrix, Quadracel, and Ipol). In some embodiments, the additional therapeutic agent is a yellow fever virus vaccine (e.g., YF-Vax). In some embodiments, the additional therapeutic agent is a Japanese encephalitis virus vaccines (e.g., Ixiaro and JE-Vax). In some embodiments, the additional therapeutic agent is a measles vaccine (e.g., M-M-R II and ProQuad). In some embodiments, the additional therapeutic agent is a mumps vaccine (e.g., M-M-R II and ProQuad). In some embodiments, the additional therapeutic agent is a rubella vaccine (e.g., M-M-R II and ProQuad). In some embodiments, the additional therapeutic agent is a varicella vaccine (e.g., ProQuad). In some embodiments, the additional therapeutic agent is a rabies vaccine (e.g., Imovax and RabAvert). In some embodiments, the additional therapeutic agent is a variola virus (smallpox) vaccine (ACAM2000). In some embodiments, the additional therapeutic agent is a hepatitis E virus (HEV) vaccine (e.g., HEV239). In some embodiments, the additional therapeutic agent is a 2019-nCov vaccine.

[0224] In some embodiments, the additional therapeutic agent is an antibody, for example a monoclonal antibody. For example, the additional therapeutic agent is an antibody against 2019-nCov selected from the group consisting of the Regeneron antibodies, the Wuxi Antibodies, the Vir Biotechnology Antibodies, antibodies that target the SARS-CoV-2 spike protein, antibodies that can neutralize SARS-CoV-2 (SARS-CoV-2 neutralizing antibodies), and combinations thereof. In some embodiments, the additional therapeutic agent is anti-SARS-CoV antibody CR-3022. In some embodiments, the additional therapeutic agent is aPD-1 antibody.

[0225] In some embodiments, the additional therapeutic agent is recombinant cytokine gene-derived protein injection.

[0226] In some embodiments, the additional therapeutic agent is a polymerase inhibitor. In some embodiments, the additional therapeutic agent is a DNA polymerase inhibitor. For example, in some embodiments, the additional therapeutic agent is cidofovir. In some embodiments, the additional therapeutic agent is a RNA polymerase inhibitor. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of ribavirin, favipiravir, lamivudine, pimodivir and combination thereof.

[0227] In some embodiments, the additional therapeutic agent is selected from the group consisting of lopinavir, ritonavir, interferon-alpha-2b, ritonavir, arbidol, hydroxychloroquine,

darunavir and cobicistat, abidol hydrochloride, oseltamivir, litonavir, emtricitabine, tenofovir alafenamide fumarate, baloxavir marboxil, ruxolitinib, and combinations thereof.

[0228] In some embodiments, the additional therapeutic agent is selected from the group consisting of 6'-fluorinated aristeromycin analogues, acyclovir fleximer analogues, disulfiram, thiopurine analogues, ASC09F, GC376, GC813, phenylisoserine derivatives, neuroiminidase inhibitor analogues, pyrithiobac derivatives, bananins and 5-hydroxychromone derivatives, SSYA10-001, griffithsin, HR2P-M1, HR2P-M2, P21S10, Dihydrotanshinone E-64-C and E-64-D, OC43-HR2P, MERS-5HB, 229E-HR1P, 229E-HR2P, resveratrol, 1-thia-4-azaspiro[4.5] decan-3-one derivatives, gemcitabine hydrochloride, loperamide, recombinant interferons, cyclosporine A, alisporivir, imatinib mesylate, dasatinib, selumetinib, trametinib, rapamycin, saracatinib, chlorpromazine, trifluprom azine, fluphenazine, thiethylperazine, promethazine, cyclophilin inhibitors, K11777, camostat, k22, teicoplanin derivatives, benzo-heterocyclic amine derivatives N30, mycophenolic acid, silvestrol, and combinations thereof.

[0229] In some embodiments, the additional therapeutic agent is an antibody. In some embodiments, the additional therapeutic agent is an antibody that binds to a coronavirus, for example an antibody that binds to SARS-CoV or MERS-CoV. In some embodiments, the additional therapeutic agent is a of 2019-nCoV virus antibody.

[0230] Compositions of the invention are also used in combination with other active ingredients. For the treatment of 2019-nCoV virus infections, preferably, the other active therapeutic agent is active against coronavirus infections, for example 2019-nCoV virus infections. The compounds and compositions of the present invention are also intended for use with general care provided patients with 2019-nCoV viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including metronidazole and cephalosporin antibiotics, such as ceftriaxone and cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin K and zinc sulfate), anti-inflammatory agents (such as ibuprofen or steroids), corticosteroids such as methylprednisolone, immonumodulatory medications (*e.g.*, interferon), other small molecule or biologics antiviral agents targeting 2019-nCoV (such as but not limited to lopinavir/ritonavir, EIDD-1931, favipiravir, ribavirine, neutralizing antibodies, etc.), vaccines, pain medications, and medications for other common diseases in the patient

population, such anti-malarial agents (including artemether and artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as ciprofloxacin, macrolide antibiotics, such as azithromycin, cephalosporin antibiotics, such as ceftriaxone, or aminopenicillins, such as ampicillin), or shigellosis. In some embodiments, the additional therapeutic agent is dihydroartemisinin/piperaquine. In some embodiments, the additional therapeutic agent is EIDD-2801 (MH-4482, Molnupiravir).

[0231] In some embodiments, the additional therapeutic agent is an immunomodulator. 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 modulators; 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; polymer polyethyleneimine (PEI); gepon; IL-12; WF-10; VGV-1; MOR-22; BMS-936559; CYT-107, interleukin-15/Fc fusion protein, AM-0015, ALT-803, NIZ-985, NKTR-255, NKTR-262, NKTR-214, normferon, peginterferon alfa-2a, peginterferon alfa-2b, recombinant interleukin-15, Xmab-24306, RPI-MN, STING modulators, RIG-I modulators, NOD2 modulators, SB-9200, and IR-103. In some embodiments, the additional therapeutic agent is fingolimod, leflunomide, or a combination thereof. In some embodiments, the additional therapeutic agent is thalidomide.

[0232] In some embodiments, the additional therapeutic agent is an IL-6 inhibitor, for example tocilizumab, sarilumab, or a combination thereof.

[0233] In some embodiments, the additional therapeutic agent is an anti-TNF inhibitor. For example, the additional therapeutic agent is adalimumab, etanercept, golimumab, infliximab, or a combination thereof.

[0234] In some embodiments, the additional therapeutic agent is a JAK inhibitor, for example the additional therapeutic agent is baricitinib, filgotinib, olumiant, or a combination thereof.

[0235] In some embodiments, the additional therapeutic agent is an inflammation inhibitor, for example pirfenidone.

[0236] In some embodiments, the additional therapeutic agent is an antibiotic for secondary bacterial pneumonia. For example, the additional therapeutic agent is macrolide antibiotics

(e.g., azithromycin, clarithromycin, and *mycoplasma pneumoniae*), fluoroquinolones (e.g., ciprofloxacin and levofloxacin), tetracyclines (e.g., doxycycline and tetracycline), or a combination thereof.

[0237] In some embodiments, the compounds disclosed herein are used in combination with pneumonia standard of care (*see* e.g., Pediatric Community Pneumonia Guidelines, CID 2011:53 (1 October)). Treatment for pneumonia generally involves curing the infection and preventing complications. Specific treatment will depend on several factors, including the type and severity of pneumonia, age and overall health of the individuals. The options include: (i) antibiotics, (ii) cough medicine, and (iii) fever reducers/pain relievers (for e.g., aspirin, ibuprofen (Advil, Motrin IB, others) and acetaminophen (Tylenol, others)). In some embodiments, the additional therapeutic agent is bromhexine anti-cough.

[0238] In some embodiments, the compounds disclosed herein are used in combination with immunoglobulin from cured COVID-19 patients. In some embodiments, the compounds disclosed herein are used in combination with plasma transfusion. In some embodiments, the compounds disclosed herein are used in combination with stem cells.

[0239] In some embodiments, the additional therapeutic agent is an TLR agonist. Examples of TLR agonists include, but are not limited to, vesatolimod (GS-9620), GS-986, IR-103, lefitolimod, tilsotolimod, rintatolimod, DSP-0509, AL-034, G-100, cobitolimod, AST-008, motolimod, GSK-1795091, GSK-2245035, VTX-1463, GS-9688, LHC-165, BDB-001, RG-7854, telratolimod, and RO-7020531.

[0240] In some embodiments, the additional therapeutic agent is selected from the group consisting of bortezomid, flurazepam, ponatinib, sorafenib, paramethasone, clocortolone, flucloxacillin, sertindole, clevidipine, atorvastatin, cinolazepam, clofazimine, fosaprepitant, and combinations thereof.

[0241] In some embodiments, the additional therapeutic agent is carrimycin, suramin, triazavirin, dipyridamole, bevacizumab, meplazumab, GD31 (rhizobium), NLRP inflammasome inhibitor, or α-ketoamine. In some embodiments, the additional therapeutic agent is recombinant human angiotensin-converting enzyme 2 (rhACE2). In some embodiments, the additional therapeutic agent is viral macrophage inflammatory protein (vMIP).

[0242] In some embodiments, the additional therapeutic agent is an anti-viroporin therapeutic. For example, the additional therapeutic agent is BIT-314 or BIT-225. In some embodiments, the additional therapeutic agent is coronavirus E protein inhibitor. For example, the additional therapeutic agent is BIT-009. Further examples of additional therapeutic agents include those described in WO-2004112687, WO-2006135978, WO-2018145148, and WO-2009018609.

[0243] In some embodiments, the additional therapeutic or prophylactic agent is molnupiravir, oseltamivir, nirmatrelvir, or ritonavir. In some embodiments, the additional therapeutic or prophylactic agent is ritonavir or cobicistat.

[0244] It is also possible to combine any compound of the invention with one or more additional active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0245] Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

[0246] Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic

agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

[0247] The combination therapy may provide "synergy" and "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect, which is greater than the predicted purely additive effects of the individual compounds of the combination.

1. **Combination Therapy for the treatment of *Pneumoviridae***

[0248] The compounds provided herein are also used in combination with other active therapeutic agents. For the treatment of *Pneumoviridae* virus infections, preferably, the other active therapeutic agent is active against *Pneumoviridae* virus infections, particularly respiratory syncytial virus infections and/or metapneumovirus infections. Non-limiting examples of these other active therapeutic agents active against RSV are ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444 (also known as RSV604), MDT-637, BMS-433771, ALN-RSV0, ALX-0171 and mixtures thereof. Other non-limiting examples of other active therapeutic agents active against respiratory syncytial virus infections include respiratory syncytial virus protein F inhibitors, such as AK-0529; RV-521, ALX-0171, JNJ-53718678, BTA-585, and presatovir; RNA polymerase inhibitors, such as lumicitabine and ALS-8112; anti-RSV G protein antibodies, such as anti-G-protein mAb; viral replication inhibitors, such as nitazoxanide.

[0249] In some embodiments, the other active therapeutic agent may be a vaccine for the treatment or prevention of RSV, including but not limited to MVA-BN RSV, RSV-F, MEDI-8897, JNJ-64400141, DPX-RSV, SynGEM, GSK-3389245A, GSK-300389-1A, RSV-MEDI

deltaM2-2 vaccine, VRC-RSVRGP084-00VP, Ad35-RSV-FA2, Ad26-RSV-FA2, and RSV fusion glycoprotein subunit vaccine.

[0250] Non-limiting examples of other active therapeutic agents active against metapneumovirus infections include sialidase modulators such as DAS-181; RNA polymerase inhibitors, such as ALS-8112; and antibodies for the treatment of Metapneumovirus infections, such as EV-046113.

[0251] In some embodiments, the other active therapeutic agent may be a vaccine for the treatment or prevention of metapneumovirus infections, including but not limited to mRNA-1653 and rHMPV-Pa vaccine.

2. Combination Therapy for the treatment of *Picornaviridae*

[0252] The compounds provided herein are also used in combination with other active therapeutic agents. For the treatment of *Picornaviridae* virus infections, preferably, the other active therapeutic agent is active against *Picornaviridae* virus infections, particularly Enterovirus infections. Non-limiting examples of these other active therapeutic agents are capsid binding inhibitors such as pleconaril, BTA-798 (vapendavir) and other compounds disclosed by Wu, et al. (US 7,078,403) and Watson (US 7,166,604); fusion sialidase protein such as DAS-181; a capsid protein VP1 inhibitor such as VVX-003 and AZN-001; a viral protease inhibitor such as CW-33; a phosphatidylinositol 4 kinase beta inhibitor such as GSK-480 and GSK-533; anti-EV71 antibody.

[0253] In some embodiments, the other active therapeutic agent may be a vaccine for the treatment or prevention of *Picornaviridae* virus infections, including but not limited to EV71 vaccines, TAK-021, and EV-D68 adenovector-based vaccine.

3. Combination Therapy for Respiratory Infections

[0254] Many of the infections of the Pneumoviridae, Picornaviridae, and Coronaviridae viruses are respiratory infections. Therefore, additional active therapeutics used to treat respiratory symptoms and sequelae of infection may be used in combination with the compounds provided herein. The additional agents are preferably administered orally or by direct inhalation. For example, other preferred additional therapeutic agents in combination with the compounds provided herein for the treatment of viral respiratory infections include, but are not limited to, bronchodilators and corticosteroids.

Glucocorticoids

[0255] Glucocorticoids, which were first introduced as an asthma therapy in 1950 (Carryer, Journal of Allergy, 21, 282-287, 1950), remain the most potent and consistently effective therapy for this disease, although their mechanism of action is not yet fully understood (Morris, J. Allergy Clin. Immunol., 75 (1 Pt) 1-13, 1985). Unfortunately, oral glucocorticoid therapies are associated with profound undesirable side effects such as truncal obesity, hypertension, glaucoma, glucose intolerance, acceleration of cataract formation, bone mineral loss, and psychological effects, all of which limit their use as long-term therapeutic agents (Goodman and Gilman, 10th edition, 2001). A solution to systemic side effects is to deliver steroid drugs directly to the site of inflammation. Inhaled corticosteroids (ICS) have been developed to mitigate the severe adverse effects of oral steroids. Non-limiting examples of corticosteroids that may be used in combinations with the compounds provided herein are dexamethasone, dexamethasone sodium phosphate, fluorometholone, fluorometholone acetate, loteprednol, loteprednol etabonate, hydrocortisone, prednisolone, fludrocortisones, triamcinolone, triamcinolone acetonide, betamethasone, beclomethasone diproprionate, methylprednisolone, fluocinolone, fluocinolone acetonide, flunisolide, fluocortin-21-butylate, flumethasone, flumetasone pivalate, budesonide, halobetasol propionate, mometasone furoate, fluticasone, AZD-7594, ciclesonide; or a pharmaceutically acceptable salts thereof.

Anti-inflammatory agents

[0256] Other anti-inflammatory agents working through anti-inflammatory cascade mechanisms are also useful as additional therapeutic agents in combination with the compounds provided herein for the treatment of viral respiratory infections. Applying "anti-inflammatory signal transduction modulators" (referred to in this text as AISTM), like phosphodiesterase inhibitors (e.g., PDE-4, PDE-5, or PDE-7 specific), transcription factor inhibitors (e.g., blocking NFκB through IKK inhibition), or kinase inhibitors (e.g., blocking P38 MAP, JNK, PI3K, EGFR or Syk) is a logical approach to switching off inflammation as these small molecules target a limited number of common intracellular pathways - those signal transduction pathways that are critical points for the anti-inflammatory therapeutic intervention (see review by P.J. Barnes, 2006). These non-limiting additional therapeutic agents include: 5-(2,4-Difluoro-phenoxy)-1-isobutyl-1H-indazole-6-carboxylic acid (2-dimethylamino-ethyl)-amide (P38 Map kinase inhibitor ARRY-797); 3-Cyclopropylmethoxy-N-(3,5-dichloro-pyridin-4-yl)-4-difluorormethoxy-benzamide (PDE-4 inhibitor Roflumilast);

4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenyl-ethyl]-pyridine (PDE-4 inhibitor CDP-840); N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-8-[(methylsulfonyl)amino]-1-dibenzofurancarboxamide (PDE-4 inhibitor Oglemilast); N-(3,5-Dichloro-pyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxo-acetamide (PDE-4 inhibitor AWD 12-281); 8-Methoxy-2-trifluoromethyl-quinoline-5-carboxylic acid (3,5-dichloro-1-oxy-pyridin-4-yl)-amide (PDE-4 inhibitor Sch 351591); 4-[5-(4-Fluorophenyl)-2-(4-methanesulfinyl-phenyl)-1H-imidazol-4-yl]-pyridine (P38 inhibitor SB-203850); 4-[4-(4-Fluoro-phenyl)-1-(3-phenyl-propyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-but-3-yn-1-ol (P38 inhibitor RWJ-67657); 4-Cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl)-cyclohexanecarboxylic acid 2-diethylamino-ethyl ester (2-diethyl-ethyl ester prodrug of Cilomilast, PDE-4 inhibitor); (3-Chloro-4-fluorophenyl)-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yl]-amine (Gefitinib, EGFR inhibitor); and 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide (Imatinib, EGFR inhibitor).

β2-adrenoreceptor agonist bronchodilators

[0257] Combinations comprising inhaled β2-adrenoreceptor agonist bronchodilators such as formoterol, albuterol or salmeterol with the compounds provided herein are also suitable, but non-limiting, combinations useful for the treatment of respiratory viral infections.

[0258] Combinations of inhaled β2-adrenoreceptor agonist bronchodilators such as formoterol or salmeterol with ICS's are also used to treat both the bronchoconstriction and the inflammation (Symbicort® and Advair®, respectively). The combinations comprising these ICS and β2-adrenoreceptor agonist combinations along with the compounds provided herein are also suitable, but non-limiting, combinations useful for the treatment of respiratory viral infections.

[0259] Other examples of Beta 2 adrenoceptor agonists are bedoradrine, vilanterol, indacaterol, olodaterol, tulobuterol, formoterol, abediterol, salbutamol, arformoterol, levalbuterol, fenoterol, and TD-5471.

Anticholinergics

[0260] For the treatment or prophylaxis of pulmonary broncho-constriction, anticholinergics are of potential use and, therefore, useful as an additional therapeutic agent in combination with the compounds provided herein for the treatment of viral respiratory infections. These anticholinergics include, but are not limited to, antagonists of the muscarinic receptor

(particularly of the M3 subtype) which have shown therapeutic efficacy in man for the control of cholinergic tone in COPD (Witek, 1999); 1-{4-Hydroxy-1-[3,3,3-tris-(4-fluoro-phenyl)-propionyl]-pyrrolidine-2-carbonyl}-pyrrolidine-2-carboxylic acid (1-methyl-piperidin-4-ylmethyl)-amide; 3-[3-(2-Diethylamino-acetoxy)-2-phenyl-propionyloxy]-8-isopropyl-8-methyl-8-azonia-bicyclo[3.2.1]octane (Ipratropium-N,N-diethylglycinate); 1-Cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (Solifenacin); 2-Hydroxymethyl-4-methanesulfinyl-2-phenyl-butyric acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (Revatropate); 2-{1-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-pyrrolidin-3-yl}-2,2-diphenyl-acetamide (Darifenacin); 4-Azepan-1-yl-2,2-diphenyl-butyramide (Buzepide); 7-[3-(2-Diethylamino-acetoxy)-2-phenyl-propionyloxy]-9-ethyl-9-methyl-3-oxa-9-azonia-tricyclo[3.3.1.02,4]nonane (Oxitropium-N,N-diethylglycinate); 7-[2-(2-Diethylamino-acetoxy)-2,2-di-thiophen-2-yl-acetoxy]-9,9-dimethyl-3-oxa-9-azonia-tricyclo[3.3.1.02,4]nonane (Tiotropium-N,N-diethylglycinate); Dimethylamino-acetic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-methyl-phenyl ester (Tolterodine-N,N-dimethylglycinate); 3-[4,4-Bis-(4-fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-1-methyl-1-(2-oxo-2-pyridin-2-yl-ethyl)-pyrrolidinium; 1-[1-(3-Fluoro-benzyl)-piperidin-4-yl]-4,4-bis-(4-fluoro-phenyl)-imidazolidin-2-one; 1-Cyclooctyl-3-(3-methoxy-1-aza-bicyclo[2.2.2]oct-3-yl)-1-phenyl-prop-2-yn-1-ol; 3-[2-(2-Diethylamino-acetoxy)-2,2-di-thiophen-2-yl-acetoxy]-1-(3-phenoxy-propyl)-1-azonia-bicyclo[2.2.2]octane (Aclidinium-N,N-diethylglycinate); or (2-Diethylamino-acetoxy)-di-thiophen-2-yl-acetic acid 1-methyl-1-(2-phenoxy-ethyl)-piperidin-4-yl ester; revefenacin, glycopyrronium bromide, umeclidinium bromide, tiotropium bromide, aclidinium bromide, bencycloquidium bromide.

Mucolytic agents

[0261] The compounds provided herein may also be combined with mucolytic agents to treat both the infection and symptoms of respiratory infections. A non-limiting example of a mucolytic agent is ambroxol. Similarly, the compounds may be combined with expectorants to treat both the infection and symptoms of respiratory infections. A non-limiting example of an expectorant is guaifenesin.

[0262] Nebulized hypertonic saline is used to improve immediate and long-term clearance of small airways in patients with lung diseases (Kuzik, *J. Pediatrics* 2007, 266). Thus, the compounds provided herein may also be combined with nebulized hypertonic saline particularly when the virus infection is complicated with bronchiolitis. The combination of

the compound provided herein with hypertonic saline may also comprise any of the additional agents discussed above. In one embodiment, nebulized about 3% hypertonic saline is used.

4. Combination Therapy for the treatment of Flaviviridae virus infections

[0263] The compounds and compositions provided herein are also used in combination with other active therapeutic agents. For the treatment of *Flaviviridae* virus infections, preferably, the other active therapeutic agent is active against *Flaviviridae* virus infections.

[0264] For treatment of the dengue virus infection, non-limiting examples of the other active therapeutic agents are host cell factor modulators, such as GBV-006; fenretinide ABX-220, BRM-211; alpha-glucosidase 1 inhibitors, such as celgosivir; platelet activating factor receptor (PAFR) antagonists, such as modipafant; cadherin-5/Factor Ia modulators, such as FX-06; NS4B inhibitors, such as JNJ-8359; viral RNA splicing modulators, such as ABX-202; a NS5 polymerase inhibitor; a NS3 protease inhibitor; and a TLR modulator.

[0265] In some embodiments, the other active therapeutic agent may be a vaccine for the treatment or prevention of dengue, including but not limited to TetraVax-DV, Dengvaxia ®, DPIV-001, TAK-003, live attenuated dengue vaccine, tetravalent dengue fever vaccine, tetravalent DNA vaccine, rDEN2delta30-7169; and DENV-1 PIV.

5. Combination Therapy for the treatment of *Filoviridae* virus infections

[0266] The compounds provided herein are also used in combination with other active therapeutic agents. For the treatment of *Filoviridae* virus infections, preferably, the other active therapeutic agent is active against *Filoviridae* virus infections, particularly Marburg virus, Ebola virus and Cueva virus infections. Non-limiting examples of these other active therapeutic agents are: ribavirin, amiodarone, dronedarone, verapamil, Ebola Convalescent Plasma (ECP), TKM-100201, BCX4430 ((2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol), TKM-Ebola, T-705 monophosphate, T-705 diphosphate, T-705 triphosphate, FGI-106 (1-N,7-N-bis[3-(dimethylamino)propyl]-3,9-dimethylquinolino[8,7-h]quinolone-1,7-diamine), rNAPc2, OS-2966, brincidofovir, remdesivir; RNA polymerase inhibitors, such as galidesivir, favipiravir (also known as T-705 or Avigan), JK-05; host cell factor modulators, such as GMV-006; cadherin-5/factor Ia modulators, such as FX-06; and antibodies for the treatment of Ebola, such as REGN-3470-3471-3479 and ZMapp.

[0267] Other non-limiting active therapeutic agents active against Ebola include an alpha-glucosidase 1 inhibitor, a cathepsin B inhibitor, a CD29 antagonist, a dendritic ICAM-3 grabbing nonintegrin 1 inhibitor, an estrogen receptor antagonist, a factor VII antagonist HLA class II antigen modulator, a host cell factor modulator, a Interferon alpha ligand, a neutral alpha glucosidase AB inhibitor, a niemann-Pick C1 protein inhibitor, a nucleoprotein inhibitor, a polymerase cofactor VP35 inhibitor, a Serine protease inhibitor, a tissue factor inhibitor, a TLR-3 agonist, a viral envelope glycoprotein inhibitor, and an Ebola virus entry inhibitors (NPC1 inhibitors).

[0268] In some embodiments, the other active therapeutic agent may be a vaccine for the treatment or prevention of Ebola, including but not limited to VRC-EBOADC076-00-VP, adenovirus-based Ebola vaccine, rVSV-EBOV, rVSVN4CT1-EBOVGP, MVA-BN Filo + Ad26-ZEBOV regimen, INO-4212, VRC-EBODNA023-00-VP, VRC-EBOADC069-00-VP, GamEvac-combi vaccine, SRC VB Vector, HPIV3/EboGP vaccine, MVA-EBOZ, Ebola recombinant glycoprotein vaccine, Vaxart adenovirus vector 5-based Ebola vaccine, FiloVax vaccine, GOVX-E301, and GOVX-E302.

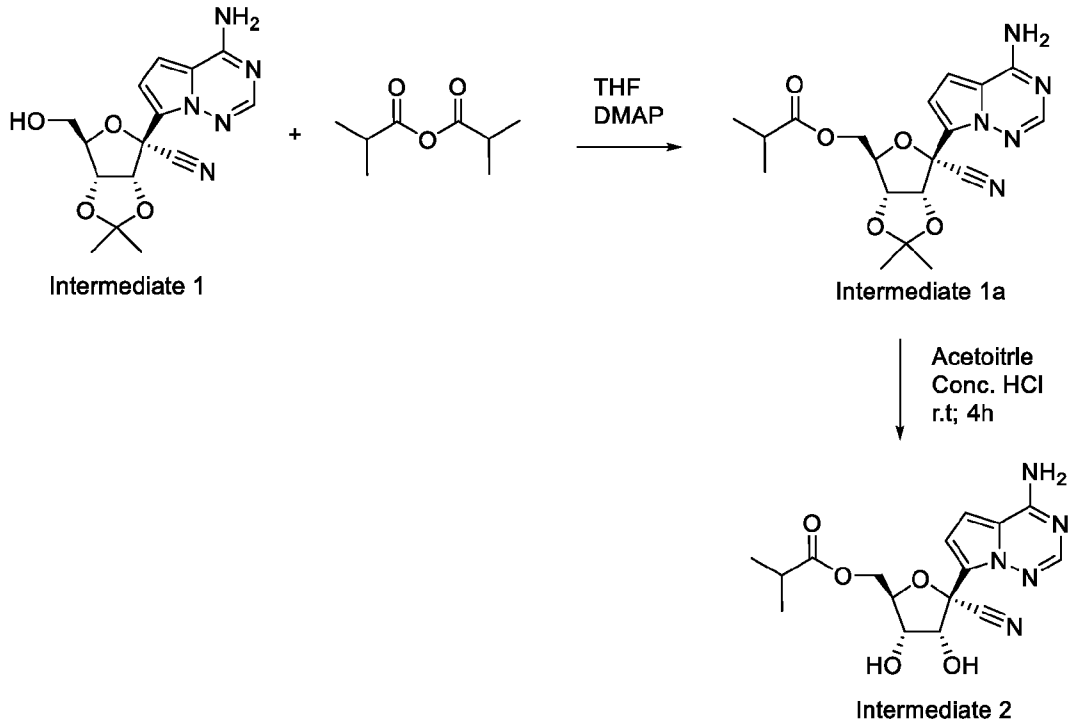
[0269] The compounds provided herein may also be used in combination with phosphoramidate morpholino oligomers (PMOs), which are synthetic antisense oligonucleotide analogs designed to interfere with translational processes by forming base-pair duplexes with specific RNA sequences. Examples of PMOs include but are not limited to AVI-7287, AVI-7288, AVI-7537, AVI-7539, AVI-6002, and AVI-6003.

[0270] The compounds provided herein are also intended for use with general care provided to patients with *Filoviridae* viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including metronidazole and cephalosporin antibiotics, such as ceftriaxone and cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin K and zinc sulfate), anti-inflammatory agents (such as ibuprofen), pain medications, and medications for other common diseases in the patient population, such anti-malarial agents (including artemether and artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as ciprofloxacin, macrolide antibiotics, such as azithromycin, cephalosporin antibiotics, such as ceftriaxone, or aminopenicillins, such as ampicillin), or shigellosis.

[0271] The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters, which can be changed or modified to yield essentially the same results.

X. EXAMPLES

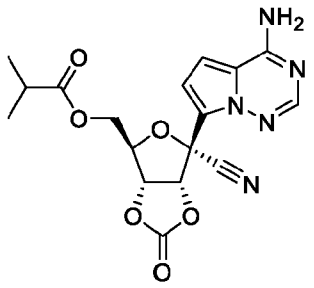
Example 1: Synthesis of intermediate 2



[0272] To a solution of (3aR,4R,6R,6aR)-4-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonitrile, **Intermediate 1** (2000 mg, 6.0 mmol) (Siegel et. al. J. Med. Chem. 2017, 60, 1648-1661) in tetrahydrofuran (THF) was added N,N-dimethylaminopyridine (DMAP) (0.03 eq). To the reaction mixture, isobutyric anhydride (1.1 eq) was added slowly. After the completion of the staring material, the reaction mixture was concentrated and purified by flash chromatography using 20% methanol in DCM as an eluant to give ((3aR,4R,6R,6aR)-6-(4- aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-cyano-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4- yl)methyl isobutyrate, **Intermediate 1a**. LCMS: MS m/z: 402.2 (M+1).

[0273] Concentrated HCl (5 eq, 1mL) was added to a solution of **Intermediate 1a** (1000 mg) in acetonitrile (10 mL), which was then stirred at room temperature for 2 hours. LCMS showed the product formation. The reaction was stopped after 4 hours. The reaction mixture was diluted with ethyl acetate and quenched with saturated bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulphate, and concentrated. The residue was purified by flash chromatography using 30% methanol DCM as an eluant. The collected fractions were concentrated to give **Intermediate 2**. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.88 (s, 1H), 6.96 – 6.85 (m, 2H), 4.50 – 4.27 (m, 4H), 4.16 (dd, J = 6.2, 5.3 Hz, 1H), 2.56 (p, J = 7.0 Hz, 1H), 1.14 (dd, J = 7.0, 3.8 Hz, 6H); LCMS: MS m/z: 362.1 (M+1).

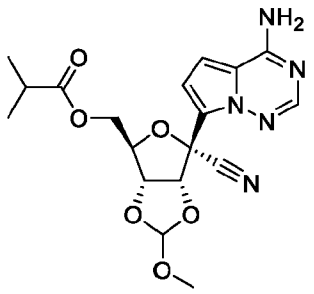
Example 2: ((3aR,4R,6R,6aR)-6-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-cyano-2-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl isobutyrate (Compound 3)



Compound 3

[0274] Diphenyl carbonate (1423 mg, 6.6 mmol) and triethylamine (560 mg, 5.5 mmol) were added to a solution of **Intermediate 2** (2000 mg, 5.5 mmol) in DMF (5 mL), which was then heated at 130 °C and stirred for 2 hours. LCMS showed the complete conversion to the product. The reaction mixture was diluted with ethyl acetate, washed with bicarbonate, water, brine, dried over sodium sulphate, concentrated, and purified by flash using dichloromethane and ethyl acetate as eluants to provide **Compound 3.** ^{1}H NMR (400 MHz, DMSO-d6) δ 7.98 (s, 2H), 6.98 – 6.87 (m, 2H), 5.99 (d, J = 7.7 Hz, 1H), 5.49 (dd, J = 7.6, 3.7 Hz, 1H), 4.81 (q, J = 4.2 Hz, 1H), 4.34 (dd, J = 12.2, 4.0 Hz, 1H), 4.23 (dd, J = 12.2, 5.2 Hz, 1H), 2.44 (p, J = 7.0 Hz, 1H), 1.00 (dd, J = 13.3, 7.0 Hz, 6H); LCMS: MS m/z: 388.1 (M+1).

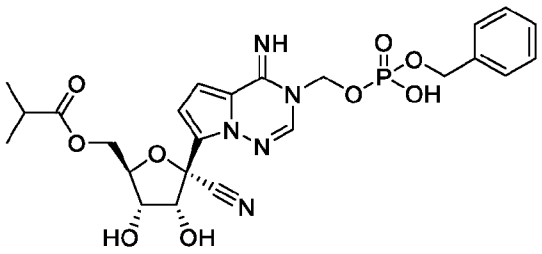
Example 3: ((3aR,4R,6R,6aR)-6-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-cyano-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl isobutyrate (Compound 4)



Compound 4

[0275] To a solution of **Intermediate 2** (250 mg, 0.67 mmol) in dichloromethane (10 mL), trimethyl orthoformate (220 mg, 2.1 mmol) was added followed by pyridinium p-toluenesulfonate (174 mg, 0.7 mmol), and the reaction mixture was stirred at room temperature for 18 hours. Alter the completion of starting material, the reaction mixture was diluted with dichloromethane (50 mL), washed with saturated sodium bicarbonate solution, water, brine, dried and concentrated. The residue was purified by slash chromatography using DCM/ethyl acetate as eluants to provide **Compound 4**. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (s, 1H), 7.04 (d, J = 4.6 Hz, 1H), 6.65 (d, J = 4.6 Hz, 1H), 6.07 (s, 1H), 5.67 (s, 2H), 5.37 (d, J = 7.2 Hz, 1H), 5.05 (dd, J = 7.2, 6.2 Hz, 1H), 4.82 (td, J = 6.1, 4.3 Hz, 1H), 4.45 (dd, J = 11.9, 4.4 Hz, 1H), 4.28 (dd, J = 11.9, 6.1 Hz, 1H), 3.70 (d, J = 0.7 Hz, 1H), 3.57 (d, J = 0.7 Hz, 3H), 2.57 (p, J = 7.0 Hz, 1H), 1.16 (dd, J = 7.0, 1.0 Hz, 6H); LCMS: MS m/z: 404.1

Example 4: ((2R,3S,4R,5R)-5-(3-((((benzyloxy)(hydroxy)phosphoryl)oxy)methyl)-4-imino-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl isobutyrate (Compound 5)

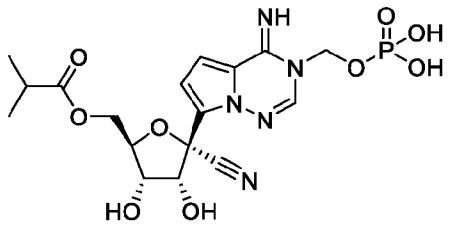


Compound 5

[0276] Dibenzyl chloromethyl phosphate (1805 mg, 5.5 mmol) in acetone (5 mL) was added slowly to a solution of **Intermediate 2** (1000 mg, 2.8 mmol) and sodium iodide (830 mg, 5.5

mmol) in acetone (20 mL), which was then stirred at room temperature for 48 hours. After completion of the reaction, the solvents were distilled off, and the residue was charged onto a flash column and eluted with dichloromethane and methanol as eluants to obtain **Compound 5**. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.53 (s, 1H), 8.52 (s, 1H), 7.49 (d, J = 4.7 Hz, 1H), 7.34 – 7.17 (m, 5H), 7.01 (d, J = 4.7 Hz, 1H), 5.69 (d, J = 11.2 Hz, 2H), 4.80 (d, J = 7.1 Hz, 2H), 4.58 (d, J = 4.8 Hz, 1H), 4.36 – 4.24 (m, 2H), 4.18 (dd, J = 13.0, 5.9 Hz, 1H), 3.93 (dd, J = 6.5, 4.8 Hz, 1H), 2.56 (d, J = 7.0 Hz, 1H), 1.06 (d, J = 7.0 Hz, 6H), ^{31P} NMR (162 MHz, DMSO-d6) δ 0.02; ^{19F} NMR (376 MHz, DMSO-d6) δ -74.94; LCMS: MS m/z: 562.2 (M+1)

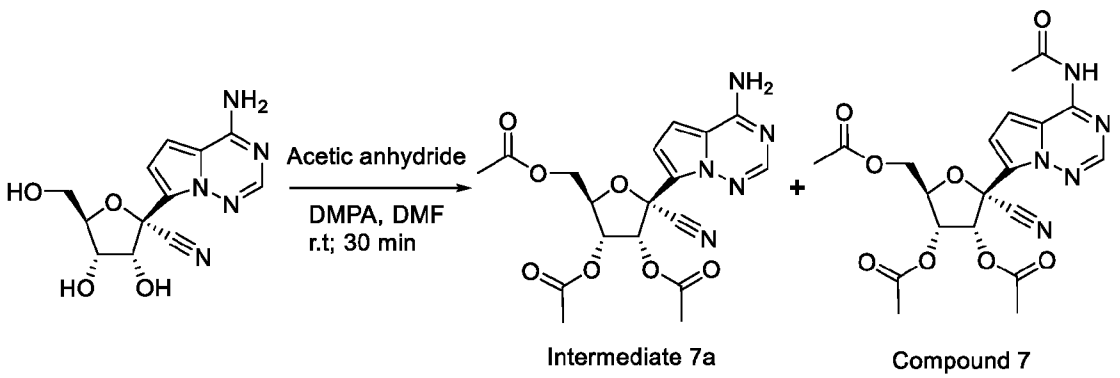
Example 5: ((2R,3S,4R,5R)-5-cyano-3,4-dihydroxy-5-(4-imino-3-((phosphonooxy)methyl)-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl isobutyrate (Compound 6)



Compound 6

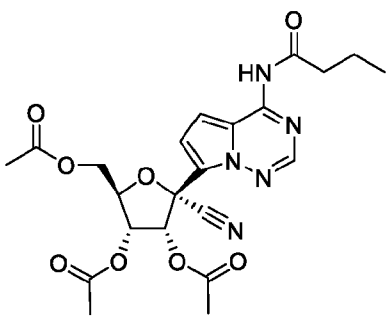
[0277] To a solution of **Compound 5** (600 mg, 1.1 mmol) in ethanol, was added 5% Palladium on Carbon (30 mg). The resulting mixture stirred under hydrogen balloon for 48 hours. The reaction was stopped. The mixture was filtered washing with ethyl acetate. The filtrate was concentrated to give a residue. The residue was purified by prep HPLC using 0.1% trifluoroacetate (TFA) in acetonitrile and 0.1% TFA in water as eluants to obtain **Compound 6** as a TFA salt. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.56 (s, 1H), 8.52 (s, 1H), 7.53 (d, J = 4.7 Hz, 1H), 7.02 (d, J = 4.7 Hz, 1H), 5.74 (d, J = 11.6 Hz, 2H), 4.59 (d, J = 4.9 Hz, 1H), 4.36 – 4.24 (m, 2H), 4.17 (dd, J = 12.9, 5.7 Hz, 1H), 3.93 (dd, J = 6.4, 4.8 Hz, 1H), 2.56 (d, J = 7.0 Hz, 1H), 1.06 (dd, J = 6.9, 0.8 Hz, 5H); ^{31P} NMR (162 MHz, DMSO-d6) δ -0.12; ^{19}F NMR (376 MHz, DMSO-d6) δ -74.47; LCMS: MS m/z: 472.1 (M+1)

Example 6: (2R,3R,4R,5R)-2-(4-acetamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-(acetoxymethyl)-2-cyanotetrahydrofuran-3,4-diyl diacetate (Compound 7)



[0278] To a suspension of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (100 mg, 3.4 mmol) and DMAP (419 mg, 3.4 mmol) in anhydrous dimethylformamide (DMF) (5 mL) was added acetic anhydride (2804 mg, 27 mmol) dropwise. The reaction mixture was stirred at room temperature for 30 min. After completion of the starting material, the reaction mixture was concentrated under high vacuum to remove DMF. The resulting residue was dissolved in ethyl acetate (200 mL), washed with saturated $NaHCO_3$ (75 mL x 3), dried, concentrated in vacuo, and purified by flash chromatography using hexanes and ethyl acetate as eluants to isolate **Intermediate 7a** and **Compound 7**. **Intermediate 7a**: LCMS: MS m/z: 418.1 (M+1). **Compound 7**: ^{1}H NMR (400 MHz, Methanol-d4) δ 8.28 (s, 1H), 7.27 (d, J = 4.8 Hz, 1H), 7.12 (d, J = 4.8 Hz, 1H), 6.25 (d, J = 5.8 Hz, 1H), 5.53 – 5.46 (m, 1H), 4.66 (td, J = 4.7, 3.5 Hz, 1H), 4.49 (dd, J = 12.3, 3.5 Hz, 1H), 4.36 (dd, J = 12.3, 4.7 Hz, 1H), 2.42 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H); LCMS: MS m/z: 460.1 (M+1)

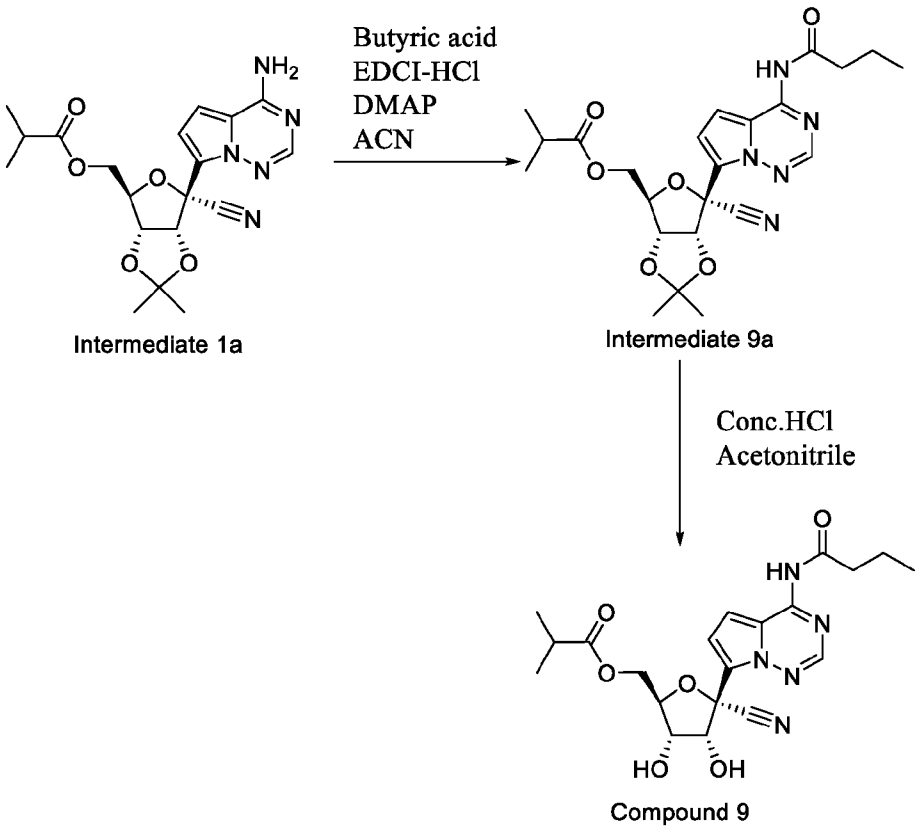
Example 7: (2R,3R,4R,5R)-5-(acetoxymethyl)-2-(4-butyramidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2-cyanotetrahydrofuran-3,4-diyl diacetate (Compound 8)



Compound 8

[0279] To a solution of **Intermediate 7a** (600 mg, 1.4 mmol) in DMF (5 mL) was added butanoic acid (253 mg, 2.9 mmol). To the solution, N,N'-diisopropylcarbodiimide (218 mg, 1.7 mmol) was added slowly followed by DMAP (176 mg, 1.4 mmol) at room temperature and stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water and brine, dried, and concentrated. The resulting residue was purified by flash chromatography using 20% methanol in DCM as an eluant to obtain **Compound 8**. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.42 (s, 1H), 7.31 (d, J = 4.8 Hz, 1H), 7.05 (d, J = 4.8 Hz, 1H), 6.06 (d, J = 5.9 Hz, 1H), 5.40 (dd, J = 5.9, 4.6 Hz, 1H), 4.63 (td, J = 4.7, 3.2 Hz, 1H), 4.38 (dd, J = 12.4, 3.3 Hz, 1H), 4.24 (dd, J = 12.4, 4.8 Hz, 1H), 2.70 (t, J = 7.2 Hz, 2H), 2.12 (d, J = 3.6 Hz, 6H), 1.99 (s, 3H), 1.64 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); LCMS: MS m/z: 488.1 (M+1)

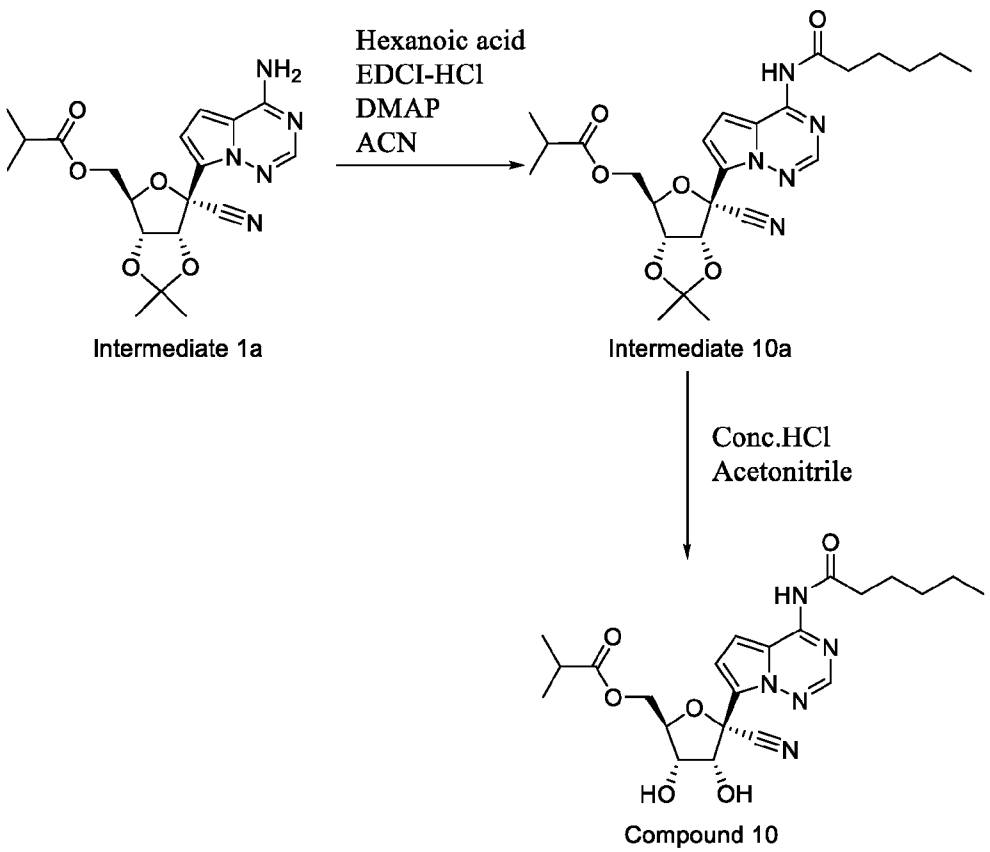
Example 8: ((2R,3S,4R,5R)-5-(4-butyramidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl isobutyrate (Compound 9)



[0280] To a mixture of **Intermediate 1a** (1100 mg, 2.74 mmol) and butyric acid (0.654 mL, 7.12 mmol) in acetonitrile (CAN) (10mL) was added DMAP (870 mg, 7.12 mmol) followed by 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1370 mg, 7.12 mmol) at room temperature. The resulting mixture was stirred at room temperature for 15 hours, quenched with MeOH, concentrated in vacuo, and purified by silica gel column chromatography (0 to 70% EtOAc in hexanes) to provide **Intermediate 9a**. LCMS: MS m/z: 472 (M+1).

[0281] To a solution of **Intermediate 9a** (1200 mg, 2.55 mmol) in ACN (15 mL) was added conc. HCl (12 mL) at room temperature. The mixture was stirred at room temperature for 1 hour, diluted with ethyl acetate (100 mL), and neutralized with saturated sodium bicarbonate (30 mL). The resulting mixture was stirred at room temperature for 5 min. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers was dried under sodium sulfate, concentrated in vacuo, and purified flash chromatography using dichloromethane and methanol as eluants to provide **Compound 9**. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.40 (s, 1H), 7.29 (d, J = 4.8 Hz, 1H), 7.06 (d, J = 4.8 Hz, 1H), 6.43 (d, J = 6.0 Hz, 1H), 5.44 (d, J = 5.9 Hz, 1H), 4.69 (t, J = 5.4 Hz, 1H), 4.36 – 4.25 (m, 2H), 4.19 (dd, J = 11.5, 4.4 Hz, 1H), 3.97 (q, J = 5.8 Hz, 1H), 2.70 (t, J = 7.3 Hz, 2H), 2.50 (m, 1H), 1.65 (h, J = 7.3 Hz, 2H), 1.05 (dd, J = 7.0, 3.5 Hz, 6H), 0.94 (t, J = 7.4 Hz, 3H); LCMS: MS m/z: 432 (M+1)

Example 9: ((2R,3S,4R,5R)-5-cyano-5-(4-hexanamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl isobutyrate (Compound 10)

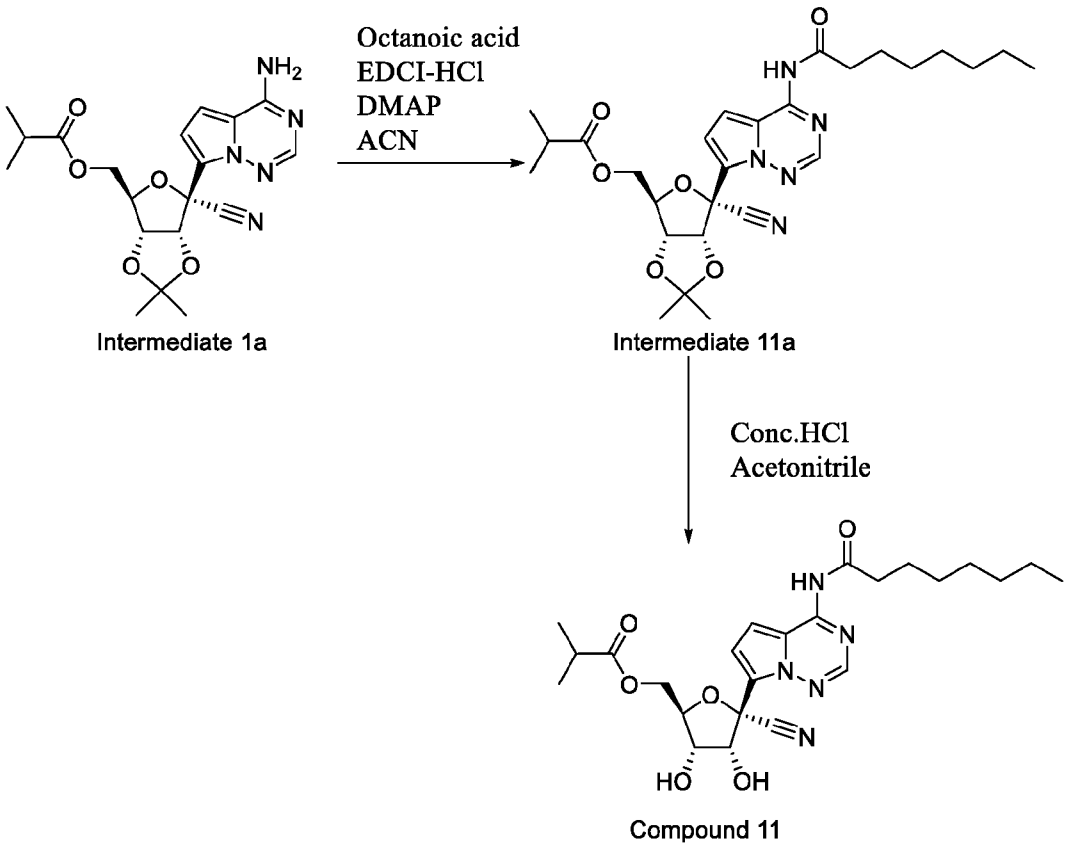


[0282] To a mixture of **Intermediate 1a** (150 mg, 0.374 mmol) and hexanoic acid (0.121 mL, 0.972 mmol) in ACN (2 mL) was added DMAP (119 mg, 0.972 mmol), and then EDCI (186 mg, 0.972 mmol) at room temperature. The resulting mixture was stirred at room temperature for 15 hours, quenched with MeOH, concentrated in vacuo, and purified by silica gel column chromatography (0 to 5% MeOH in DCM) to obtain **Intermediate 10a**. LCMS: MS m/z: 500.2 (M+1)

[0283] To a solution of **Intermediate 10a** (160 mg, 0.32 mmol) in ACN (2 mL) was added conc. HCl (0.16 mL) at room temperature. The mixture was stirred at room temperature for 1 hour, neutralized in water bath with triethanolamine (TEA) (0.4 mL), and purified by HPLC (10% to 100% ACN in water for 15 min, then 100% ACN for 3 min, total run 20 min) to provide **Compound 10**. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.40 (s, 1H), 7.29 (d, J = 4.8 Hz, 1H), 7.06 (d, J = 4.7 Hz, 1H), 6.43 (d, J = 6.1 Hz, 1H), 5.44 (d, J = 5.9 Hz, 1H), 4.68 (t, J = 5.5 Hz, 1H), 4.38 – 4.24 (m, 2H), 4.18 (dd, J = 11.6, 4.5 Hz, 1H), 3.96 (q, J = 5.8 Hz, 1H), 2.71 (t, J = 7.4 Hz, 2H), 2.51 (m, 1H), 1.62 (td, J = 12.2, 9.7, 5.1 Hz, 2H), 1.32

(h, J = 4.7, 3.9 Hz, 4H), 1.05 (dd, J = 7.0, 3.6 Hz, 6H), 0.93 – 0.83 (m, 3H); LCMS: MS m/z: 460.3 (M+1)

Example 10: ((2R,3S,4R,5R)-5-cyano-3,4-dihydroxy-5-(4-octanamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl isobutyrate (Compound 11)



[0284] To a mixture of **Intermediate 1a** (1100 mg, 2.74 mmol) and butyric acid (0.654 mL, 7.12 mmol) in ACN (10mL) was added DMAP (870 mg, 7.12 mmol), and then EDCI (1370 mg, 7.12 mmol) at room temperature. The resulting mixture was stirred at room temperature for 15 hours, quenched with MeOH, concentrated in vacuo, and purified by silica gel column chromatography (0 to 5% MeOH in DCM) to provide **Intermediate 11a**. LCMS: MS m/z: 528.2 (M+1)

[0285] To a solution of **Intermediate 11a** (90 mg, 0.171 mmol) in ACN (1 mL) was added conc. HCl (0.10 mL) at room temperature. The mixture was stirred at room temperature for 1 hour, neutralized in water bath with TEA (0.4 mL), and purified by HPLC (10% to 100%

ACN in water for 15 min, then 100% ACN for 3 min, total run 20 min) to provide **Compound 11**. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.40 (s, 1H), 7.28 (d, J = 4.7 Hz, 1H), 7.06 (d, J = 4.7 Hz, 1H), 6.43 (d, J = 6.0 Hz, 1H), 5.44 (d, J = 5.9 Hz, 1H), 4.68 (t, J = 5.4 Hz, 1H), 4.36 – 4.23 (m, 2H), 4.23 (s, 0H), 3.96 (q, J = 5.5 Hz, 1H), 2.71 (t, J = 7.4 Hz, 2H), 2.51 (m, 1H), 1.62 (t, J = 7.3 Hz, 2H), 1.39 – 1.21 (m, 8H), 1.05 (dd, J = 7.0, 3.7 Hz, 6H), 0.92 – 0.78 (m, 3H); LCMS: MS m/z: 488.2 (M+1)

Example A: ***HEp-2 RSV-Luc5 384-well Assay***

[0286] HEp-2 cell line was purchased from ATCC (Manassas, VA Cat # CCL-23) and maintained in Dulbecco's Minimum Essential Medium (DMEM) (Corning, New York, NY, Cat # 15-018CM) supplemented with 10% fetal bovine serum (FBS) (Hyclone, Logan, UT, Cat # SH30071-03) and 1X Penicillin-Streptomycin-L-Glutamine (Corning, New York, NY, Cat #30-009-CI). Cells were passaged 2 times per week to maintain sub-confluent densities and were used for experiments at passage 5-20. Respiratory syncytial virus recombinant with luciferase (RSV-Luc5) (≥1 x107 TCID50/ml) was purchased from Microbiologics (Saint Cloud, MN). Viral replication was determined in HEp-2 cells in the following manner.

[0287] Compounds are prepared in 100% DMSO in 384-well polypropylene plates (*Greiner, Monroe, NC,* Cat# 784201) with 8 compounds per plate in grouped replicates of 4 at 10 serially diluted concentrations (1:3). The serially diluted compounds were transferred to low dead volume Echo plates (Labcyte, Sunnyvale, CA, Cat# LP-0200).

[0288] The test compounds were spotted to 384-well assay plates (Greiner, Monroe, NC, Cat# 781091) at 200nL per well. HEp-2 cells were harvested and suspended in DMEM (supplemented with 10% FBS and 1X Penicillin-Streptomycin-L-Glutamine) and seeded to the pre-spotted assay plates at 4,000 cells per well in 30μL. RSV-Luc5 viruses were diluted in DMEM (supplemented with 10% FBS and 1X Penicillin-Streptomycin-L-Glutamine) at 200,000 Infectious Units (IU) per mL and 10μL per well was added to the assay plates containing cells and compounds, for an MOI=0.5. The assay plates were incubated for 3 days at 37°C and 5% CO_2. At the end of incubation, One-Glo reagent (Promega, Madison, WI, Cat #E6120) was prepared. The assay plates and One-Glo reagent were equilibrated to room temperature for at least 15 minutes. 40 μL per well of One-Glo reagent was added and the plates were incubated at room temp for 15 minutes before reading the luminescence signal on

an EnVision multimode plate reader (Perkin Elmer, Waltham, MA). Remdesivir was used as positive control and DMSO was used as negative control. Values were normalized to the positive and negative controls (as 0% and 100% replication, respectively) and data was fitted using non-linear regression analysis by Gilead's dose response tool. The EC_{50} value for each compound was then determined as the concentration reducing the viral replication by 50%.

Example B: ***A549-hACE2 SARS-CoV2-NLuc 384-well Assay***

[0289] A549-hACE2 cell line was maintained in Dulbecco's Minimum Essential Medium (DMEM) (Corning, New York, NY, Cat # 15-018CM) supplemented with 10% fetal bovine serum (FBS) (Hyclone, Logan, UT, Cat # *SH30071-03*), 1X *Penicillin-Streptomycin-L-Glutamine* (Corning, New York, NY, Cat *#30-009-CI*) and 10µg/mL blasticidin (Life Technologies Corporation, Carlsbad, CA, Cat #A11139-03). Cells were passaged 2 times per week to maintain sub-confluent densities and were used for experiments at passage 5-20. SARS Coronavirus 2 recombinant with NanoLuc (SARS-CoV2-NLuc) was obtained from University of Texas Medical Branch (Galveston, TX). Viral replication was determined in A549-hACE2 cells in the following manner.

[0290] Compounds are prepared in 100% DMSO in 384-well polypropylene plates (*Greiner, Monroe, NC,* Cat# 784201) with 8 compounds per plate in grouped replicates of 4 at 10 serially diluted concentrations (1:3). The serially diluted compounds were transferred to low dead volume Echo plates (Labcyte, Sunnyvale, CA, Cat# LP-0200).

[0291] The test compounds were spotted to 384-well assay plates (Greiner, Monroe, NC, Cat# 781091) at 200nL per well using an Echo acoustic dispenser (Labcyte, Sunnyvale, CA). A549-hACE2 cells were harvested and suspended in DMEM (supplemented with 2% FBS and 1X Penicillin-Streptomycin-L-Glutamine) and seeded to the pre-spotted assay plates at 10,000 cells per well in 30µL. SARS-CoV2-NLuc virus was diluted in DMEM (supplemented with 2% FBS and 1X Penicillin-Streptomycin-L-Glutamine) at 350,000 Infectious Units (IU) per mL and 10µL per well was added to the assay plates containing cells and compounds, for an MOI of 0.35. The assay plates were incubated for 2 days at 37°C and 5% CO_2. At the end of incubation, Nano-Glo reagent (Promega, Madison, WI, Cat # N1150) was prepared. The assay plates and Nano-Glo reagent were equilibrated to room temperature for at least 15 minutes. 40µL per well of Nano-Glo reagent was added and the

plates were incubated at room temperature for 15 minutes before reading the luminescence signal on an EnVision multimode plate reader (Perkin Elmer, Waltham, MA). Remdesivir was used as positive control and DMSO was used as negative control. Values were normalized to the positive and negative controls (as 0% and 100% replication, respectively) and data was fitted using non-linear regression analysis by Gilead's dose response tool. The EC_{50} value for each compound was defined as the concentration reducing the viral replication by 50%.

Example C: NHBE *RSV-Luc5 384-well Assay*

[0292] Normal Human Bronchial Epithelial (NHBE) cells were purchased from Lonza (*Walkersville, MD* Cat # *CC2540*) and maintained in *BEGM Bronchial Epithelial Cell Growth Medium BulletKit* (Lonza CC-3170).

[0293] Cells were thawed, expanded, and were used for experiments at passage 2. Respiratory syncytial virus recombinant with luciferase (RSV-Luc5) (> 1 $x10^7$ Infectious Units/ml (IU/ml) determined by $TCID_{50}$) was purchased from Microbiologics (Saint Cloud, MN). Viral replication was determined in NHBE cells in the following manner.

[0294] Compounds are prepared in 100% DMSO in 384-well polypropylene plates (*Greiner, Monroe, NC,* Cat# 784201) with 8 compounds per plate in grouped replicates of 4 at 10 serially diluted concentrations (1:3). The serially diluted compounds were transferred to low dead volume Echo plates (Labcyte, Sunnyvale, CA, Cat# LP-0200).

[0295] The test compounds were spotted to 384-well assay plates (Greiner, Monroe, NC, Cat# 781091) at 200nL per well. NHBE cells were harvested and suspended in BEGM Bronchial Epithelial Cell Growth Medium BulletKit and seeded to the pre-spotted assay plates at 5,000 cells per well in 30µL. RSV-Luc5 virus was diluted in BEGM Bronchial Epithelial Cell Growth Medium BulletKit at 500,000 Infectious Units (IU) per mL and 10µL per well was added to the assay plates containing cells and compounds, for an MOI of 1. The assay plates were incubated for 3 days at 37°C and 5% CO_2. At the end of incubation, One-Glo reagent (Promega, Madison, WI, Cat #E6120) was prepared. The assay plates and One-Glo reagent were equilibrated to room temperature for at least 15 minutes. 40µL per well of One-Glo reagent was added and the plates were incubated at room temperature for 15 minutes before reading the luminescence signal on an EnVision multimode plate reader

(Perkin Elmer, Waltham, MA). Remdesivir was used as positive control and DMSO was used as negative control. Values were normalized to the positive and negative controls (as 0% and 100% replication, respectively) and data was fitted using non-linear regression analysis by Gilead's dose response tool. The EC_{50} value for each compound was defined as the concentration reducing the viral replication by 50%.

Example D: CC50 MT4

[0296] Cytotoxicity of the compounds was determined in uninfected cells using the cell viability reagent in a similar fashion as described before for other cell types (Cihlar et al., Antimicrob Agents Chemother. 2008,52(2):655-65). HEp-2 (1.5 × 103 cells/well) and MT-4 (2 × 103 cells/well) cells were plated in 384-well plates and incubated with the appropriate medium containing 3-fold serially diluted compound ranging from 15 nM to 100,000 nM. Cells were cultured for 4-5 days at 37 °C. Following the incubation, the cells were allowed to equilibrate to 25°C, and cell viability was determined by adding Cell-Titer Glo viability reagent. The mixture was incubated for 10 min, and the luminescence signal was quantified using an Envision plate reader. Untreated cell and cells treated at 2 μM puromycin (Sigma, St. Louis, MO) serve as 100% and 0% cell viability control, respectively. The percent of cell viability was calculated for each tested compound concentration relative to the 0% and 100% controls and the CC_{50} value was determined by non-linear regression as a compound concentration reducing the cell viability by 50%.

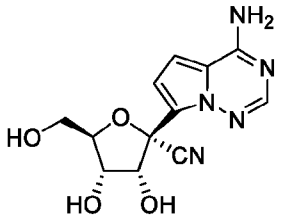
Table D1:

Compound No.	**RSV Hep2 EC_{50} (nM)**	**RSV NHBE EC_{50} (nM)**	**SARS-CoV2 EC_{50} (nM)**	**MT4 CC_{50} (μM)**
3	330	512	1748	50000
4			>50000	>5000
5			>50000	>50000
6	719	3553	3646	50000

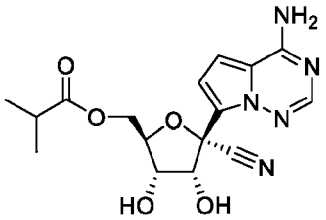
7		932	5538	
8		405	3136	
9	529		1951	>50000
10			1217	>50000
11		188	935	42385

Example E: Rat pharmacokinetics assay

[0297] Ester Reference Compound, Compound 3 and **Compound 6** were dosed orally by gavage to male Sprague-Dawley rats (n=3/group); **Ester Reference Compound** at 6 mg/kg in 2.5% Dimethyl sulfoxide; 10% Kolliphor HS-15; 10% Labrasol; 2.5% Propylene glycol and 75% water, pH 2.5; **Compound 3** at 6.65 mg/kg in 10% Dimethyl sulfoxide; 40% Kolliphor HS-15; 40% Labrasol and 10% Propylene glycol and **Compound 6** at 8.1 mg/kg in 2.5% Dimethyl sulfoxide; 10% Kolliphor HS-15; 10% Labrasol; 2.5% Propylene glycol and 75% water, pH 2.8. Blood samples were collected into pre-chilled collection tubes containing K_2EDTA and processed to plasma at 10 time points over a span of pre-dose to 24 h post-administration. Plasma samples were subject to protein precipitation with a 12.5-fold volume of methanol, vortexed and centrifuged. Supernatants were transferred and evaporated to dryness under nitrogen and reconstituted with 5% acetonitrile in water. Separation was achieved on a Phenomenex Synergi Polar-RP column, a mobile phase A of 10 mM ammonium formate with 0.1% formic acid in water and a mobile phase B of 0.1% formic acid in acetonitrile with a step-wise linear gradient from 5 to 95% mobile phase B. An LC-MS/MS method was used to measure the concentrations of the **Reference Compound A** and either **Ester Reference Compound, Compound 3** or **Compound 6** in plasma. Data for **Reference Compound A** following oral administration of either **Ester Reference Compound**, **Compound 3** or **Compound 6** is tabulated below.



Reference Compound A



Ester Reference Compound

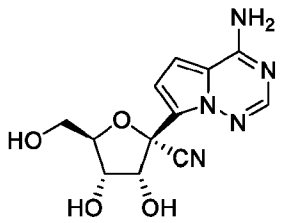
Table E1:

Compound	**Oral Dose mg/kg**	**Oral Dose (mg-eq Reference Compound A)/kg**	**Reference Compound A C_{max} (nM)**	**Reference Compound A $AUC_{inf.}$ (nM.h)**	**Reference Compound A F%[a]**
Ester Reference Compound	6	4.8	2100	7570	63.6
3	6.65	5	2280	10700	84.7
6	8.1	5	3080	6860	54.4

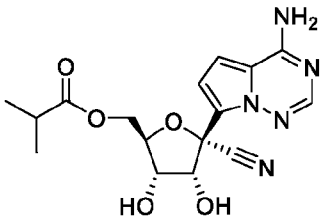
[a] based on reference compound A mg-eq/kg dose; using IV data from 1 mg/kg dose of reference Compound A

Example F: Monkey pharmacokinetics assay

[0298] Ester Reference Compound, **Compound 3** and **Compound 6** were dosed orally by gavage to male and female rhesus monkeys (n=3/group)**; Ester Reference Compound** at 12.4 mg/kg in 2.5% DMSO; 10% Kolliphor HS-15; 10% Labrasol; 2.5% Propylene glycol and 75% water, pH 2.2; **Compound 3** at 13.3 mg/kg in 10% Dimethyl sulfoxide; 40% Kolliphor HS-15; 40% Labrasol and 10% Propylene glycol and **Compound 6** at 9.3 mg/kg in 2.5% Dimethyl sulfoxide; 10% Kolliphor HS-15; 10% Labrasol; 2.5% Propylene glycol and 75% water, pH 2.3. Blood samples were collected into pre-chilled collection tubes containing K_2EDTA with dichlorvos (2 mM final concentration with blood added) and processed to plasma at 10 timepoints over a span of pre-dose to 24 h post-administration. Plasma samples were subject to protein precipitation with a 12.5-fold volume of methanol, vortexed and centrifuged. Supernatants were transferred and evaporated to dryness under nitrogen and reconstituted with 5% acetonitrile in water. Separation was achieved on a Phenomenex Synergi Polar-RP column, a mobile phase A of 10 mM ammonium formate with 0.1% formic acid in water and a mobile phase B of 0.1% formic acid in acetonitrile with a step-wise linear gradient from 5 to 95% mobile phase B. An LC-MS/MS method was used to measure the concentrations of the **Reference Compound A** and either **Ester Reference Compound, Compound 3** or **Compound 6** in plasma. Data for **Reference Compound A** following oral administration of either **Ester Reference Compound**, **Compound 3** or **Compound 6** is tabulated below.



Reference Compound A



Ester Reference Compound

Table F1:

Compound	Oral Dose mg/kg	Oral Dose (mg-eq Reference Compound A)/kg	Reference Compound A C_{max} (nM)	Reference Compound A $AUC_{inf.}$ (nM.h)	Reference Compound A F%[a]
Ester Reference Compound	12.4	10	4100	11300	18.9
3	13.3	10	1760	9550	15.9
6	9.3	5.75	2540	9390	27.2

[a] based on reference compound A mg-eq/kg dose; using IV data from 1 mg/kg dose in study of reference compound A

Example G: GI S9 Stability

[0299] Duplicate aliquots of test compound or positive control substrate (GS-7340) were added to S9 stock diluted with 100 mM phosphate buffered saline, pH 7.4, to obtain a protein concentration of 1.0 mg/mL. The S9 metabolic reactions were initiated by the addition of the substrates to the S9 reaction mixture to a final concentration of 2 µM. At 0, 10, 20, 30, 60 and 120 min, 25 µL aliquots of the reaction mixture were transferred to plates containing 225 µl of IS/Q solution. After quenching, the plates were centrifuged at 3000 × g for 30 minutes, and 150 µL aliquots of each supernatant were diluted with 150 µL water. Aliquots (10 µL) of the diluted supernatant were analyzed on a Thermo Q-Exactive mass spectrometer as described below.

Example H: Plasma stability

[0300] Duplicate aliquots of plasma were warmed to 37 °C and the metabolic reactions initiated by the addition of test compound (6 µL of 0.1 mM DMSO stock) or plasma stability

standard (GS-7340) to obtain a final substrate concentration of 2 μM. At 0.05, 0.5, 1, 2, 3 and 4 hr, 25 μL aliquots of the reaction mixture were transferred to plates containing 225 μl of IS/Q quenching solution. After quenching, the plates were centrifuged at 3000 × g for 30 minutes, and 150 μL supernatant was diluted with 150μL water. Aliquots (10 μL) of the diluted supernatant were analyzed on a Thermo Q-Exactive mass spectrometer as described below.

Example I: CES1/2 stability

[0301] Test compounds or positive control substrates (oseltamivir for CES1 enzymes or procaine for CES2) are incubated with individual Supersome preparations (final CES concentration 1.5 mg/ml) in 0.1 M potassium phosphate buffer (pH 7.4) at 37°C. Substrates are added to a final concentration of 2 μM to initiate the reaction. The final incubation volume is 250 μL. Aliquots are removed after incubation for 0, 10, 30, 60 and 120 min. The reactions is stopped by the addition of IS/Q. Following protein precipitation and centrifugation, 150 μL of supernatant is diluted with an equal volume of water prior to LC-MS analysis. For procaine 150 μL of supernatant is dried down and reconstituted with 250 μL water. All samples are analyzed by LC-MS and the PAR values are used for quantification.

Example J: Hepatic S9 stability

[0302] Duplicate aliquots of test compound or positive control substrate (GS-7340) were added to S9 stock diluted with 100 mM potassium phosphate buffer, pH 7.4, to obtain a protein concentration of 2.4 mg/mL. The S9 metabolic reactions were initiated by the addition of the substrates to the S9 reaction mixture to a final concentration of 2 μM. At 2, 12, 25, 45, 65 and 90 min, 25 μL aliquots of the reaction mixture were transferred to plates containing 225 μl of IS/Q solution. After quenching, the plates were centrifuged at 3000 × g for 30 minutes, and 150 μL aliquots of each supernatant were diluted with 150 μL water. Aliquots (10 μL) of the diluted supernatant were analyzed on a Thermo Q-Exactive mass spectrometer as described below.

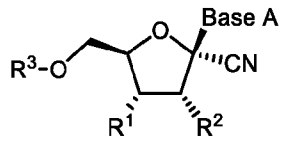
Example K: Liquid Chromatography/Mass Spectroscopy methods for S9 and Plasma Stability

Quantification of test compounds and controls was performed by analyte/internal standard peak area ratio (PAR) values measured on a Thermo Q-Exactive mass spectrometer coupled to a Dionex UltiMate 3000 HPLC with a Leap Technologies HTC PAL autosampler. The column used was a Thermo Hypersil GOLD (1.9 μm particle size, 2.1 × 50 mm). Mobile phase A consisted of 0.1% (v/v) formic acid in water. Mobile phase B consisted of 0.1% (v/v) formic acid in acetonitrile. Elution of analytes was achieved by a series of linear gradients of acetonitrile in water containing 0.1% (v/v) formic acid. The mass spectrometer was calibrated on a weekly basis and mass tolerance of 5 ppm was used.

[0303] 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. The description is made with the understanding that it is to be considered an exemplification of the claimed subject matter and is not intended to limit the appended claims to the specific embodiments illustrated.

CLAIMS

1. A compound of Formula A:



Formula A

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are taken together to form -OC(=O)O-, -OCHR^{6}O-, or -OP(=O)(OR^{14})O-;

R^6 is H, C_1-C_6 alkyl, C_6-C_{10} aryloxy, or C_1-C_6 alkoxy;

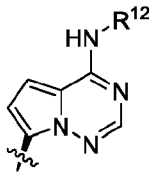
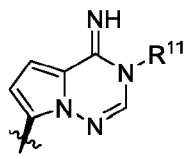
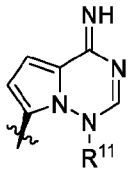
R^3 is -C(=O)R^7;

R^7 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein each C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^7 is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N$_3$, -OR^8, -NR^{9}R^{10}, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

each R^8 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^9 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^{10} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

Base A is , , or ;

R^{11} is C_1-C_6 alkyl optionally substituted with -OP(=O)(OH)$_2$

R^{12} is H, C_1-C_6 alkyl, -C(=O)R^{13} or -C(=O)OR^{13};

each R^{13} is independently H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{13} is optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl, wherein phenyl is optionally substituted with -OP(=O)(OH)(OR^{14}); and

each R^{14} is independently H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein

C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OC(=O)O- or -OCHR^{6}O-.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OC(=O)O-.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OCHR^{6}O-.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OCH(OCH$_3$)O-.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OP(=O)(OR^{14})O-.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OP(=O)(OH)O-.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OC(=O)O-, -OCH(OCH$_3$)O-, or -OP(=O)(OH)O-.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are taken together to form -OC(=O)O- or -OCH(OCH$_3$)O-.

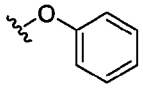
10. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

11. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_1-C_6 alkyl.

12. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_1-C_3 alkyl.

13. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-CH_3$.

14. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_6-C_{10} aryloxy.

15. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is .

16. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_1-C_6 alkoxy.

17. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_1-C_3 alkoxy.

18. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-OCH_2CH_3$, $-OCH(CH_3)_2$, or $-OCH_3$.

19. The compound of any one of claims 1, 2, and 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-OCH_3$.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein each C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^7 is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^8$, $-NR^9R^{10}$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^8$, $-NR^9R^{10}$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

22. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^8$, $-NR^9R^{10}$, and phenyl.

23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

24. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is C_1-C_6 alkyl.

25. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

26. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is $-CH_3$.

27. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is C_1-C_6 haloalkyl.

28. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^8 is C_3-C_6 cycloalkyl.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is H.

30. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is C_1-C_6 alkyl.

31. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

32. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is $-CH_3$.

33. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is C_1-C_6 haloalkyl.

34. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^9 is C_3-C_6 cycloalkyl.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is H.

36. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_1-C_6 alkyl.

37. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is $-CH_3$.

38. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

39. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_1-C_6 haloalkyl.

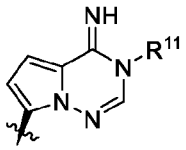
40. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_3-C_6 cycloalkyl.

41. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_8 alkyl.

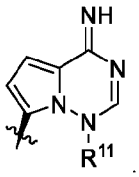
42. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_6 alkyl.

43. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$.

44. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^7 is $-CH(CH_3)_2$.

45. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein Base A is 

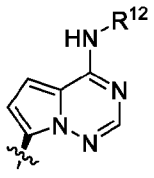
.

46. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein Base A is 

.

47. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^{11} is C_1-C_3 alkyl substituted with $-OP(=O)(OH)_2$.

48. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^{11} is $-(CH_2)OP(=O)(OH)_2$.

49. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein Base A is .

50. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is $-C(=O)R^{13}$.

51. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is $-C(=O)OR^{13}$.

52. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl; wherein phenyl is optionally substituted with $-OP(=O)(OH)(OR^{14})$.

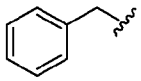
53. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is H.

54. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

55. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

56. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is C_1-C_3 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

57. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is C_1-C_3 alkyl substituted with one phenyl.

58. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt thereof, wherein R^{14} is .

59. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is H.

60. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from halogen, cyano, and phenyl.

61. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is C_1-C_8 alkyl.

62. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$.

63. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt thereof, wherein R^{13} is $-CH_2CH(CH_3)_2$ or $-(CH_2)_2CH_3$.

64. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is H.

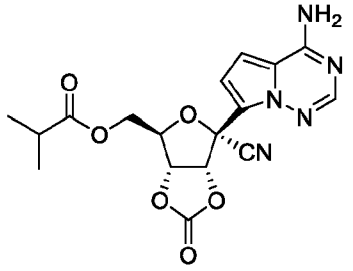
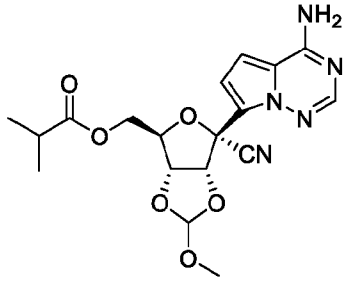
65. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is C_1-C_6 alkyl.

66. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is $-C(=O)(CH_2)_2CH_3$.

67. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is $-C(=O)OCH_2CH(CH_3)_2$.

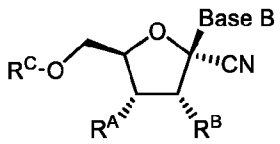
68. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt thereof, wherein R^{12} is $-C(=O)OCH_2CH(CH_3)_2$ or $-C(=O)(CH_2)_2CH_3$.

69. The compound of claim 1, wherein the compound of Formula A is

Compound 3	
Compound 4	

or a pharmaceutically acceptable salt thereof.

70. A compound of Formula B:



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^A is -OH, $-OC(=O)R^D$, or $-OC(=O)OR^D$;

R^B is -OH, $-OC(=O)R^E$, or $-OC(=O)OR^E$; or

R^A and R^B are taken together to form -OC(=O)O- or $-OCHR^FO-$;

R^F is H, C_1-C_6 alkyl or C_6-C_{10} aryl;

R^C is $-C(=O)R^G$;

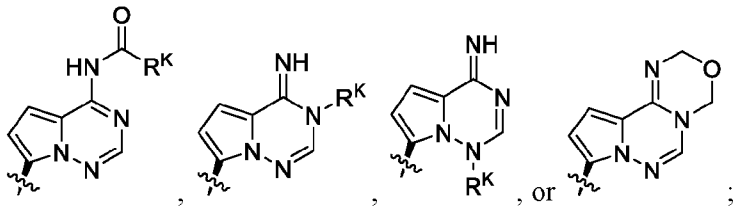
R^D and R^E are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^D and R^E are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

R^G is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^G are each optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

each R^H is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^I is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

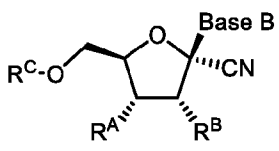
each R^J is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

Base B is ;

R^K is C_6-C_{10} aryl, $-O$-C_6-C_{10} aryl, $-O$-C_1-C_{10} alkyl, or C_1-C_{10} alkyl optionally substituted with $-OP(=O)(OH)(OR^L)$; and

R^L is H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl of R^L is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

71. A compound of Formula B:



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^A is -OH, -OC(=O)R^D, or -OC(=O)OR^D;

R^B is -OH, -OC(=O)R^E, or -OC(=O)OR^E; or

R^A and R^B are taken together to form -OC(=O)O- or –OCHR^FO-;

R^F is H, C_1-C_6 alkyl or C_6-C_{10} aryl;

R^C is -C(=O)R^G;

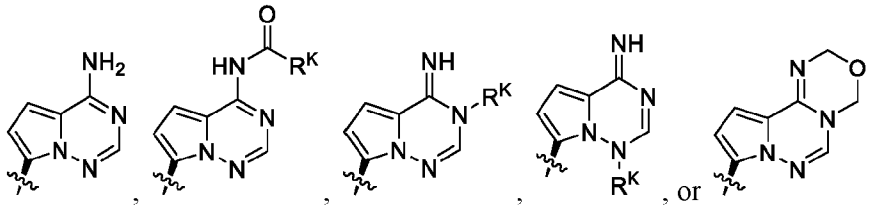
R^D and R^E are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^D and R^E are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

R^G is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)(OH)(OR^L), and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl;

each R^H is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

each R^I is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

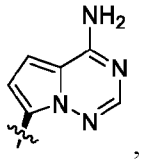
each R^J is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_6 cycloalkyl;

Base B is , , , , or ;

R^K is C_6-C_{10} aryl, -O-C_6-C_{10} aryl, -O-C_1-C_{10} alkyl, or C_1-C_{10} alkyl optionally substituted with -OP(=O)(OH)(OR^L); and

R^L is H, C_1-C_8 alkyl, C_3-C_8 carbocyclyl, C_6-C_{10} aryl, or 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S; wherein C_1-C_8 alkyl of R^L is

optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl;

provided when Base B is , R^G is C_1-C_8 alkyl substituted with one, two or three -OP(=O)(OH)(OR^L).

72. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OC(=O)R^D.

73. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OC(=O)OR^D.

74. The compound of any one of claims 71-73, or a pharmaceutically acceptable salt thereof, wherein R^B is -OC(=O)R^E.

75. The compound of any one of claims 71-73, or a pharmaceutically acceptable salt thereof, wherein R^B is -OC(=O)OR^E.

76. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OC(=O)R^D and R^B is -OC(=O)R^E.

77. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OH, and R^B is -OC(=O)R^E or -OC(=O)OR^E.

78. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OC(=O)R^D or -OC(=O)OR^D, and R^B is -OH.

79. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^4 are each, independently, optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, -N_3, -OR^H, -NR^IR^J, -OP(=O)$(OH)_2$, C_3-C_8 carbocyclyl and

phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

80. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)_2$, C_3-C_8 carbocyclyl and phenyl.

81. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is C_1-C_8 alkyl.

82. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is C_1-C_6 alkyl.

83. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is C_1-C_3 alkyl.

84. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$.

85. The compound of any one of claims 71-73, 76, and 78, or a pharmaceutically acceptable salt thereof, wherein R^D is $-CH_3$ or $-CH(CH_3)_2$.

86. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^4 are each, independently, optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)_2$, C_3-C_8 carbocyclyl and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

87. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is C_1-C_8 alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)_2$, C_3-C_8 carbocyclyl and phenyl.

88. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is C_1-C_8 alkyl.

89. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is C_1-C_6 alkyl.

90. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is C_1-C_3 alkyl.

91. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$.

92. The compound of any one of claims 72, 74-77, and 79-85, or a pharmaceutically acceptable salt thereof, wherein R^E is $-CH_3$ or $-CH(CH_3)_2$.

93. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is -OH.

94. The compound of any one of claims 71-73 and 93, or a pharmaceutically acceptable salt thereof, wherein R^B is -OH.

95. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are both -OH.

96. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A is OH, $OC(O)CH(CH_3)_2$, or $OC(O)CH_3$, and R^B is OH, $OC(O)CH(CH_3)_2$, or $OC(O)CH_3$.

97. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein both R^A and R^B are $OC(O)CH_3$.

98. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are taken together to form -OC(=O)O-.

99. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are taken together to form $–OCHR^FO-$.

100. The compound of claim 71 or 99, or a pharmaceutically acceptable salt thereof, wherein R^F is H.

101. The compound of claim 71 or 99, or a pharmaceutically acceptable salt thereof, wherein R^F is C_1-C_6 alkyl.

102. The compound of claim 71 or 99, or a pharmaceutically acceptable salt thereof, wherein R^F is C_6-C_{10} aryl.

103. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G are each independently C_3-C_8 carbocyclyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

104. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G are each independently C_6-C_{10} aryl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

105. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G are each independently 5 to 6 membered heteroaryl containing 1, 2, or 3 heteroatoms selected form N, O, and S optionally substituted with one, two or three

substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

106. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

107. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G are each independently C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; wherein C_1-C_8 alkyl, C_2-C_8 alkenyl, and C_2-C_8 alkynyl of R^G are each, independently, optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl.

108. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, $-N_3$, $-OR^H$, $-NR^IR^J$, $-OP(=O)(OH)(OR^L)$, and phenyl; wherein phenyl is optionally substituted with one, two or three substituents independently selected from halo, cyano, and C_1-C_6 alkyl.

109. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is C_1-C_8 alkyl.

110. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-C(CH_3)_3$.

111. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is C_1-C_4 alkyl.

112. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is $-(CH_2)_2CH_3$ and $-CH(CH_3)_2$.

113. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is $-CH(CH_3)_2$.

114. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is H.

115. The compound of any one of claims 71-102, or a pharmaceutically acceptable salt thereof, wherein R^G is $-(CH_2)OP(=O)(OH)_2$.

116. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is H.

117. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is C_1-C_6 alkyl.

118. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

119. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is $-CH_3$.

120. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is C_1-C_6 haloalkyl.

121. The compound of any one of claims 71-108, or a pharmaceutically acceptable salt thereof, wherein R^H is C_3-C_6 cycloalkyl.

122. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is H.

123. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is C_1-C_6 alkyl.

124. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

125. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is $-CH_3$.

126. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is C_1-C_6 haloalkyl.

127. The compound of any one of claims 71-108 and 116-121, or a pharmaceutically acceptable salt thereof, wherein R^I is C_3-C_6 cycloalkyl.

128. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is H.

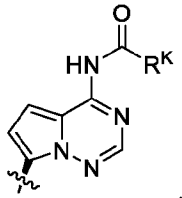
129. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is C_1-C_6 alkyl.

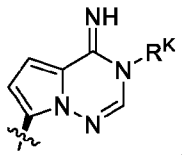
130. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, or $-CH(CH_3)_2$.

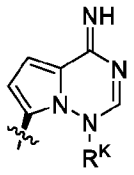
131. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is $-CH_3$.

132. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is C_1-C_6 haloalkyl.

133. The compound of any one of claims 71-108 and 116-127, or a pharmaceutically acceptable salt thereof, wherein R^J is C_3-C_6 cycloalkyl.

134. The compound of any one of claims 71-134, or a pharmaceutically acceptable salt thereof, wherein Base B is .

135. The compound of any one of claims 71-134, or a pharmaceutically acceptable salt thereof, wherein Base B is .

136. The compound of any one of claims 71-134, or a pharmaceutically acceptable salt thereof, wherein Base B is .

137. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is C_1-C_6 alkyl substituted with -OP(=O)(OH)(OR^L).

138. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is -(CH_2)OP(=O)(OH)(OR^L).

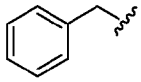
139. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is H.

140. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is H or C_1-C_8 alkyl; wherein C_1-C_8 alkyl of R^{14} is optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

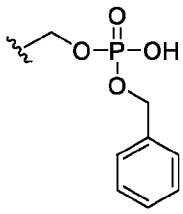
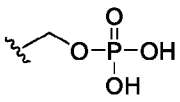
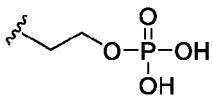
141. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is C_1-C_8 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

142. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is C_1-C_3 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of halogen, cyano, and phenyl.

143. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is C_1-C_3 alkyl substituted with one phenyl.

144. The compound of any one of claims 71-138, or a pharmaceutically acceptable salt thereof, wherein R^L is .

145. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is

, , or .

146. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is C_1-C_{10} alkyl.

147. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is C_1-C_7 alkyl.

148. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_4CH_3$, or $-(CH_2)_6CH_3$.

149. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is C_6-C_{10} aryl.

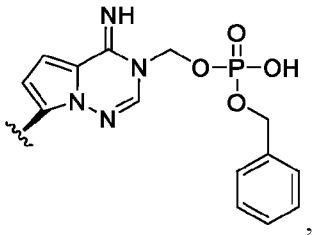
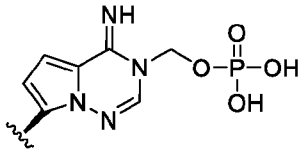
150. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is phenyl.

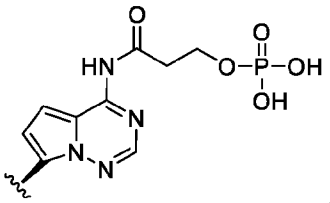
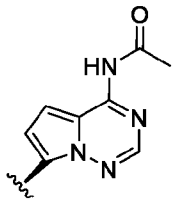
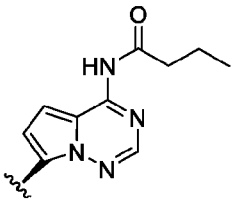
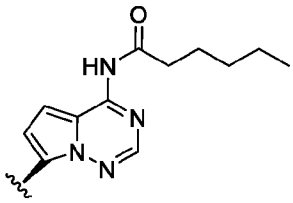
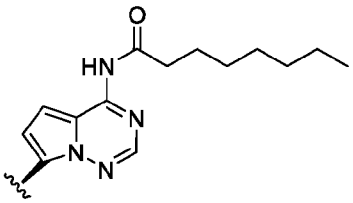
151. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is -O-C_6-C_{10} aryl.

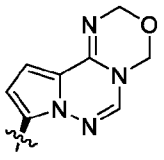
152. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is -O-phenyl.

153. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is -O-C_1-C_{10} alkyl.

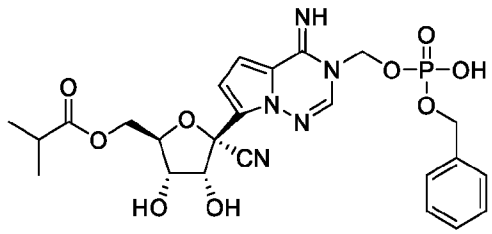
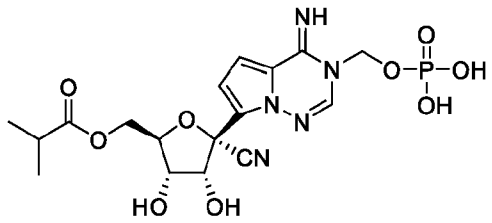
154. The compound of any one of claims 71-136, or a pharmaceutically acceptable salt thereof, wherein R^K is -O-CH_3, -O-CH_2CH_3, -O-$(CH_2)_2CH_3$, -O-$(CH_2)_4CH_3$, or -O-$(CH_2)_6CH_3$.

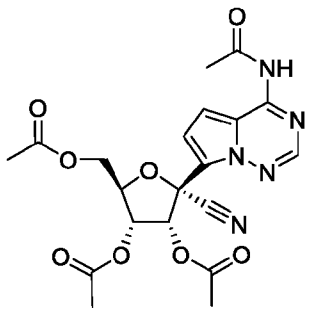
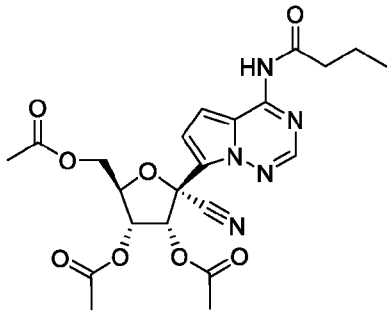
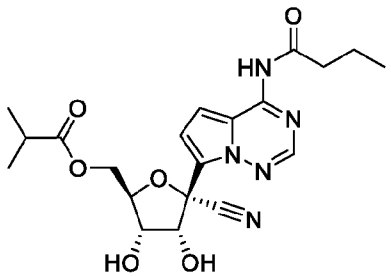
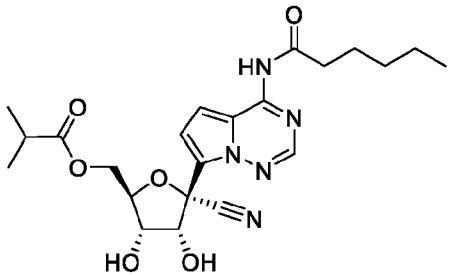
155. The compound of any one of claims 71-134, or a pharmaceutically acceptable salt thereof, wherein Base B is , ,

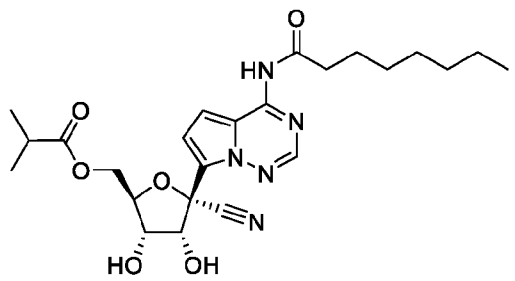

, 
, 
, 
or 
.

156. The compound of any one of claims 71-134, or a pharmaceutically acceptable salt thereof, wherein Base B is 
.

157. The compound of claim 71, wherein the compound of Formula B is

Compound 5	
Compound 6	

Compound 7	
Compound 8	
Compound 9	
Compound 10	

Compound 11	

or a pharmaceutically acceptable salt thereof.

158. A pharmaceutical composition comprising the compound of any one of claims 1-157, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

159. The pharmaceutical composition of claim 158, wherein the pharmaceutical formulation is for subcutaneous, intramuscular, intravenous, oral, or inhalation administration.

160. The pharmaceutical composition of claim 159, wherein the pharmaceutical formulation is for oral administration.

161. A method of treating or preventing a viral infection in a human in need thereof, wherein the method comprises administering to the human the compound of any one of the claims 1-157, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any one of claims 158-159.

162. The method of claim 161, wherein the compound, or pharmaceutically acceptable salt thereof, or pharmaceutical composition, is administered to the human via oral, intramuscular, intravenous, subcutaneous, or inhalation administration.

163. The method of claim 161 or 162, wherein the method comprises administering to the human at least one additional therapeutic or prophylactic agent.

164. The method of claim 163, wherein the additional therapeutic or prophylactic agent is molnupiravir, oseltamivir, nirmatrelvir, or ritonavir.

165. The method of any one of claims 161-164, wherein the viral infection is a coronavirus infection.

166. The method of any one of claims 161-164, wherein the viral infection is a zoonotic coronavirus infection.

167. The method of any one of claims 161-164, wherein the viral infection is caused by a virus having at least 70% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2.

168. The method of any one of claims 161-164, wherein the viral infection is caused by a virus having at least 80% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2.

169. The method of any one of claims 161-164, wherein the viral infection is caused by a virus having at least 90% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2.

170. The method of any one of claims 161-164, wherein the viral infection is caused by a virus having at least 95% sequence homology to a viral polymerase selected from the group consisting of SARS-CoV polymerase, MERS-CoV polymerase and SARS-CoV-2.

171. The method of any one of claims 161-164, wherein the viral infection is selected form the group consisting of 229E virus infection, NL63 virus infection, OC43 virus infection, and HKU1 virus infection.

172. The method of any one of claims 161-164, wherein the viral infection is SARS-CoV-2 infection (COVID-19).

173. The method of any one of claims 161-164, wherein the viral infection is a SARS-CoV virus infection.

174. The method of any one of claims 161-164, wherein the viral infection is a MERS-CoV virus infection.

175. The method of any one of claims 161-164, wherein the viral infection is a pneumoviridae virus infection.

176. The method of claim 175, wherein the pneumoviridae virus infection is respiratory syncytial virus infection.

177. The method of claim 175, wherein the pneumoviridae virus infection is human metapneumovirus infection.

178. The method of any one of claims 161-164, wherein the viral infection is a picornaviridae virus infection.

179. The method of any one of claims 161-164, wherein the viral infection is an enterovirus infection.

180. The method of any one of claims 161-164, wherein the viral infection is selected from the group consisting of Coxsackie A virus infection, Coxsackie A virus infection, enterovirus D68 infection, enterovirus B69 infection, enterovirus D70 infection, enterovirus A71 infection, and poliovirus infection.

181. The method of claim 179, wherein the picornaviridae virus infection is human rhinovirus infection (HRV).

182. The method of claim 179, wherein the picornaviridae virus infection is HRV-A, HRV-B, or HRV-C infection.

183. The method of any one of claims 161-164, wherein the viral infection is a flaviviridae virus infection.

184. The method of claim 183, wherein the flaviviridae virus infection is a dengue virus infection, yellow fever virus infection, West Nile virus infection, tick borne encephalitis, Kunjin Japanese encephalitis, St. Louis encephalitis, Murray valley encephalitis, Omsk hemorrhagic fever, bovine viral diarrhea, zika virus infection, or a HCV infection.

185. The method of any one of claims 161-164, wherein the viral infection is a filoviridae virus infection.

186. The method of claim 185, wherein the filoviridae virus infection is an ebola virus infection or a Marburg virus infection.

187. The method of any one of claims 161-164, wherein the viral infection is an orthomyxovirus infection.

188. The method of any one of claims 161-164, wherein the viral infection is an influenza virus infection.

189. The method of any one of claims 161-164, wherein the viral infection is an influenza A virus infection or influenza B virus infection.

190. The method of any one of claims 161-164, wherein the viral infection is a paramyxoviridae virus infection.

191. The method of any one of claims 161-164, wherein the viral infection is a human parainfluenza virus, Nipah virus, Hendra virus, measles, or mumps infection.

192. A method for manufacturing a medicament for treating or preventing a viral infection in a human in need thereof, characterized in that a compound of any one of claims 1-157, or a pharmaceutically acceptable salt thereof.

193. Use of a compound of any one of claims 1-157, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a viral infection in a human in need thereof.

194. The use of claim 193, wherein the medicament is used with at least one additional therapeutic or prophylactic agent.

195. The use of claim 194, wherein the additional therapeutic or prophylactic agent is molnupiravir, oseltamivir, nirmatrelvir, or ritonavir.

196. A composition comprising a compound of any one of claims 1-157, or a pharmaceutically acceptable salt thereof, for use in treatment or prevention of a viral infection in a human in need thereof.

197. The composition of claim 196, wherein the composition comprises at least one additional therapeutic agent or prophylactic agent.

198. The composition of claim 197, wherein the additional therapeutic or prophylactic agent is molnupiravir, oseltamivir, nirmatrelvir, or ritonavir.