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(54) Title: N4-HYDROXYCYTIDINE AND DERIVATIVES AND ANTI-VIRAL USES RELATED THERETO

(57) Abstract: This disclosure relates to certain N4-hydroxycytidine derivatives, pharmaceutical compositions, and methods related thereto. In certain embodiments, the disclosure relates to the treatment or prophylaxis of viral infections, such as Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively), Chikungunya fever (CHIK), Ebola, Influenza, RSV, and Zika virus infection with the disclosed compounds.

N4-HYDROXYCYTIDINE AND DERIVATIVES AND ANTI-VIRAL USES RELATED THERETO

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This invention was made with government support under grant nos. HDTRA1-13-C-0072 and HDTRA1-15-C-0075 awarded by the Department of Defense and grant no. HHSN272201500008C awarded by National Institutes of Health. The government has certain rights in the invention.

FIELD

This disclosure relates to N4-hydroxycytidine nucleoside and derivatives, as well as compositions and methods related thereto. In certain embodiments, the disclosure relates to the treatment or prophylaxis of viral infections, in particular, Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively), Chikungunya fever (CHIK), Ebola, Influenza, RSV, and Zika virus infections.

BACKGROUND

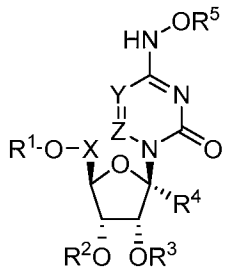
The causative agents for Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively) and Chikungunya fever (CHIK) are vector-borne viruses (family *Togaviridae*, genus *Alphavirus*) that can be transmitted to humans through mosquito bites. The equine encephalitis viruses are CDC Category B pathogens, and the CHIK virus is Category C. There is considerable concern about the use of virulent strains of VEE virus, delivered via aerosol, as a bioweapon against warfighters. Animal studies have demonstrated that infection with VEE virus by aerosol exposure rapidly leads to a massive infection of the brain, with high mortality and morbidity. See Roy et al., Pathogenesis of aerosolized Eastern equine encephalitis virus infection in guinea pigs. *Virol J*, 2009, 6:170.

Stuyver et al., report β-D-N(4)-hydroxycytidine (NHC) was found to have antipestivirus and antihepacivirus activities. *Antimicrob Agents Chemother*, 2003, 47(1):244-54. Constantini et al. report evaluations on the efficacy of 2'-C-MeC, 2'-F-2'-C-MeC, and NHC on Norwalk virus. See also Purohit et al., *J Med Chem*, 2012, 55(22):9988-9997; Ivanov et al., *Collection of Czechoslovak Chem Commun*, 2006, 71(7):1099-1106; and Fox et al., *JACS*, 1959, 81:178-87.

What are needed are new compounds and treatments for viral infections. The compounds and methods disclosed herein addressed these needs.

SUMMARY

This disclosure relates to certain N4-hydroxycytidine and derivatives, combinations, pharmaceutical compositions, and methods related thereto. In certain embodiments, the disclosure relates to a compound having Formula I,



Formula A

or a pharmaceutically acceptable salt, derivative, or prodrug thereof, as defined herein.

In certain embodiments, the disclosure contemplates derivatives of compounds disclosed herein, such as those containing one or more, the same or different, substituents.

In certain embodiments, the disclosure contemplates pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound disclosed herein. In certain embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, or aqueous buffer, such as a saline or phosphate buffer.

In certain embodiments, the disclosed pharmaceutical compositions can comprise a compound disclosed herein and a propellant. In certain embodiments, the propellant is an aerosolizing propellant such as compressed air, ethanol, nitrogen, carbon dioxide, nitrous oxide, hydrofluoroalkanes (HFAs), 1,1,1,2,-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or combinations thereof.

In certain embodiments, the disclosure contemplates a pressurized or unpressurized container comprising a compound or pharmaceutical composition as described herein. In certain embodiments, the container is a manual pump spray, inhaler, meter-dosed inhaler, dry powder inhaler, nebulizer, vibrating mesh nebulizer, jet nebulizer, or ultrasonic wave nebulizer.

In certain embodiments, the disclosure relates to methods of increasing bioavailability for treating or preventing a viral infection comprising administering an effective amount of a compound or pharmaceutical composition disclosed herein to a subject in need thereof.

In certain embodiments, the disclosure relates to methods of treating or preventing a viral infection comprising administering an effective amount of a compound or pharmaceutical composition disclosed herein to a subject in need thereof. In certain embodiments, the viral infection is a Zika virus infection. In other embidiments, the viral infection is Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively), Chikungunya fever (CHIK), Ebola, Influenza, or RSV.

In certain embodiments, the compound or pharmaceutical composition is administered orally, intravenously, or through the lungs, i.e., pulmonary administration.

In certain embodiments, the disclosure relates to the use of a compound as described herein in the production of a medicament for the treatment or prevention of a viral infection, such as Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively), Chikungunya fever (CHIK), Ebola, Influenza, RSV, or Zika virus infection.

In certain embodiments, the disclosure relates to method of making compounds disclosed herein by mixing starting materials and reagents disclosed herein under conditions such that the compounds are formed.

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

BRIEF DESCRIPTION OF THE FIGURES

The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects described below.

Figure 1 is a scheme illustrating the preparation of β-D-N-hydroxycytidine. The steps of the synthesis are a.) TBSCl, DMAP, DIPEA, DCM; b.) (2,4,6-iPr)$PhSO_2Cl$, DIPEA, DMAP, DCM; c.) NH_2OH-HCl, DIPEA, DCM; d.) F- source; and e.) aq NH_2OH, AcOH, 50 °C.

Figure 2 illustrates certain exemplary compounds.

Figure 3 illustrates certain exemplary compounds.

Figure 4 shows mean plasma concentrations and pharmacokinetic parameters from mice treated with an exemplary compound.

Figure 5 shows nucleoside accumulation in mouse organs in mice treated with an exemplary compound.

Figure 6 shows triphosphate accumulation in mouse organs in mice treated with an exemplary compound.

Figure 7 shows reduction in footpad swelling in CHIKV-challenged mice treated with an exemplary compound.

Figure 8 shows reduction of CHIKV-RNA copies by PCR in CHIKV-challenged mice treated with an exemplary compound.

Figure 9 shows the survival of ZIKV-challenged mice treated with an exemplary compound for 7 days.

Figure 10 shows the survival of ZIKV-challenged mice treated with an exemplary compound for 7 days, with varying treatment initiation times post-infection.

Figure 11 shows the N4-hydroxycytidine nucleoside tissue concentrations from a cynomolgus macaque orally administered EIDD-1931 (100mg/kg).

Figure 12 shows the N4-hydroxycytidine nucleoside tissue concentrations from a cynomolgus macaque intravenously administered EIDD-1931 (10mg/kg).

Figure 13 shows the structure of compounds orally administered to cynomolgus macaques.

Figure 14 shows the mean N4-hydroxycytidine nucleoside plasma concentrations from cynomolgus macaques orally administered with an ester derivative.

Figure 15 shows the mean maximum concentration of N4-hydroxycytidine nucleoside in plasma from cynomolgus macaques orally administered with an ester derivative.

Figure 16 shows virus titer from nasal lavage and fever in Influenza A/California/07/2009 (H1N1) infected ferrets treated orally with EIDD-2801 BID or vehicle.

Figure 17 shows virus titer from nasal lavage, fever, and virus titer in nasal turbinates in Influenza A/Wisconsin/67/2005 (H3N2) infected ferrets treated orally with EIDD-2801 BID or vehicle.

Figure 18 shows the effect of EIDD-2801 treatment on survival of intranasal VEEV infected mice.

Figure 19 shows the effect of EIDD-2801 time of treatment initiation on survival of intranasal VEEV infected mice.

Figure 20 shows the effect of EIDD-2801 prophylactic treatment on lung viral titers of SARS infected mice.

Figure 21 shows the effect of EIDD-2801 time of treatment on lung hemhorrage scores of SARS infected mice.

Figure 22 shows the effect of EIDD-2801 time of treatment on lung viral titers of SARS infected mice.

Figure 23 shows the effect of EIDD-2801 treatment on lung hemhorrage scores of MERS infected mice.

DETAILED DESCRIPTION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure

belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features, which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, organic chemistry, biochemistry, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

In certain embodiments, a pharmaceutical agent, which may be in the form of a salt or prodrug, is administered in methods disclosed herein that is specified by a weight. This refers to the weight of the recited compound. If in the form of a salt or prodrug, then the weight is the molar equivalent of the corresponding salt or prodrug.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

"Subject" refers any animal, preferably a human patient, livestock, or domestic pet.

As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset. It is not intended that the present disclosure be limited to complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g., patient) is cured and the disease is eradicated. Rather, embodiments, of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "combination with" when used to describe administration with an additional treatment means that the agent can be administered prior to, together with, or after the additional treatment, or a combination thereof.

As used herein, "alkyl" means a straight or branched chain saturated hydrocarbon moieties such as those containing from 1 to 10 carbon atoms. A "higher alkyl" refers to saturated hydrocarbon having 11 or more carbon atoms. A "C_6-C_{16}" refers to an alkyl containing 6 to 16 carbon atoms. Likewise a "C_6-C_{22}" refers to an alkyl containing 6 to 22 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like.

As used herein, the term "alkenyl" refers to unsaturated, straight or branched hydrocarbon moieties containing a double bond. Unless otherwise specified, C_2-C_{24} (e.g., C_2-C_{22}, C_2-C_{20}, C_2-C_{18}, C_2-C_{16}, C_2-C_{14}, C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6, or C_2-C_4) alkenyl groups are intended. Alkenyl groups may contain more than one unsaturated bond. Examples include ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl, and 1-ethyl-2-methyl-2-propenyl. The term "vinyl" refers to a group having the structure –CH=CH_2; 1-propenyl refers to a group with the structure–CH=CH-CH_3; and 2- propenyl refers to a group with the structure –CH_2-CH=CH_2. Asymmetric structures such as $(Z^1Z^2)C=C(Z^3Z^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C.

As used herein, the term "alkynyl" represents straight or branched hydrocarbon moieties containing a triple bond. Unless otherwise specified, C_2-C_{24} (e.g., C_2-C_{24}, C_2-C_{20}, C_2-C_{18}, C_2-C_{16}, C_2-C_{14}, C_2-C_{12}, C_2-C_{10}, C_2-C_8, C_2-C_6, or C_2-C_4) alkynyl groups are intended. Alkynyl groups may contain more than one unsaturated bond. Examples include C_2-C_6-alkynyl, such as ethynyl, 1-propynyl, 2-propynyl (or propargyl), 1-butynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 3-methyl-1-butynyl, 1-methyl-2-butynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 3-methyl-1-pentynyl, 4-methyl-1-pentynyl, 1-methyl-2-pentynyl, 4-methyl-2-pentynyl, 1-methyl-3-pentynyl, 2-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 3,3-dimethyl-1-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl, and 1-ethyl-1-methyl-2-propynyl.

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, and the like.

"Heterocarbocycles" or heterocarbocyclyl" groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which can be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized. Heterocarbocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

The term "aryl" refers to aromatic homocyclic (i.e., hydrocarbon) mono-, bi- or tricyclic ring-containing groups preferably having 6 to 12 members such as phenyl, naphthyl and biphenyl. Phenyl is a preferred aryl group. The term "substituted aryl" refers to aryl groups substituted with one or more groups, preferably selected from alkyl, substituted alkyl, alkenyl (optionally substituted), aryl (optionally substituted), heterocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl, (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane, sulfonyl, and, the like, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

As used herein, "heteroaryl" or "heteroaromatic" refers an aromatic heterocarbocycle having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems can, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term "heteroaryl" includes N-alkylated derivatives such as a 1-methylimidazol- 5-yl substituent.

As used herein, "heterocycle" or "heterocyclyl" refers to mono- and polycyclic ring systems having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. The mono- and polycyclic ring systems can be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

"Alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH_3).

"Alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n- pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i- propoxy, n-butoxy, s-butoxy, t-butoxy.

"Alkylamino" refers an alkyl group as defined above with the indicated number of carbon atoms attached through an amino bridge. An example of an alkylamino is methylamino, (i.e., -NH-CH_3).

"Alkanoyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a carbonyl bride (i.e., -(C=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfonyl bridge (i.e., -S(=O)$_2$alkyl) such as mesyl and the like, and "Arylsulfonyl" refers to an aryl attached through a sulfonyl bridge (i.e., - S(=O)$_2$aryl).

"Alkylsulfamoyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfamoyl bridge (i.e., -NHS(=O)$_2$alkyl), and an "Arylsulfamoyl" refers to an alkyl attached through a sulfamoyl bridge (i.e., - NHS(=O)$_2$aryl).

"Alkylsulfinyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfinyl bridge (i.e. -S(=O)alkyl).

The terms "cycloalkyl" and "cycloalkenyl" refer to mono-, bi-, or tri homocyclic ring groups of 3 to 15 carbon atoms which are, respectively, fully saturated and partially unsaturated. The term "cycloalkenyl" includes bi- and tricyclic ring systems that are not aromatic as a whole, but contain aromatic portions (e.g., fluorene, tetrahydronapthalene, dihydroindene, and the like). The rings of multi-ring cycloalkyl groups can be either fused, bridged and/or joined through one or more spiro unions. The terms "substituted cycloalkyl" and "substituted cycloalkenyl" refer, respectively, to cycloalkyl and cycloalkenyl groups substituted with one or more groups, preferably selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane, sulfonyl, and the like.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine, and iodine.

The term "substituted" refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are "substituents." The molecule can be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context can include halogen, hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -NRaRb, -NRaC(=O)Rb, -NRaC(=O)NRaNRb, -NRaC(=O)ORb, - $NRaSO_2Rb$, -C(=O)Ra, -C(=O)ORa, -C(=O)NRaRb, -OC(=O)NRaRb, -ORa, -SRa, -SORa, - $S(=O)_2Ra$, $-OS(=O)_2Ra$ and $-S(=O)_2ORa$. Ra and Rb in this context can be the same or different and independently hydrogen, halogen hydroxyl, alkyl, alkoxy, alkyl, amino, alkylamino, dialkylamino, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

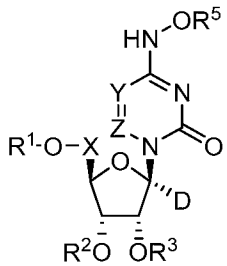
The term "optionally substituted," as used herein, means that substitution with an additional group is optional and therefore it is possible for the designated atom to be unsubstituted. Thus, by use of the term "optionally substituted" the disclosure includes examples where the group is substituted and examples where it is not.

Examples of prodrugs that can be used to improve bioavailability include esters, optionally substituted esters, branched esters, optionally substituted branched esters, carbonates, optionally substituted carbonates, carbamates, optionally substituted carbamates, thioesters, optionally substituted thioesters, branched thioesters, optionally substituted branched thioesters, thiocarbonates, optionally substituted thiocarbonates, S-thiocarbonate, optionally substituted S-

thiocarbonate, dithiocarbonates, optionally substituted dithiocarbonates, thiocarbamates, optionally substituted thiocarbamates, oxymethoxycarbonyl, optionally substituted oxymethoxycarbonyl, oxymethoxythiocarbonyl, optionally substituted oxymethoxythiocarbonyl, oxymethylcarbonyl, optionally substituted oxymethylcarbonyl, oxymethylthiocarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, sulfenyl, optionally substituted sulfenyl, imidate, optionally substituted imidate, hydrazonate, optionally substituted hydrazonate, oximyl, optionally substituted oximyl, imidinyl, optionally substituted imidinyl, imidyl, optionally substituted imidyl, aminal, optionally substituted aminal, hemiaminal, optionally susbstituted hemiaminal, acetal, optionally substituted acetal, hemiacetal, optionally susbstituted hemiacetal, carbonimidate, optionally substituted carbonimidate, thiocarbonimidate, optionally substituted thiocarbonimidate, carbonimidyl, optionally substituted carbonimidyl, carbamimidate, optionally substituted carbamimidate, carbamimidyl, optionally substituted carbamimidyl, thioacetal, optionally substituted thioacetal, S-acyl-2-thioethyl, optionally substituted S-acyl-2-thioethyl, bis-(acyloxybenzyl)esters, optionally substituted bis-(acyloxybenzyl)esters, (acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters.

Compounds

In certain embodiments, the disclosure relates to a compound of Formula I,



Formula I

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

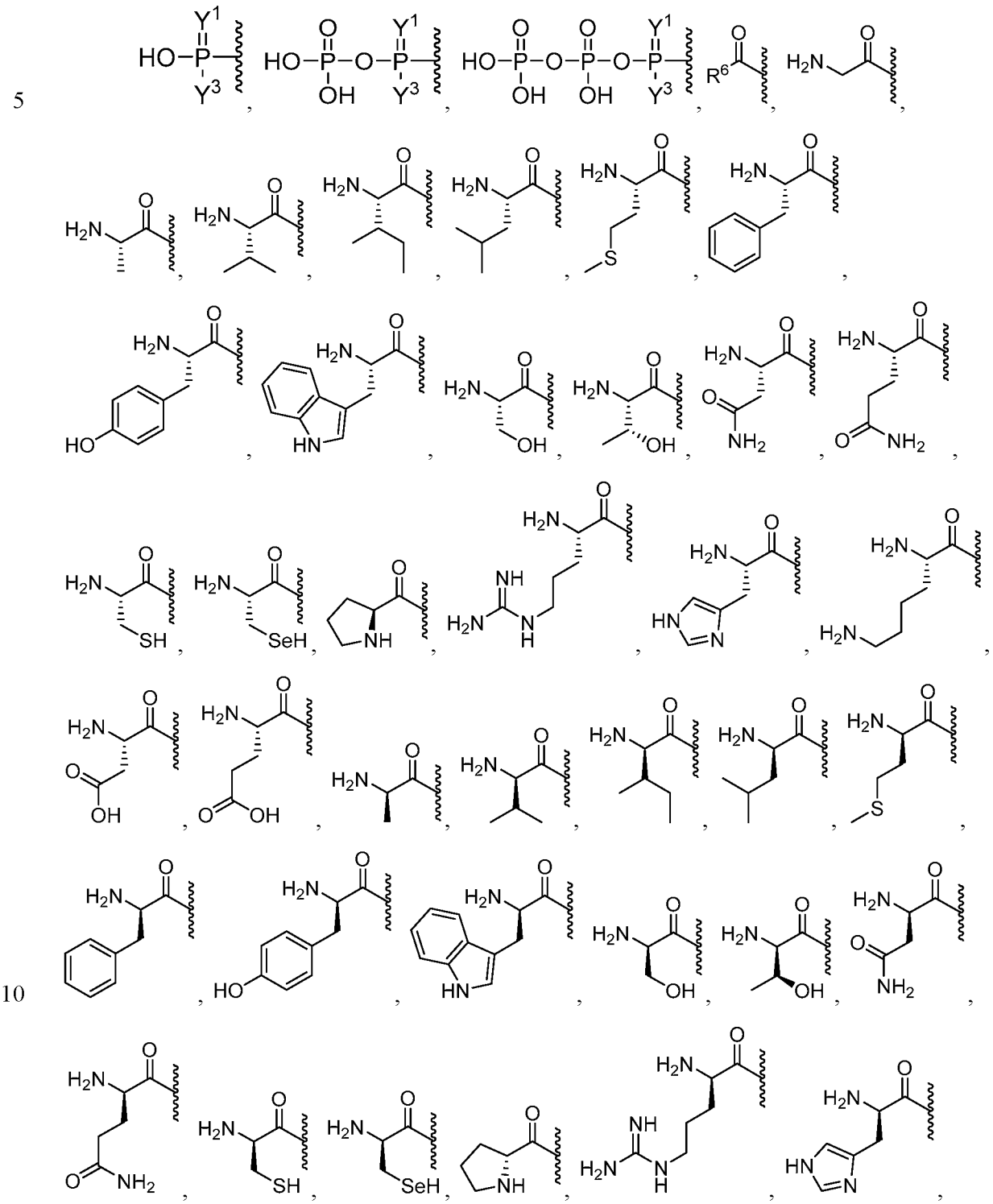
Y is N or CR';

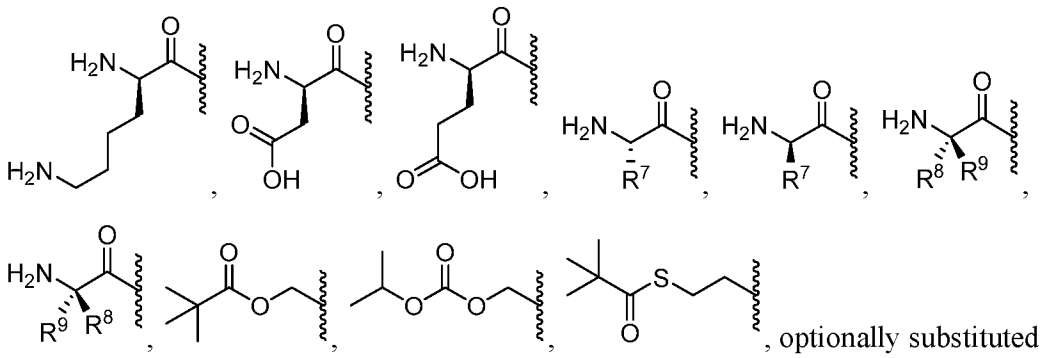
Z is N or CR";

R' is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R" is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H,





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

Y^1 is O or S;

Y^3 is OH or $BH_3^-M^+$;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy,

carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy,

carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In certain embodiments, the lipid is a fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids.

In certain embodiments, the lipid is an unsaturated, polyunsaturated, omega unsaturated, or omega polyunsaturated fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids.

In certain embodiments, the lipid is a fatty alcohol, fatty amine, or fatty thiol derived from essential and non-essential fatty acids that have one or more of its carbon units substituted with an oxygen, nitrogen, or sulfur.

In certain embodiments, the lipid is an unsaturated, polyunsaturated, omega unsaturated, or omega polyunsaturated fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids that have one or more of its carbon units substituted with an oxygen, nitrogen, or sulfur.

In certain embodiments, the lipid is a fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids that is optionally substituted.

In certain embodiments, the lipid is an unsaturated, polyunsaturated, omega unsaturated, or omega polyunsaturated fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids that is optionally substituted.

In certain embodiments, the lipid is a fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids that have one or more of its carbon units substituted with an oxygen, nitrogen, or sulfur that is optionally substituted.

In certain embodiments, the lipid is an unsaturated, polyunsaturated, omega unsaturated, or omega polyunsaturated fatty alcohol, fatty amine, or fatty thiol derived from essential and/or non-essential fatty acids that have one or more of its carbon units substituted with an oxygen, nitrogen, or sulfur that is also optionally substituted.

In certain embodiments, the lipid is hexadecyloxypropyl.

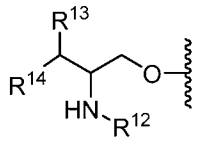
In certain embodiments, the lipid is 2-aminohexadecyloxypropyl.

In certain embodiments, the lipid is 2-aminoarachidyl.

In certain embodiments, the lipid is 2-benzyloxyhexadecyloxypropyl.

In certain embodiments, the lipid is lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, or lignoceryl.

In certain embodiments, the lipid is a sphingolipid of the formula:

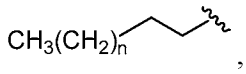
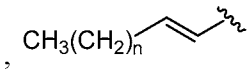
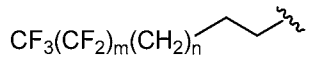


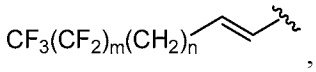
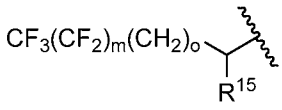
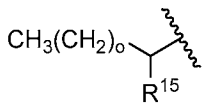
wherein,

R^{12} of the sphingolipid is hydrogen, alkyl, $C(=O)R^{16}$, $C(=O)OR^{16}$, or $C(=O)NHR^{16}$;

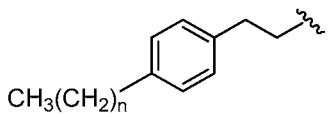
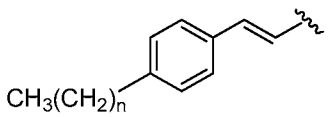
R^{13} of the sphingolipid is hydrogen, fluoro, OR^{16}, $OC(=O)R^{16}$, $OC(=O)OR^{16}$, or $OC(=O)NHR^{16}$;

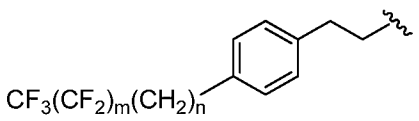
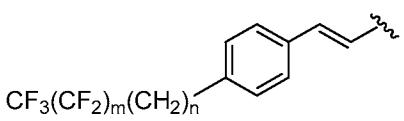
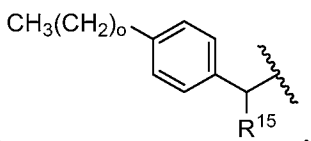
R^{14} of the sphingolipid is a saturated or unsaturated alkyl chain of greater than 6 and less than 22 carbons optionally substituted with one or more halogen or hydroxy or a structure of the following formula:

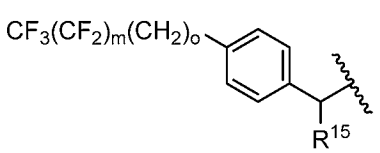
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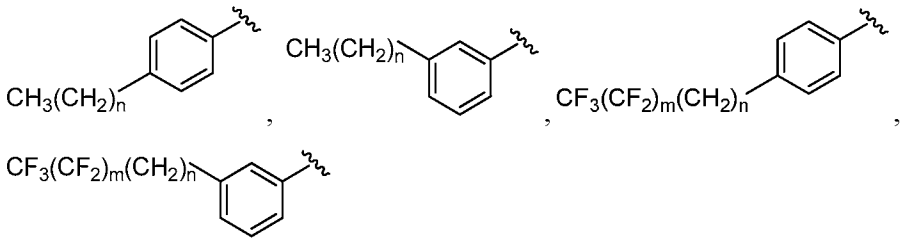
wherein n is 8 to 14 or less than or equal to 8 to less than or equal to 14, o is 9 to 15 or less than or equal to 9 to less than or equal to 15, the total or m and n is 8 to 14 or less than or equal to 8 to less than or equal to 14, the total of m and o is 9 to 15 or less than or equal to 9 to less than or equal to 15; or

, ,

, , ,

;

wherein n is 4 to 10 or less than or equal to 4 to less than or equal to 10, o is 5 to 11 or less than or equal to 5 to less than or equal to 11, the total of m and n is 4 to 10 or less than or equal to 4 to less than or equal to 10, and the total of m and o is 5 to 11 or less than or equal to 5 to less than or equal to 11; or



wherein n is 6 to 12 or n is less than or equal to 6 to less than or equal to 12, the total of m and n is 6 to 12 or n is less than or equal to 6 to less than or equal to 12;

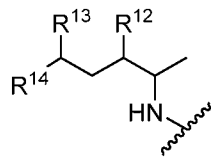
R^{15} of the sphingolipid is OR^{16}, $OC(=O)R^{16}$, $OC(=O)OR^{16}$, or $OC(=O)NHR^{16}$;

R^{16} of the sphingolipid is hydrogen, cyano, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, or lipid; wherein R^{16} is optionally substituted with one or more, the same or different R^{17}; and

R^{17} of the sphingolipid is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl.

In certain embodiments, R^{12} of the sphingolipid is H, methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or phenyl.

In certain embodiments, the sphingolipid is a sphingolipid of the formula:

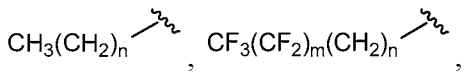


wherein,

R^{12} of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{16}, $OC(=O)R^{16}$, $OC(=O)OR^{16}$, or $OC(=O)NHR^{16}$;

R^{13} of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{16}, $OC(=O)R^{16}$, $OC(=O)OR^{16}$, or $OC(=O)NHR^{16}$;

R^{14} of the sphingolipid is a saturated or unsaturated alkyl chain of greater than 6 and less than 22 carbons optionally substituted with one or more halogens or a structure of the following formula:



wherein n is 8 to 14 or less than or equal to 8 to less than or equal to 14, the total or m and n is 8 to 14 or less than or equal to 8 to less than or equal to 14;

R^{16} of the sphingolipid is hydrogen, cyano, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, or lipid; wherein R^{16} is optionally substituted with one or more, the same or different R^{17}; and

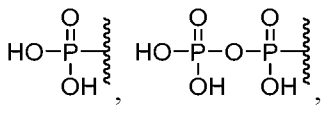
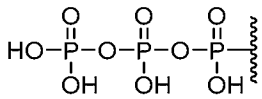
R^{17} of the sphingolipid is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, esteryl, formyl, carboxy, carbamoyl, amido, or acyl.

In certain embodiments, R^{16} of the sphingolipid is H, methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or benzyl.

Suitable sphingolipids include, but are not limited to, sphingosine, ceramide, or sphingomyelin, or 2-aminoalkyl optionally substituted with one or more substituents.

Other suitable sphingolipids include, but are not limited to, 2-aminooctadecane-3,5-diol; (2S,3S,5S)-2-aminooctadecane-3,5-diol; (2S,3R,5S)-2-aminooctadecane-3,5-diol; 2-(methylamino)octadecane-3,5-diol; (2S,3R,5S)-2-(methylamino)octadecane-3,5-diol; 2-(dimethylamino)octadecane-3,5-diol; (2R,3S,5S)-2-(dimethylamino)octadecane-3,5-diol; 1-(pyrrolidin-2-yl)hexadecane-1,3-diol; (1S,3S)-1-((S)-pyrrolidin-2-yl)hexadecane-1,3-diol; 2-

amino-11,11-difluorooctadecane-3,5-diol; (2S,3S,5S)-2-amino-11,11-difluorooctadecane-3,5-diol; 11,11-difluoro-2-(methylamino)octadecane-3,5-diol; (2S,3S,5S)-11,11-difluoro-2-(methylamino)octadecane-3,5-diol; N-((2S,3S,5S)-3,5-dihydroxyoctadecan-2-yl)acetamide; N-((2S,3S,5S)-3,5-dihydroxyoctadecan-2-yl)palmitamide;1-(1-aminocyclopropyl)hexadecane-1,3-diol; (1S,3R)-1-(1-aminocyclopropyl)hexadecane-1,3-diol; (1S,3S)-1-(1-aminocyclopropyl)hexadecane-1,3-diol; 2-amino-2-methyloctadecane-3,5-diol; (3S,5S)-2-amino-2-methyloctadecane-3,5-diol; (3S,5R)-2-amino-2-methyloctadecane-3,5-diol; (3S,5S)-2-methyl-2-(methylamino)octadecane-3,5-diol; 2-amino-5-hydroxy-2-methyloctadecan-3-one; (Z)-2-amino-5-hydroxy-2-methyloctadecan-3-one oxime; (2S,3R,5R)-2-amino-6,6-difluorooctadecane-3,5-diol; (2S,3S,5R)-2-amino-6,6-difluorooctadecane-3,5-diol; (2S,3S,5S)-2-amino-6,6-difluorooctadecane-3,5-diol; (2S,3R,5S)-2-amino-6,6-difluorooctadecane-3,5-diol; and (2S,3S,5S)-2-amino-18,18,18-trifluorooctadecane-3,5-diol, which can be optionally substituted with one or more substituents.

In exemplified embodiments of Formula I, R^1 is hydrogen, , .

In exemplified embodiments of Formula I, R' is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

In exemplified embodiments of Formula I, R'' is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

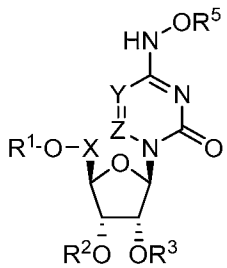
In exemplified embodiments of Formula I, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula I, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula I, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula I, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In certain embodiments, the disclosure relates to a compound of Formula II,



Formula II

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

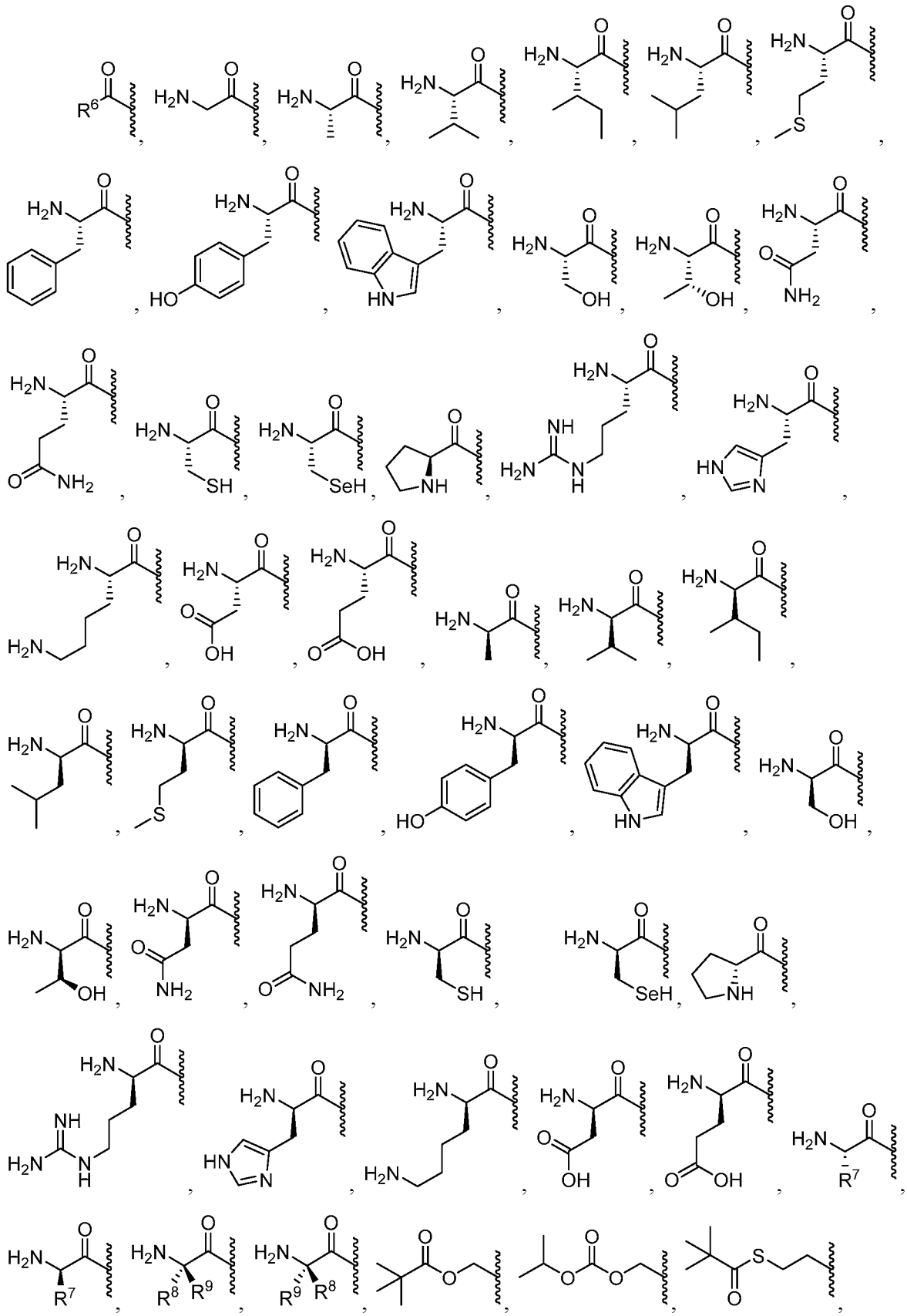
Y is N or CR';

Z is N or CR";

R' is deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R" is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H,



optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally

substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino,

heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula II, R' is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

In exemplified embodiments of Formula II, R" is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

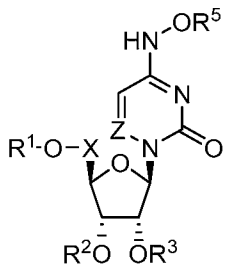
In exemplified embodiments of Formula II, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula II, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula II, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula II, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In certain embodiments, the disclosure relates to a compound of Formula III,



Formula III

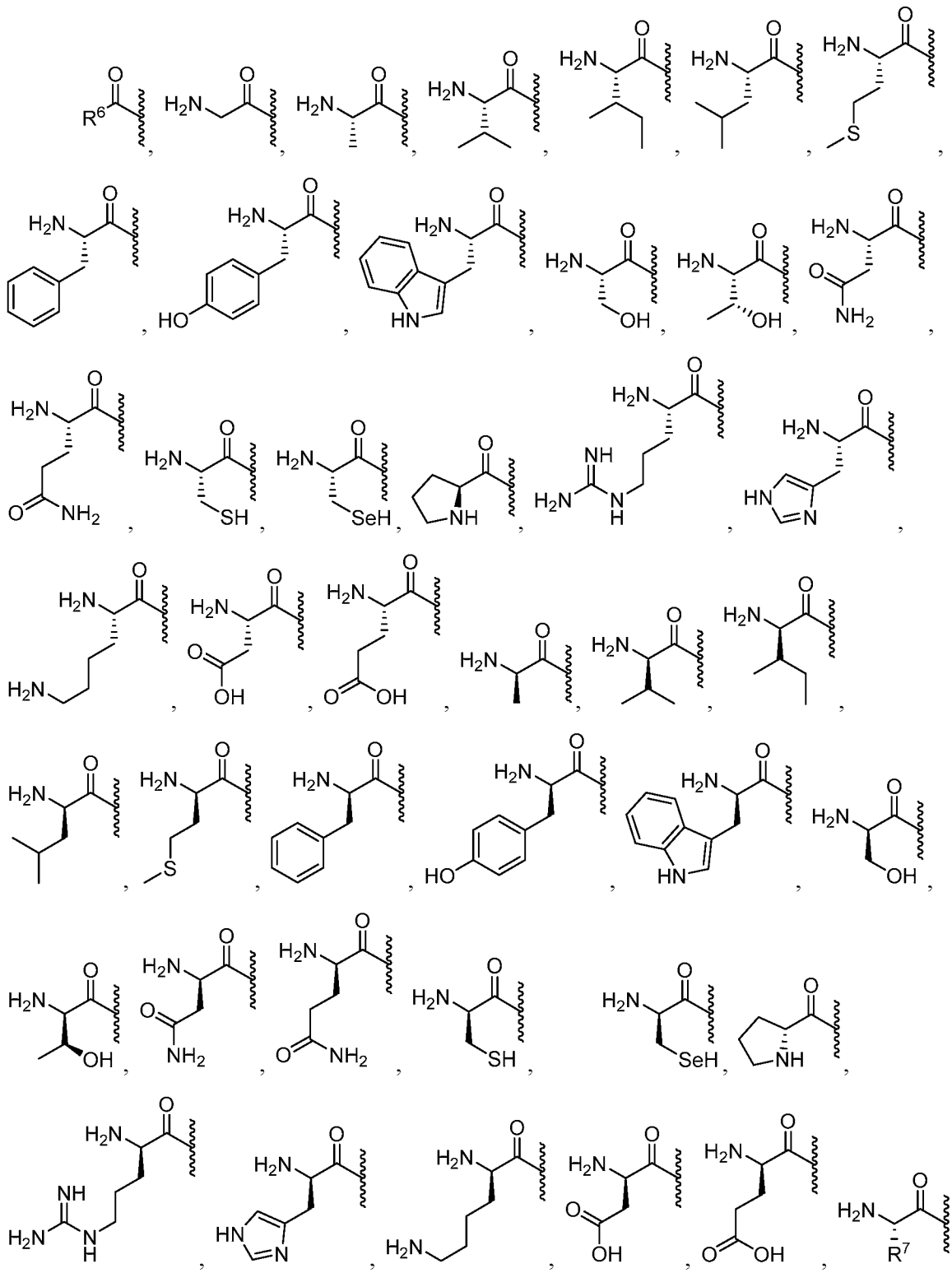
or a pharmaceutical or physiological salt thereof, wherein

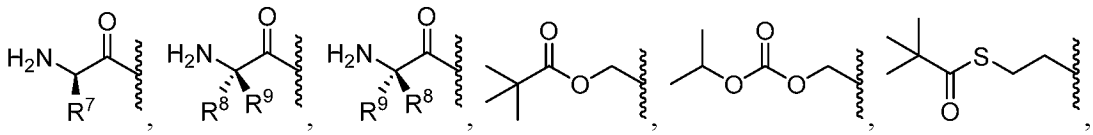
X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

Z is N or CR";

R" is deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H,





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio,

cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula III, R" is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

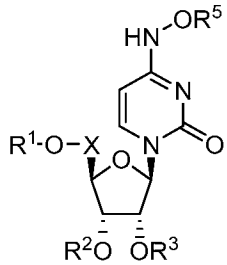
In exemplified embodiments of Formula III, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula III, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula III, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula III, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In certain embodiments, the disclosure relates to a compound of Formula IV,

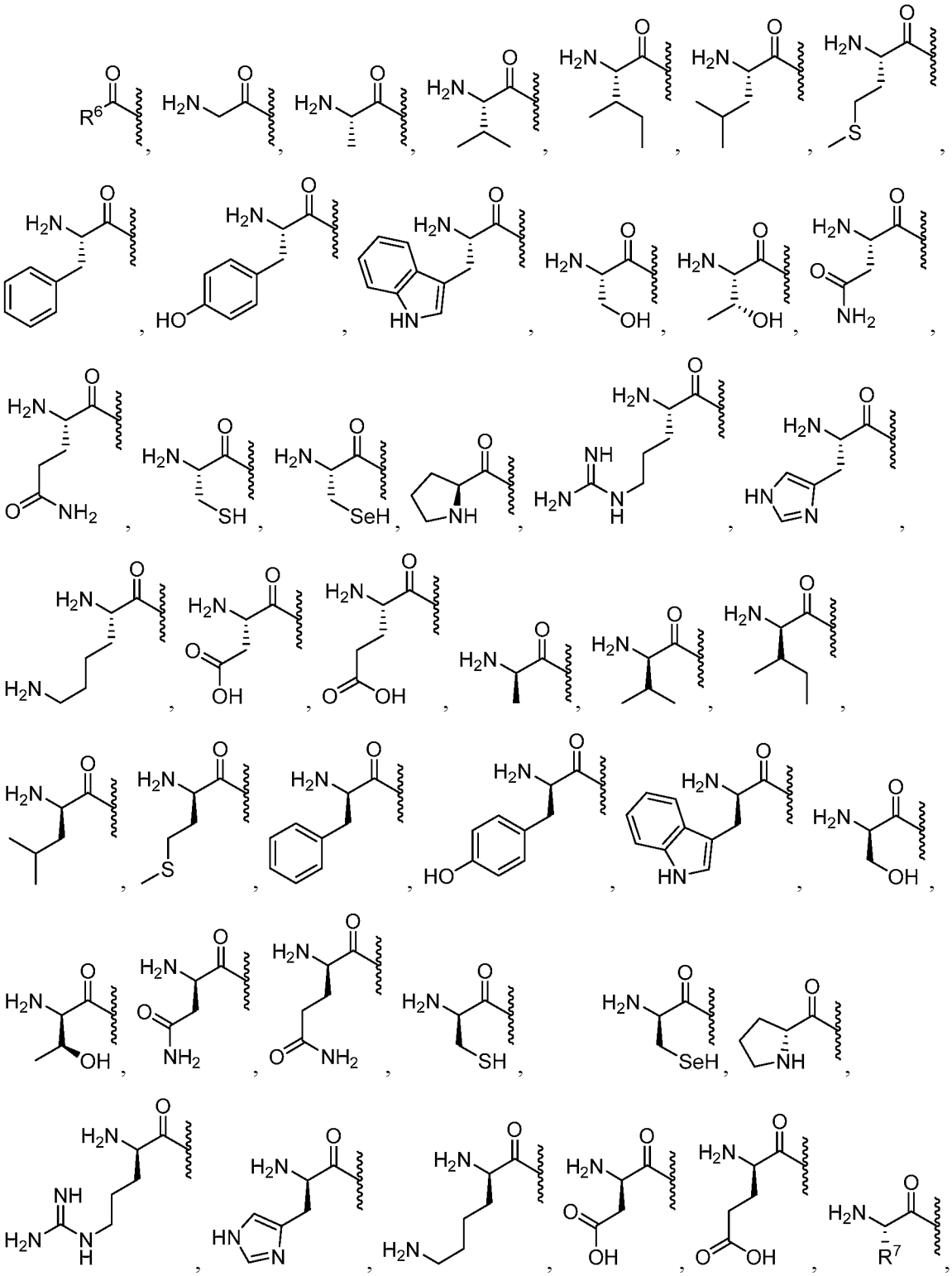


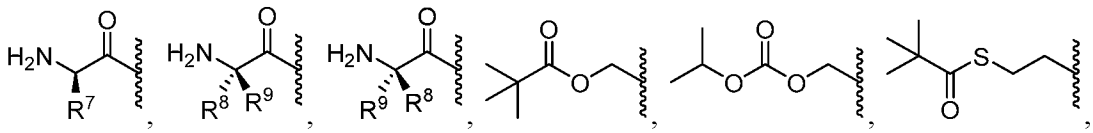
Formula IV

or a pharmaceutical or physiological salt thereof, wherein

X is $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

R^1, R^2, R^3, and R^5 are each independently selected from H,





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio,

cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

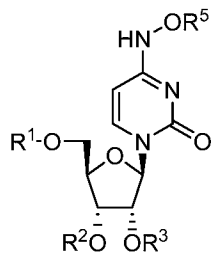
In exemplified embodiments of Formula IV, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula IV, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula IV, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula IV, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

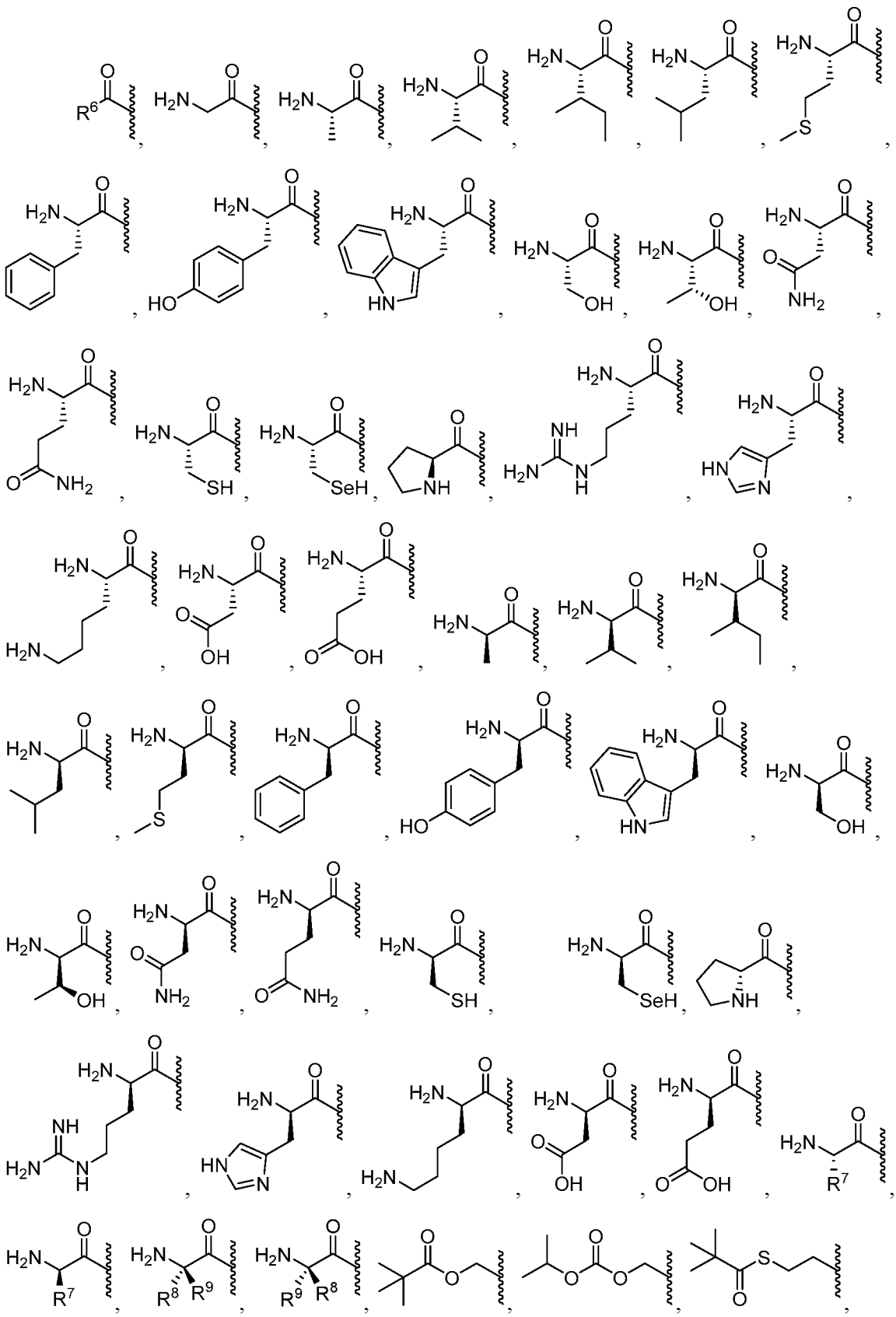
In certain embodiments, the disclosure relates to a compound of Formula V,



Formula V

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, R^3, and R^5 are each independently selected from the following:



optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally

substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula V, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-

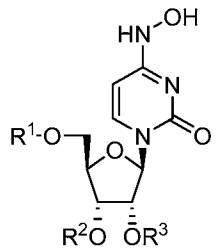
butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula V, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula V, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula V, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

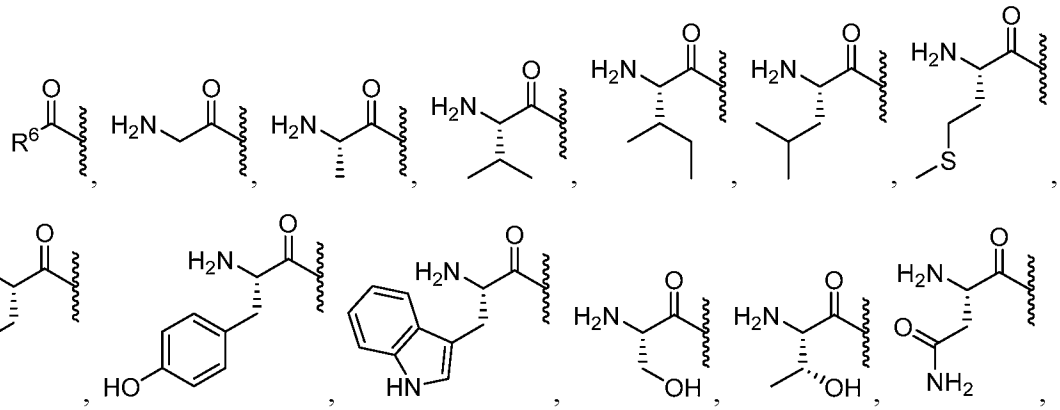
In certain embodiments, the disclosure relates to a compound of Formula VI,

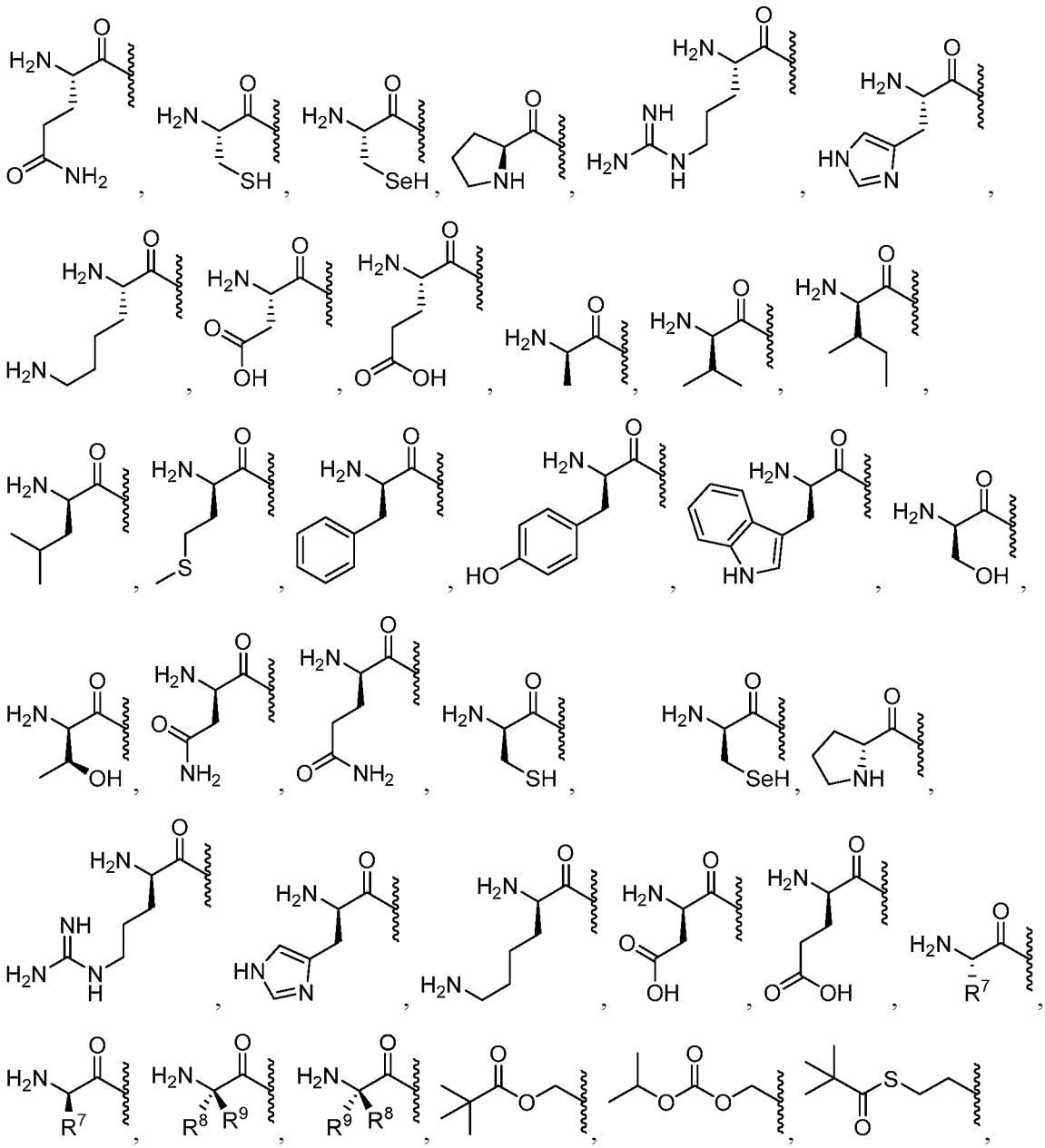


Formula VI

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^3 are each independently selected from the following:





optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, optionally substituted phenyl, optionally substituted aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula VI, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

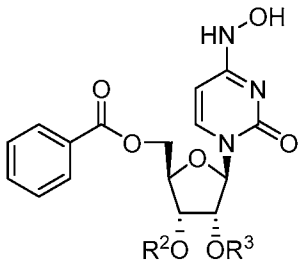
In exemplified embodiments of Formula VI, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VI, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl,

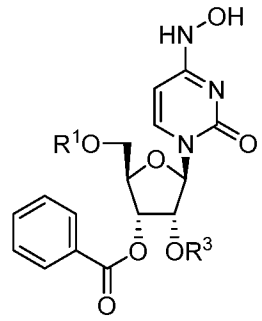
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VI, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

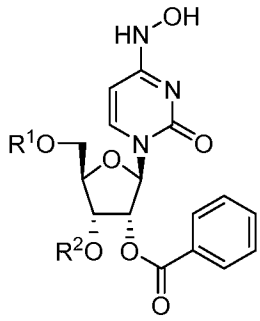
In certain embodiments, the disclosure relates to a compound of Formula VIa-f,



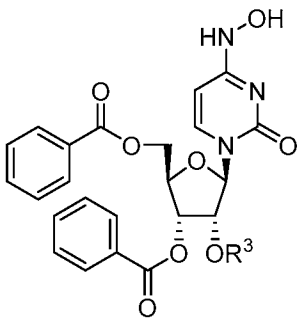
Formula VIa



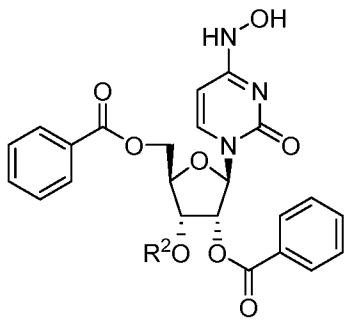
Formula VIb



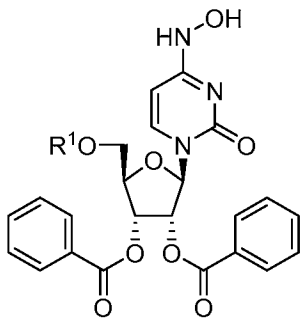
Formula VIc



Formula VId



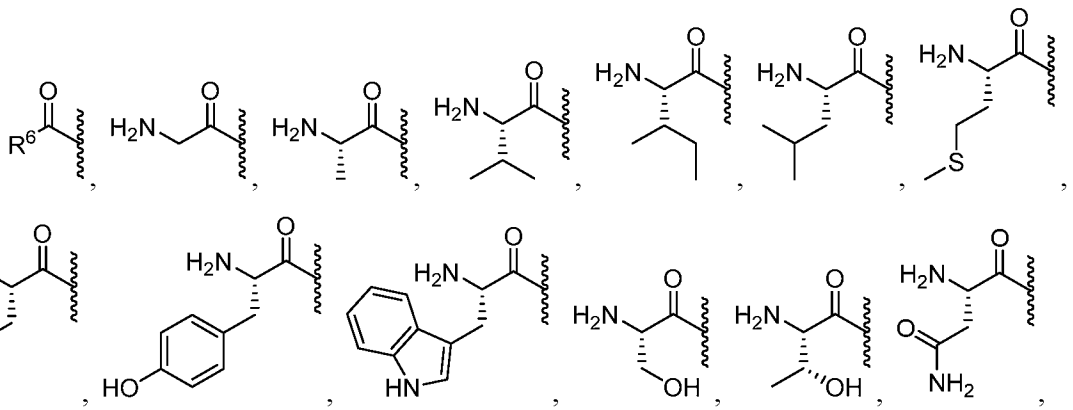
Formula VIe

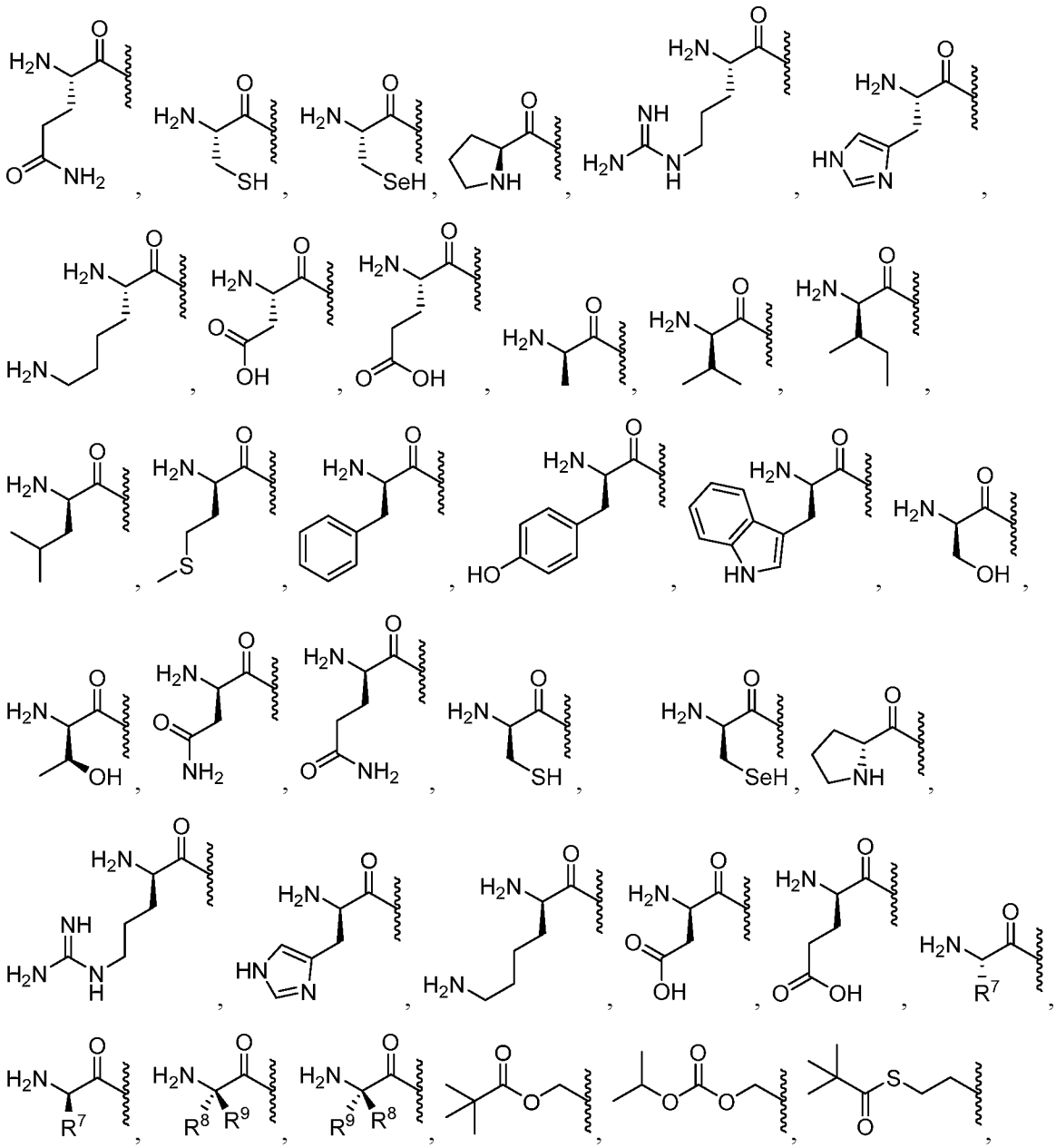


Formula VIf

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^3 are each independently selected from the following:





optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, optionally substituted phenyl, optionally substituted aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula VIa-f, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

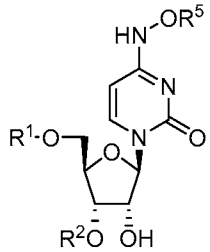
In exemplified embodiments of Formula VIa-f, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VIa-f, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VIa-f, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

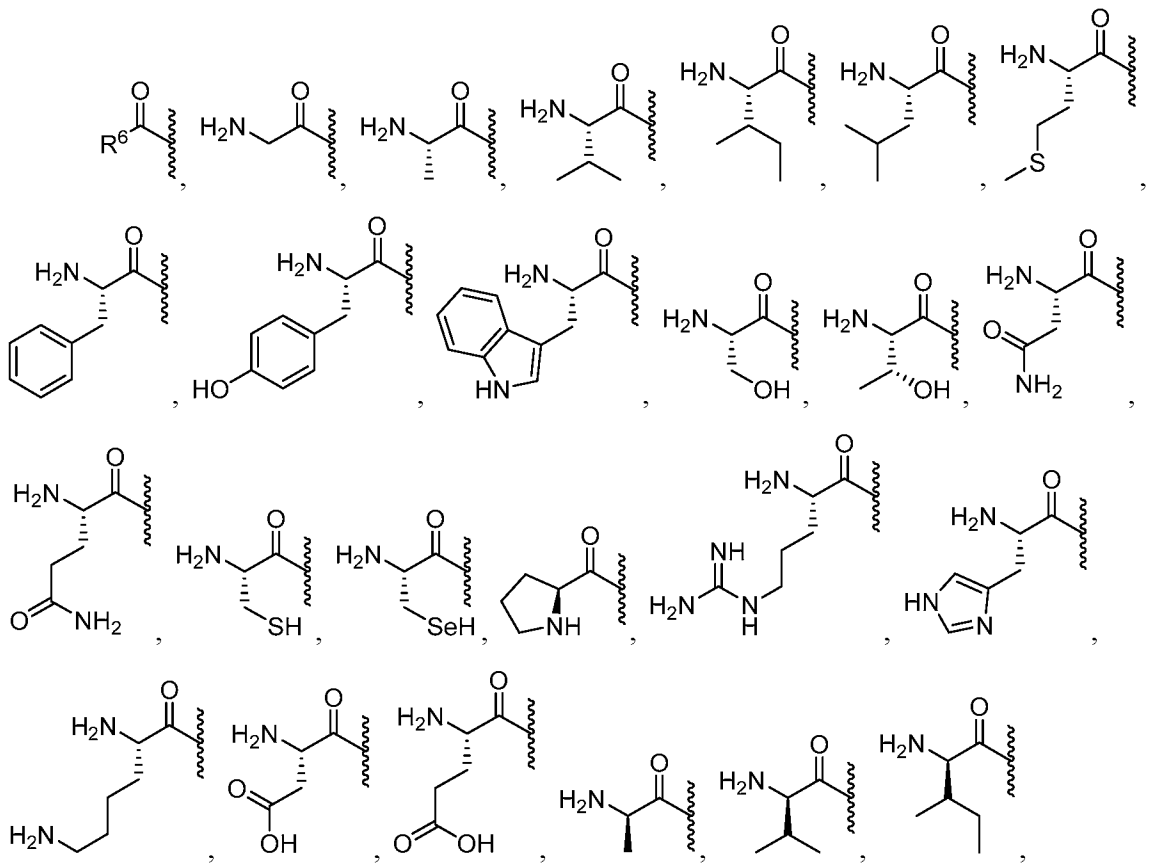
In certain embodiments, the disclosure relates to a compound of Formula VII,

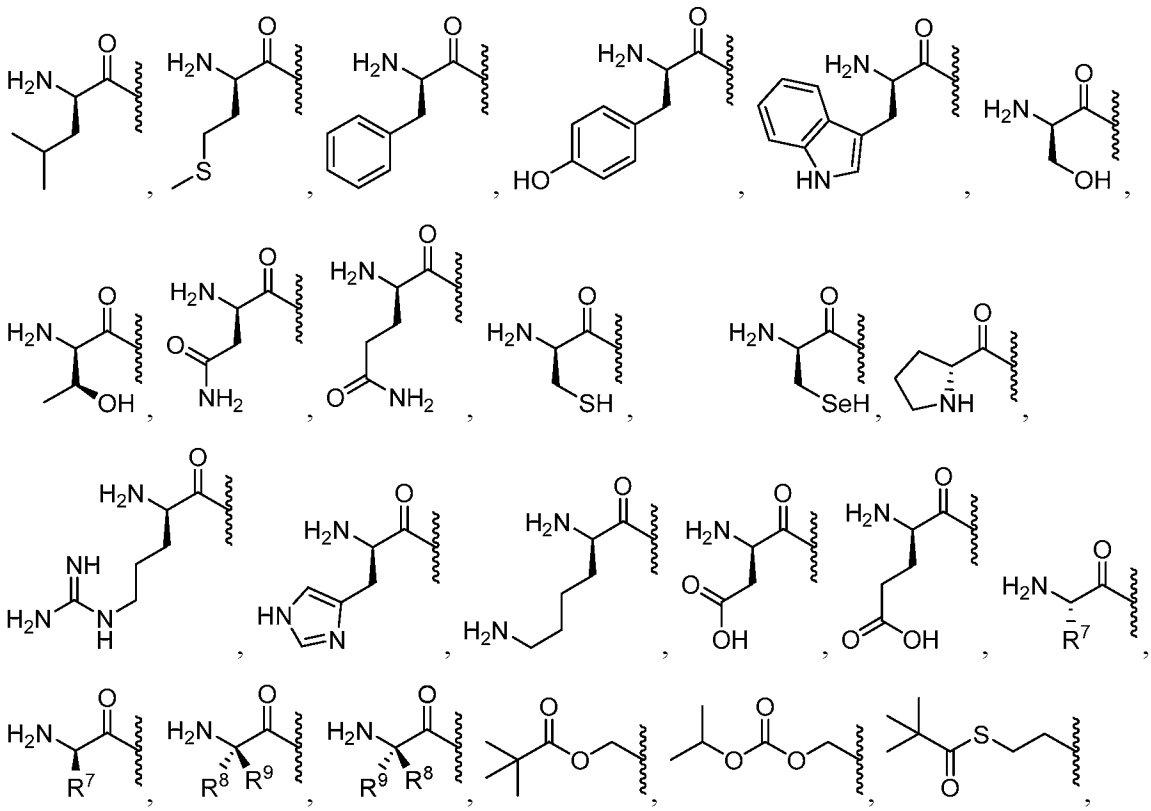


Formula VII

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^5 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy,

heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

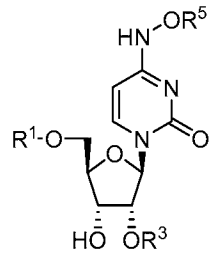
In exemplified embodiments of Formula VII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula VII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VII, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

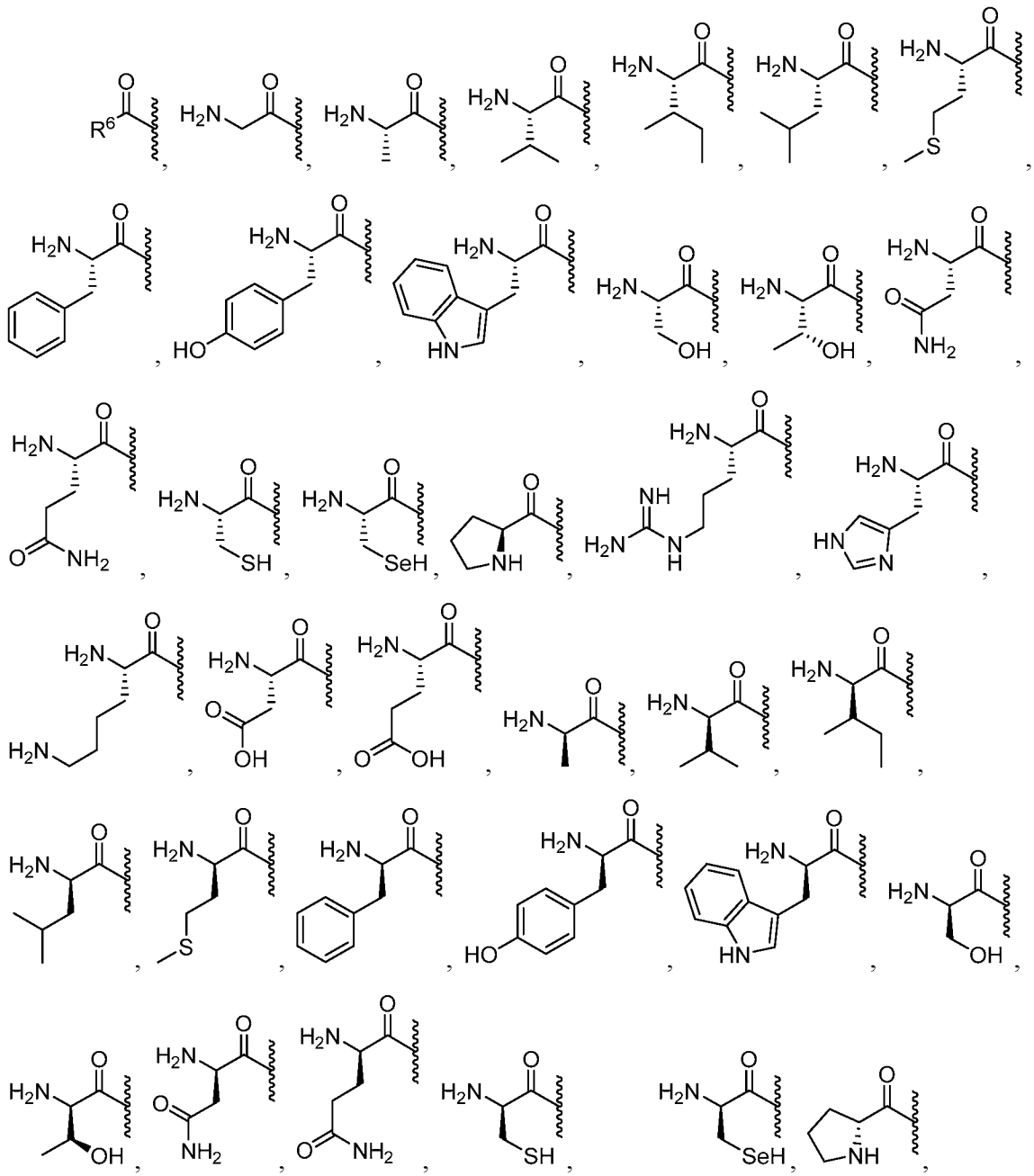
In certain embodiments, the disclosure relates to a compound of Formula VIII,

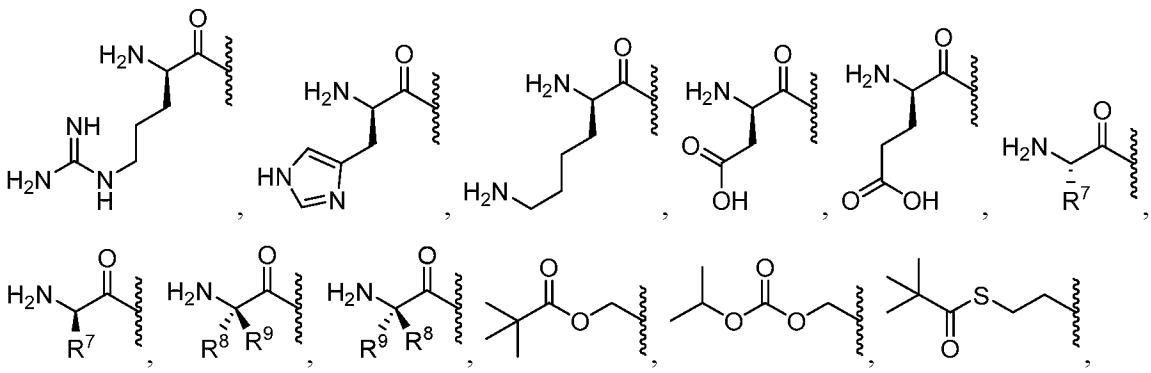


Formula VIII

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^3, and R^5 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

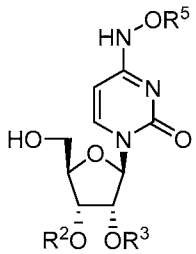
In exemplified embodiments of Formula VIII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula VIII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VIII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula VIII, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

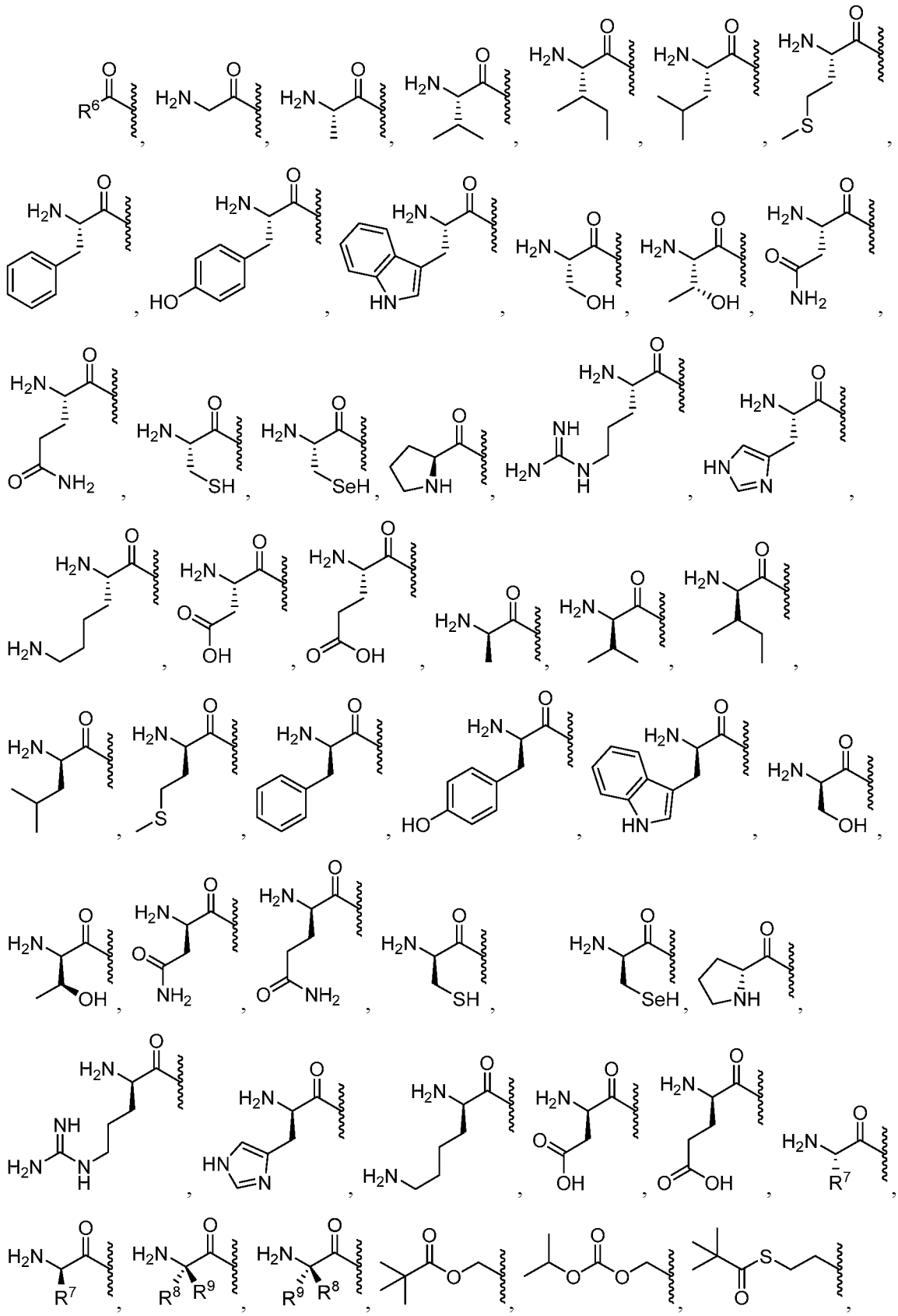
In certain embodiments, the disclosure relates to a compound of Formula IX,



Formula IX

or a pharmaceutical or physiological salt thereof, wherein

R^2, R^3, and R^5 are each independently selected from the following:



optionally substituted esters, optionally substituted branched esters, optionally substituted

carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino,

heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula IX, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-

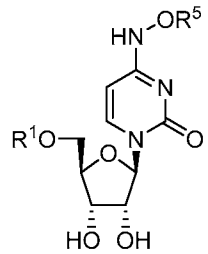
butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula IX, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula IX, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula IX, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

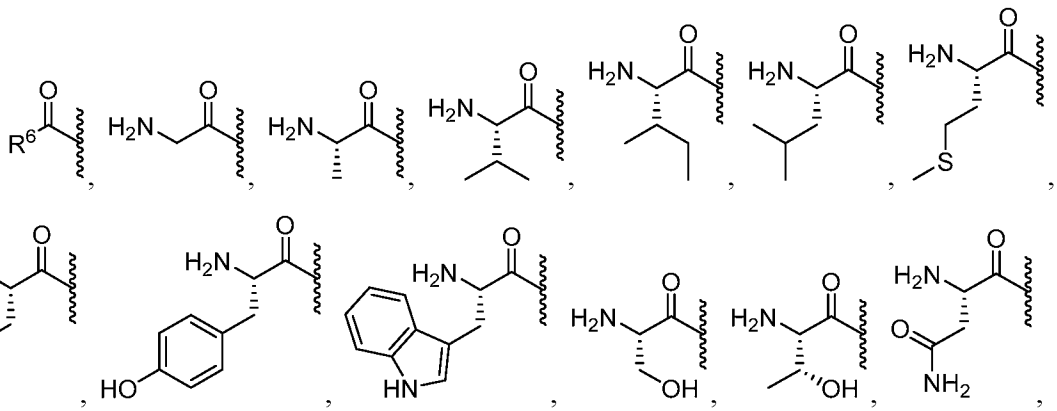
In certain embodiments, the disclosure relates to a compound of Formula X,

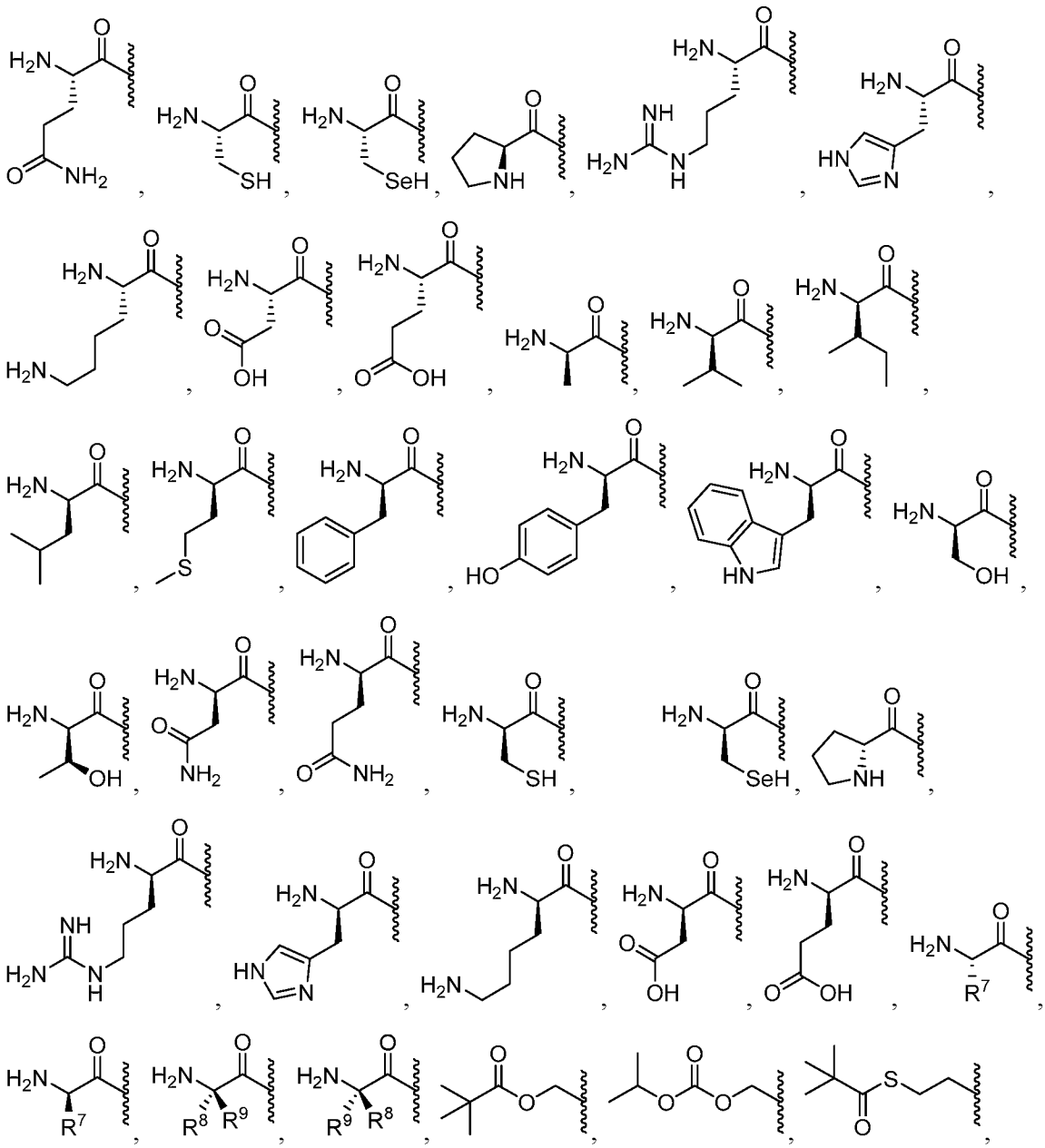


Formula X

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^5 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally

substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula X, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

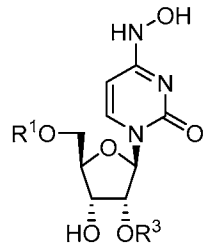
In exemplified embodiments of Formula X, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula X, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula X, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

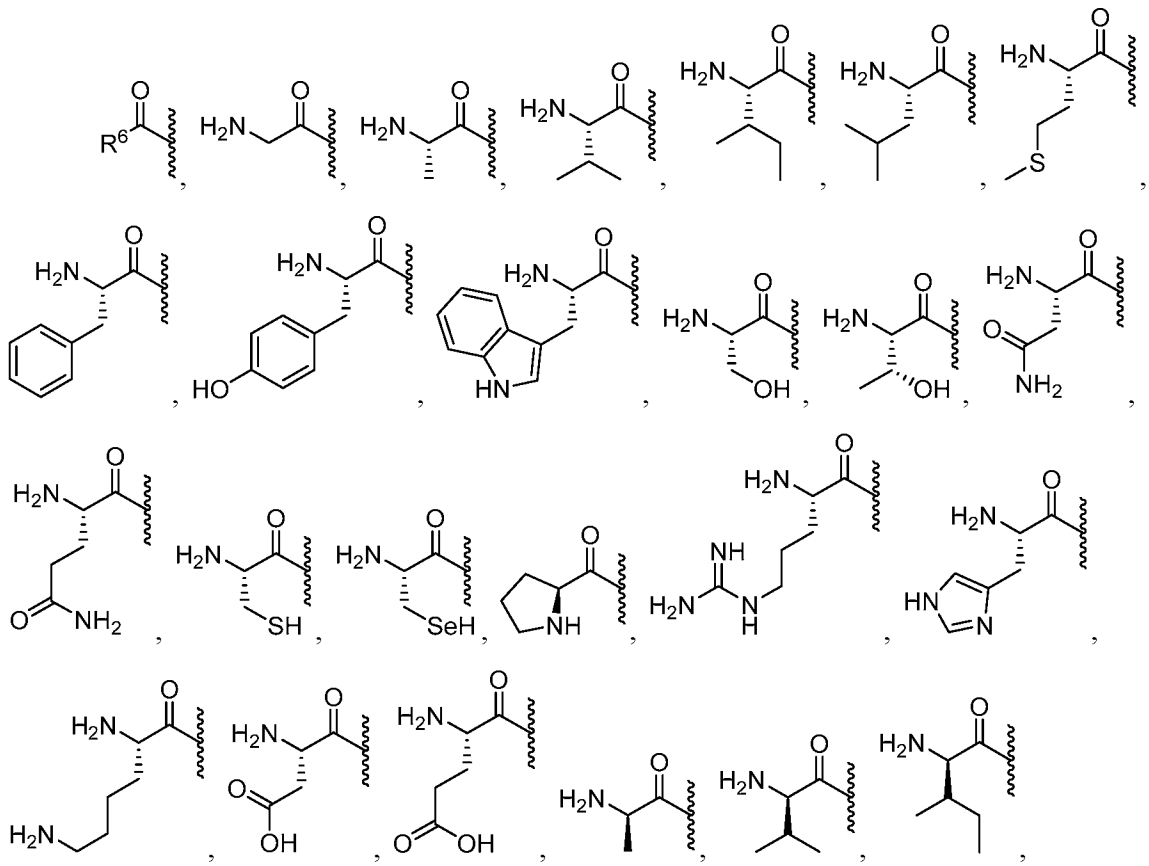
In certain embodiments, the disclosure relates to a compound of Formula XI,

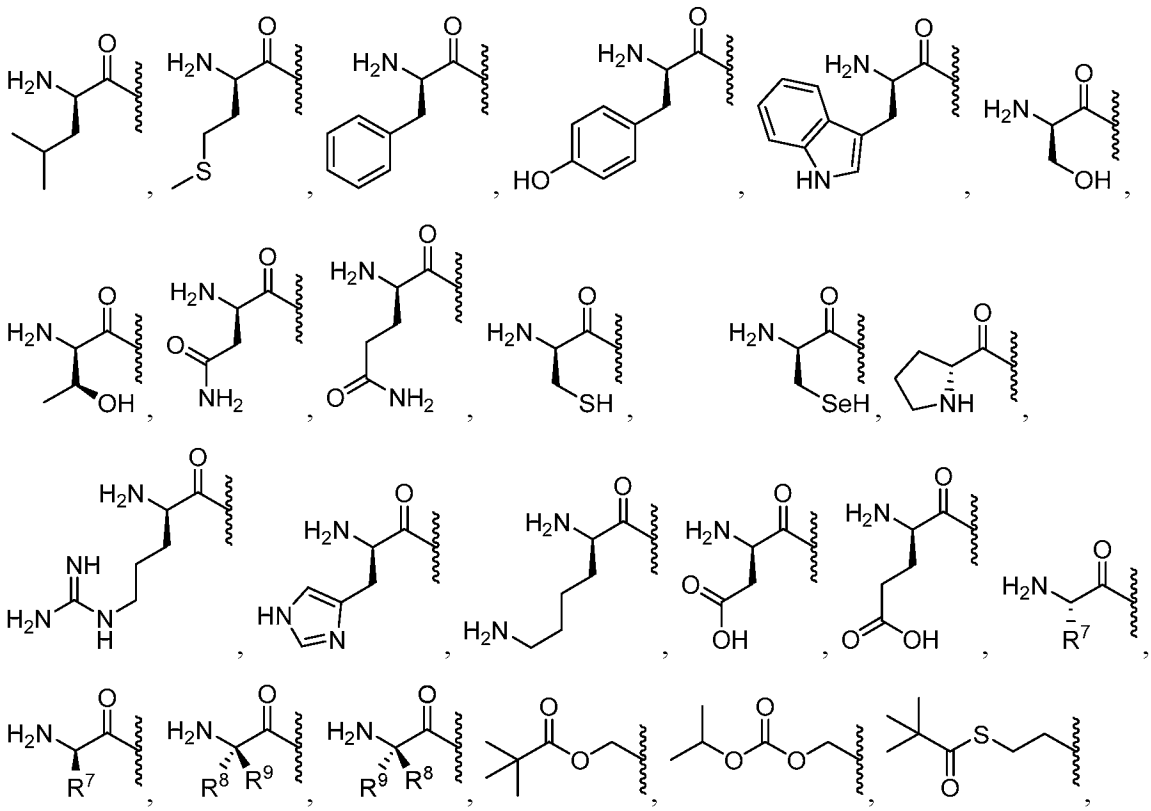


Formula XI

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^3 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy,

heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

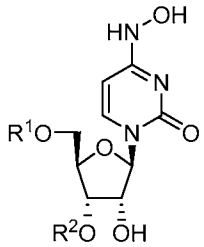
In exemplified embodiments of Formula XI, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XI, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XI, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XI, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

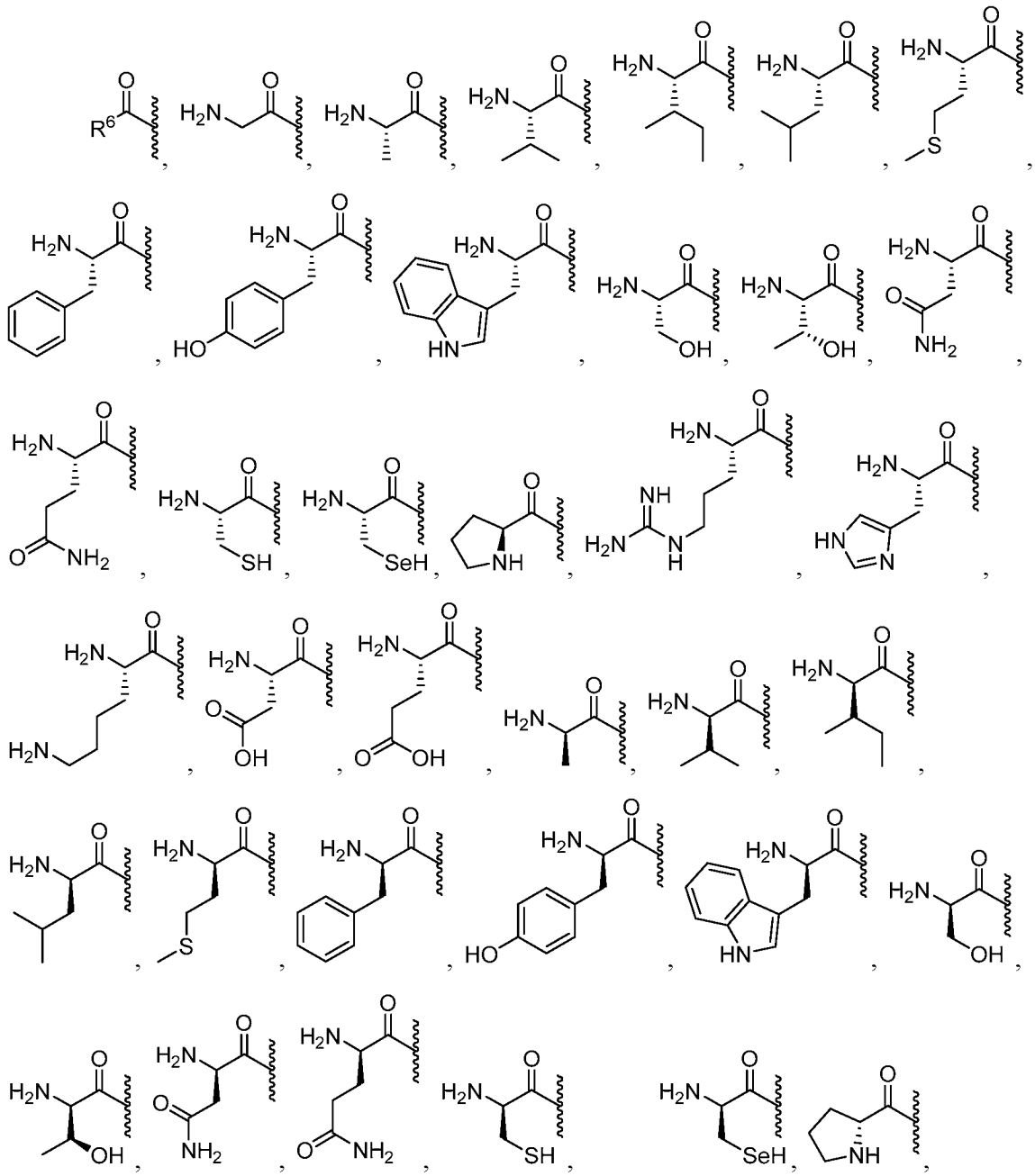
In certain embodiments, the disclosure relates to a compound of Formula XII,

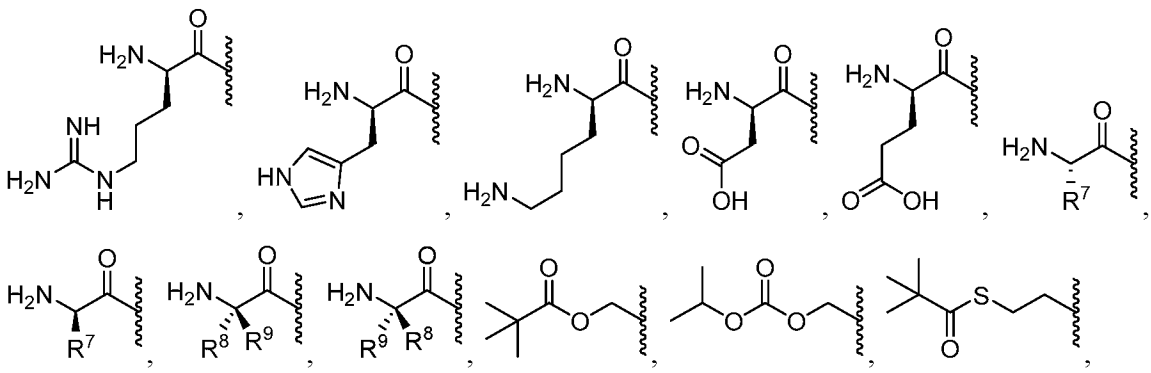


Formula XII

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^2 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^2 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

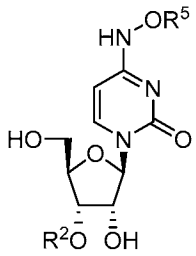
In exemplified embodiments of Formula XII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XII, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

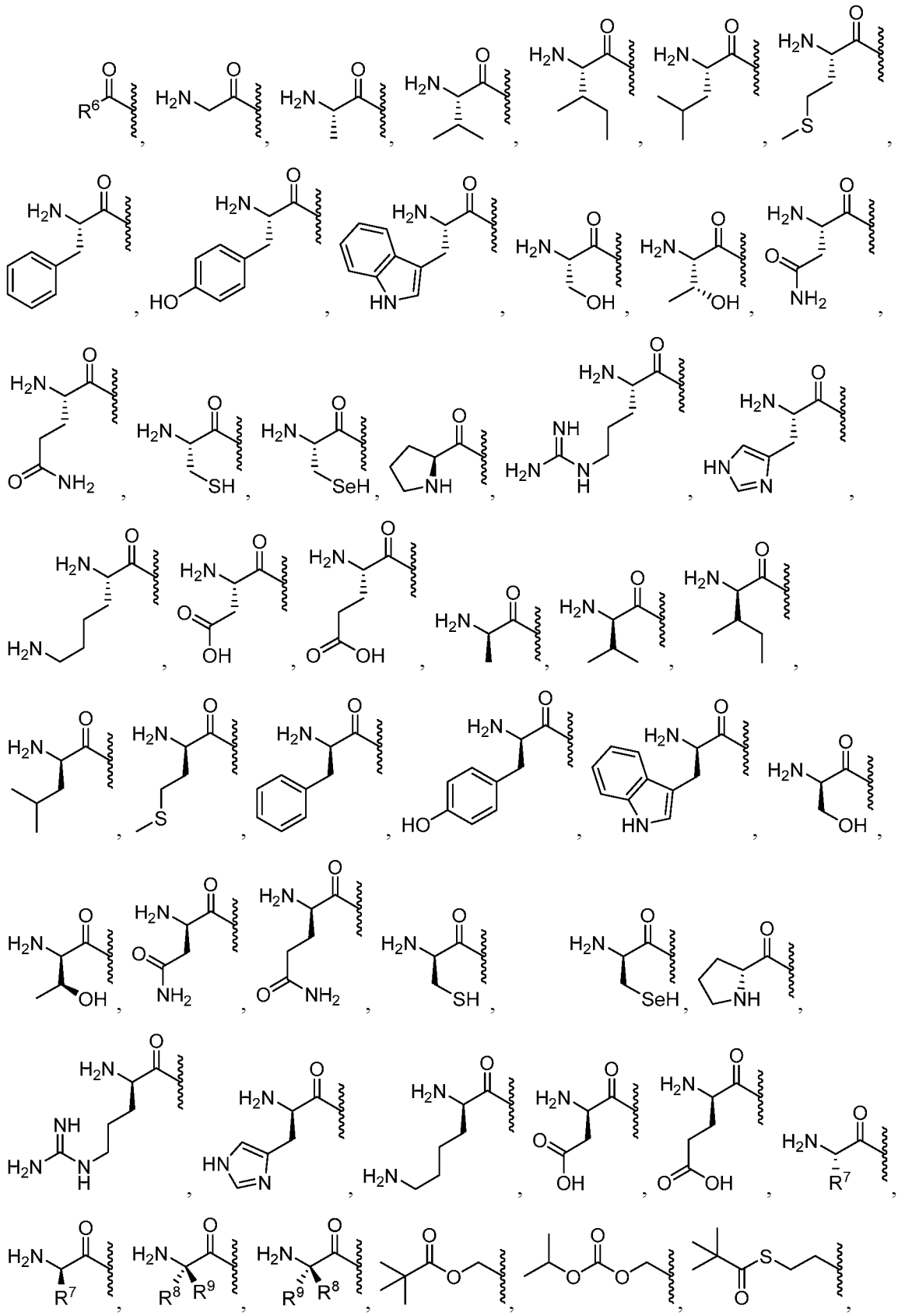
In certain embodiments, the disclosure relates to a compound of Formula XIII,



Formula XIII

or a pharmaceutical or physiological salt thereof, wherein

R^2 and R^5 are each independently selected from the following:



optionally substituted esters, optionally substituted branched esters, optionally substituted

carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino,

heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula XIII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-

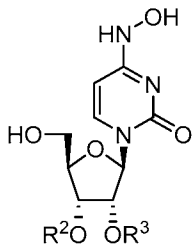
butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XIII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIII, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

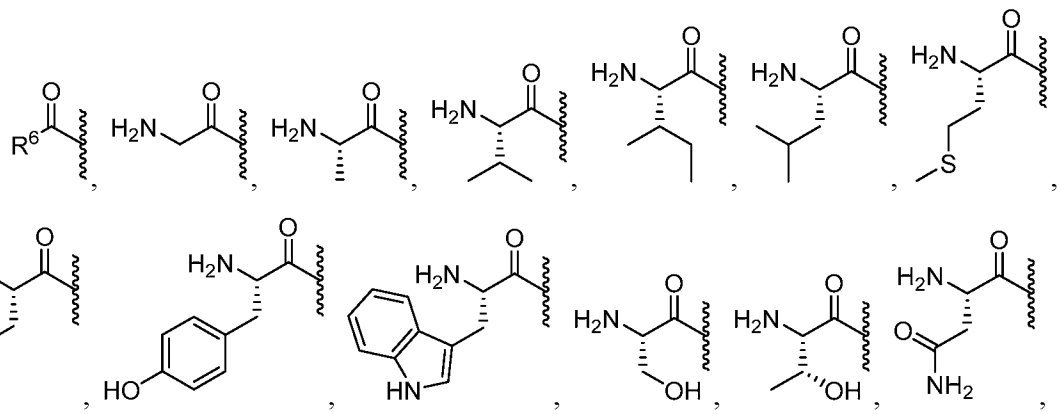
In certain embodiments, the disclosure relates to a compound of Formula XIV,

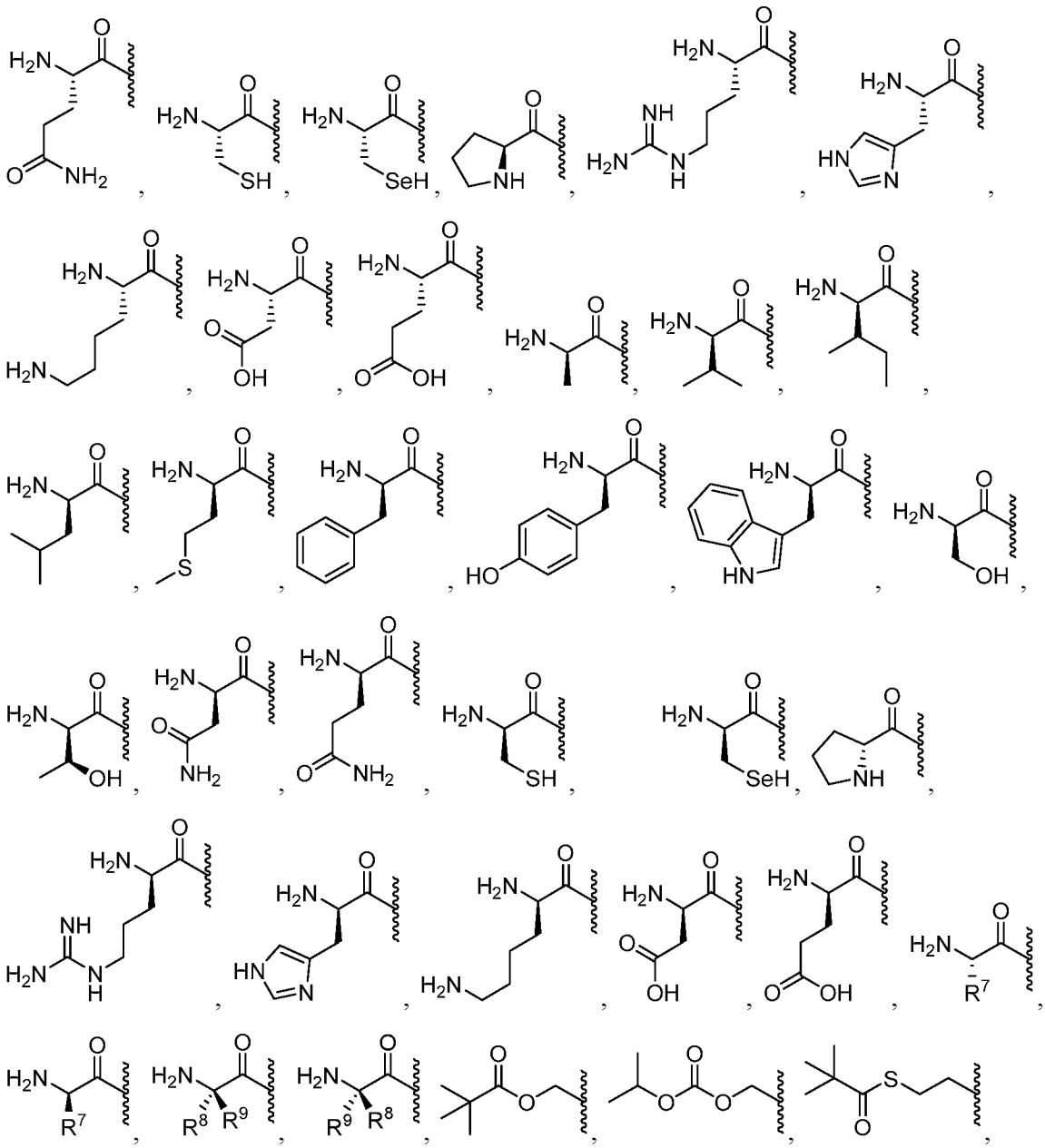


Formula XIV

or a pharmaceutical or physiological salt thereof, wherein

R^2 and R^3 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally

substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula XIV, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

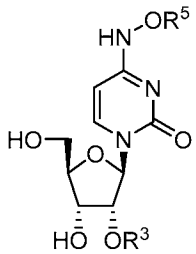
In exemplified embodiments of Formula XIV, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIV, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIV, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

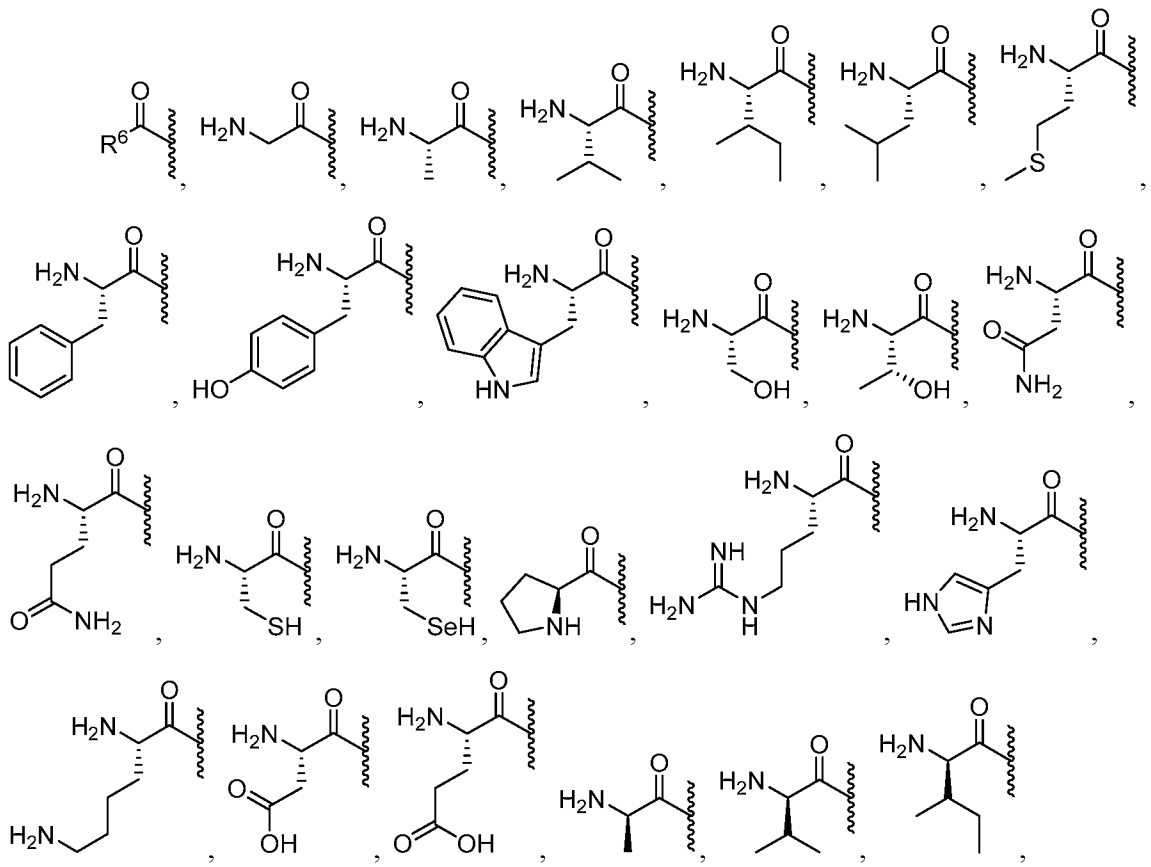
In certain embodiments, the disclosure relates to a compound of Formula XV,

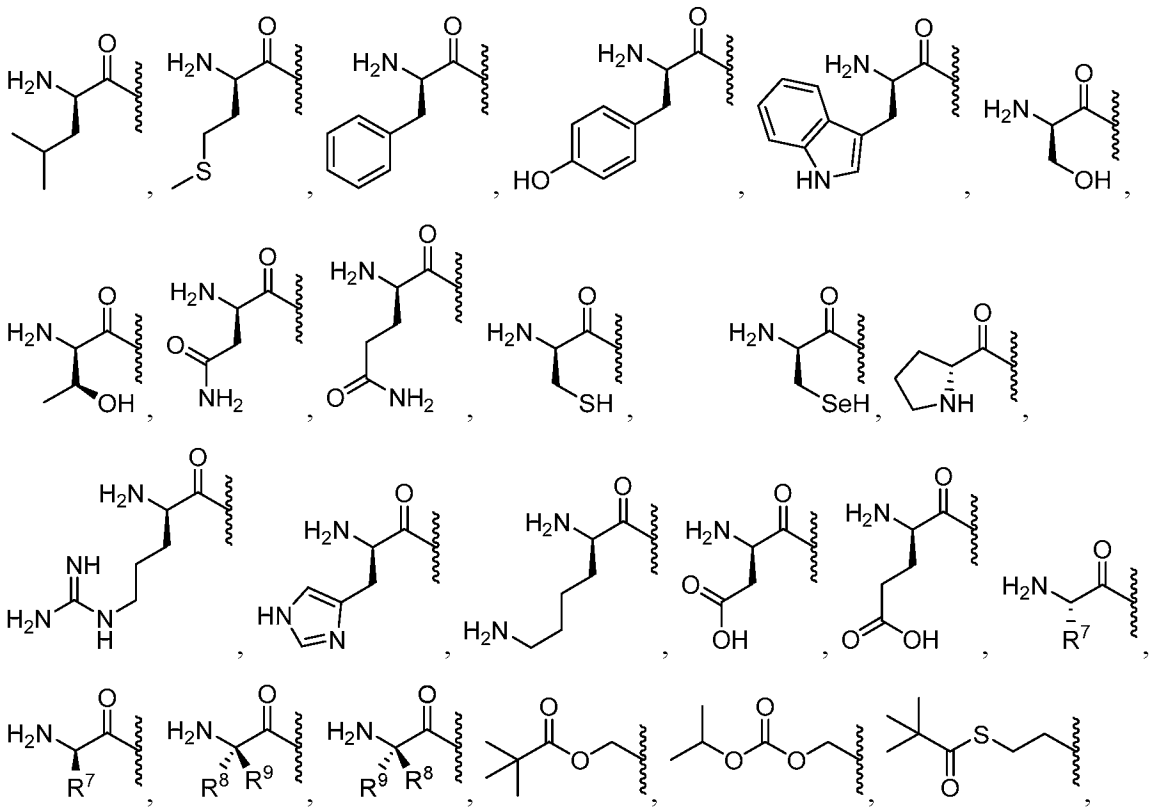


Formula XV

or a pharmaceutical or physiological salt thereof, wherein

R^3 and R^5 are each independently selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^3 and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy,

heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

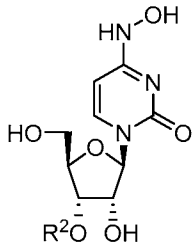
In exemplified embodiments of Formula XV, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XV, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XV, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XV, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

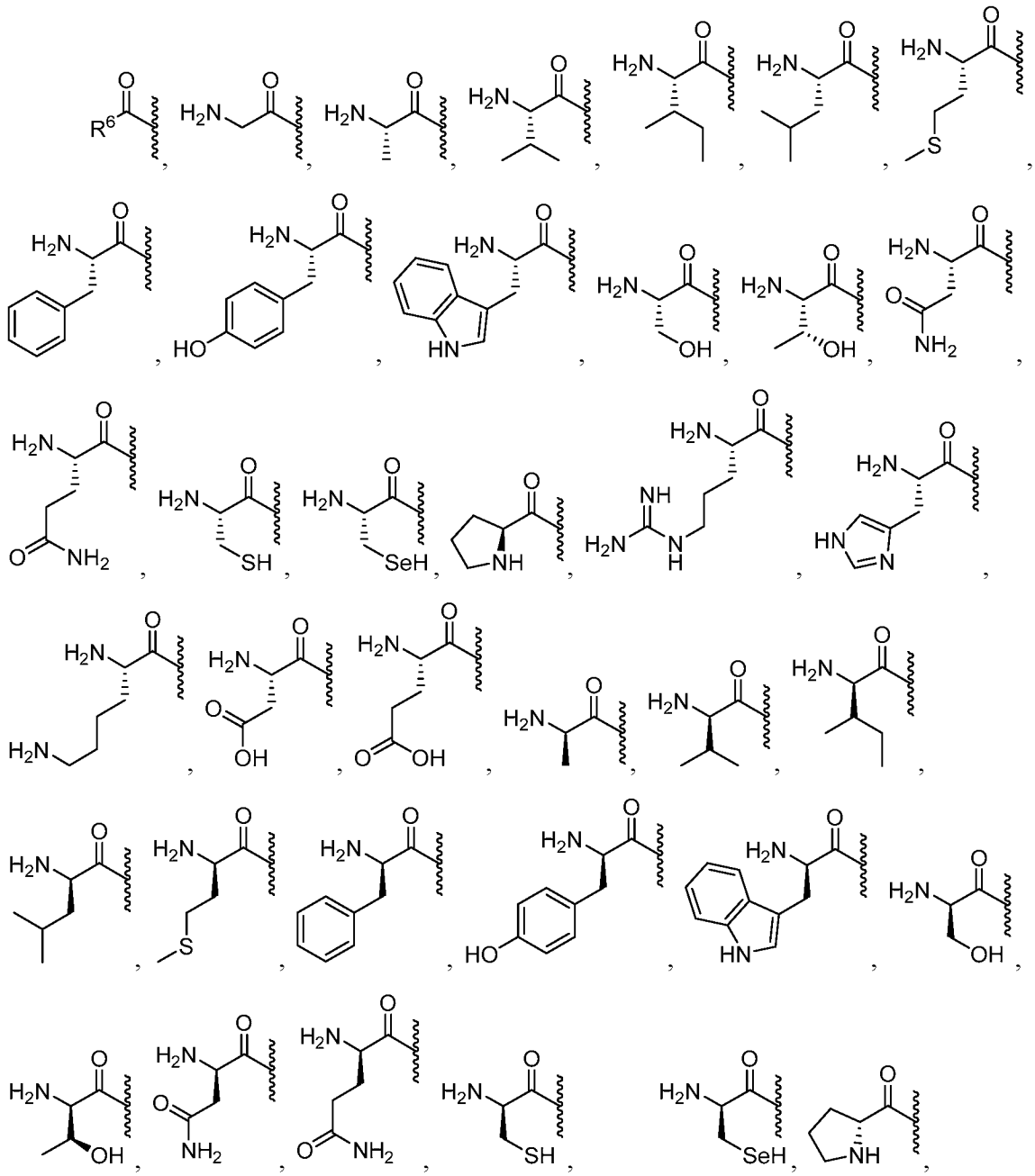
In certain embodiments, the disclosure relates to a compound of Formula XVI,

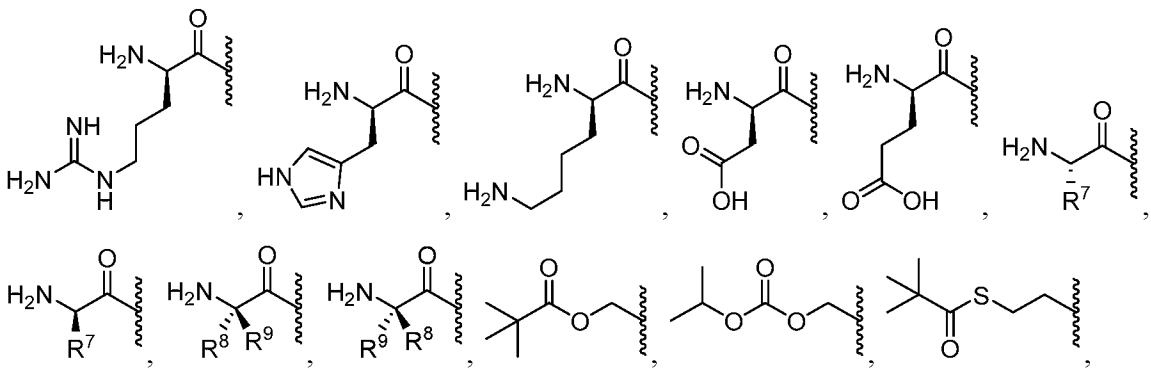


Formula XVI

or a pharmaceutical or physiological salt thereof, wherein

R^2 is selected from the following:





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

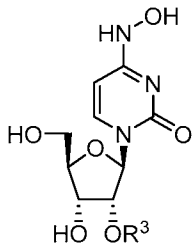
In exemplified embodiments of Formula XVI, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XVI, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XVI, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XVI, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

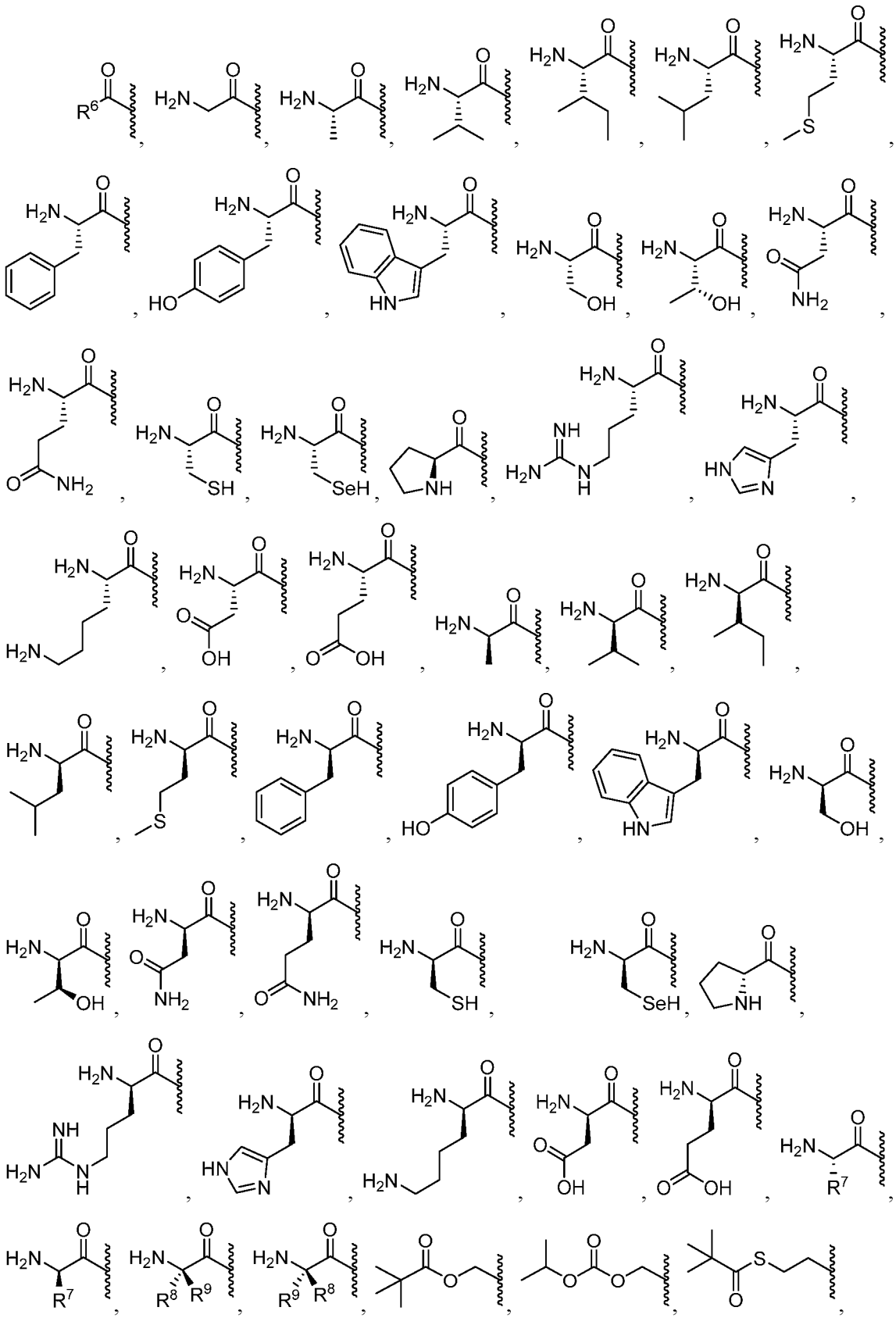
In certain embodiments, the disclosure relates to a compound of Formula XVII,



Formula XVII

or a pharmaceutical or physiological salt thereof, wherein

R^3 is selected from the following:



optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally

substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^3 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio,

heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula XVII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-

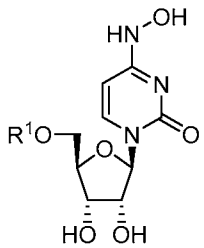
butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XVII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XVII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula I, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

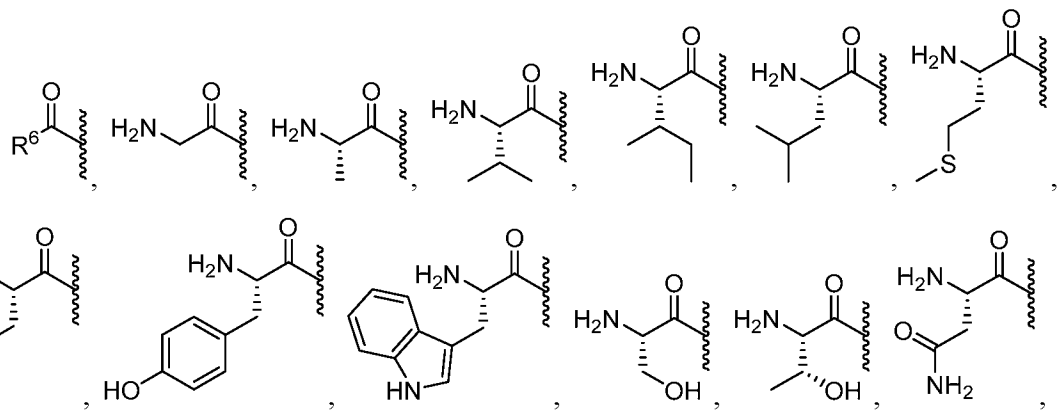
In certain embodiments, the disclosure relates to a compound of Formula XVIII,

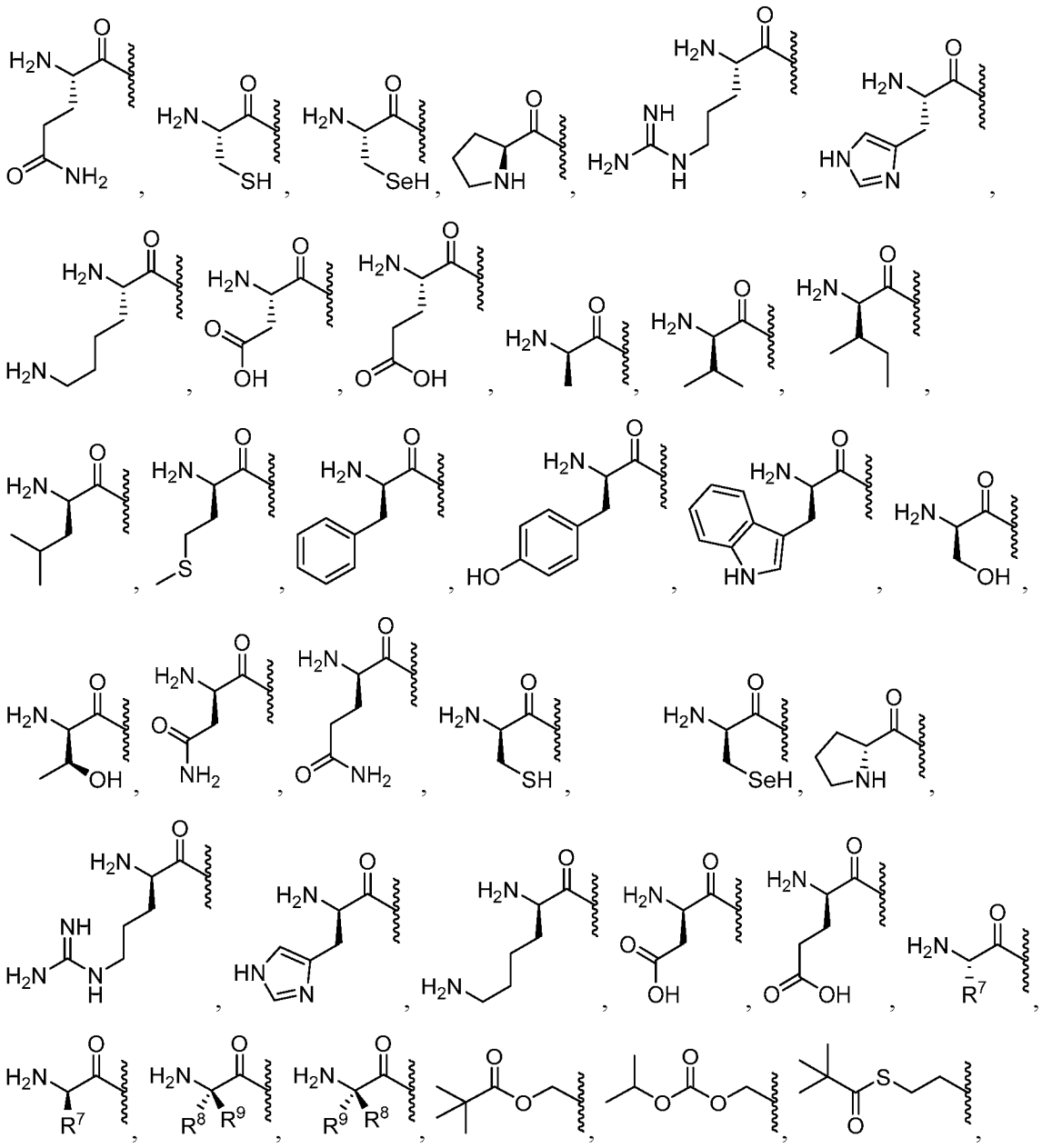


Formula XVIII

or a pharmaceutical or physiological salt thereof, wherein

R^1 is selected from the following:





optionally substituted branched esters, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally

substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, C_1-C_7 n-alkyl, C_9-C_{22} n-alkyl, optionally substituted C_8 n-alkyl, branched alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, -O(C_1-C_6 n-alkyl), -O(C_8-C_{21} n-alkyl), optionally substituted –O(C_7 n-alkyl), -O(branched alkyl) carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, -NH(C_1-C_6 n-alkyl), -NH(C_8-C_{21} n-alkyl), optionally substituted -NH(C7 n-alkyl), -NH(branched alkyl) (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy,

cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

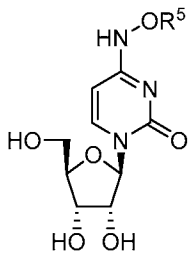
In exemplified embodiments of Formula XVIII, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

In exemplified embodiments of Formula XVIII, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XVIII, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XVIII, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

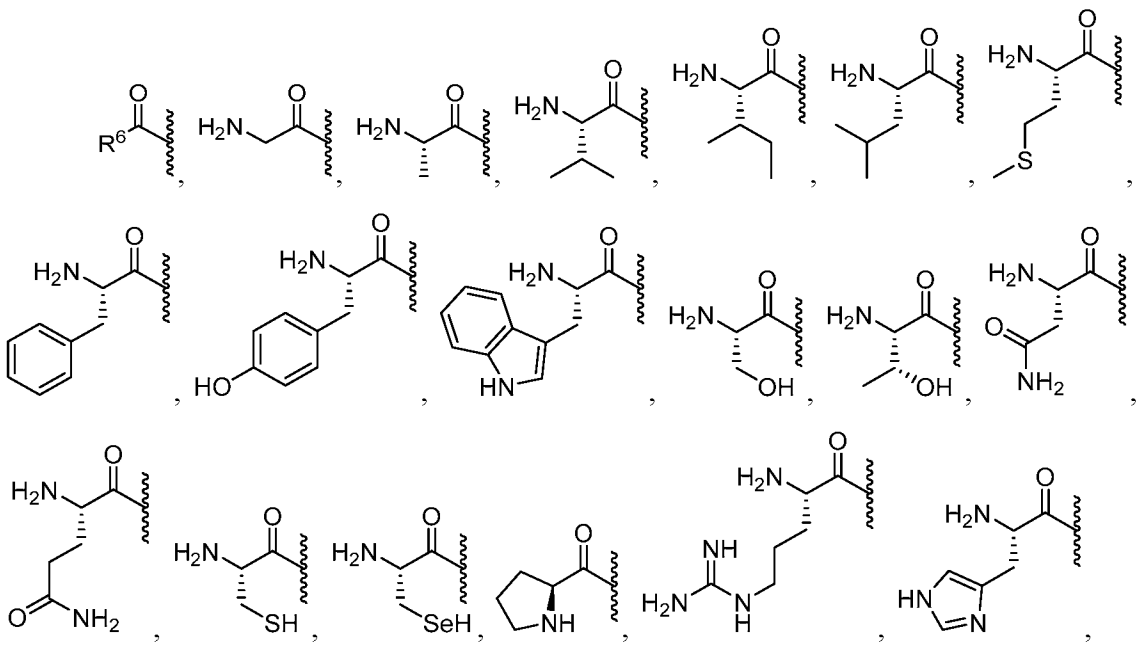
In certain embodiments, the disclosure relates to a compound of Formula XIX,

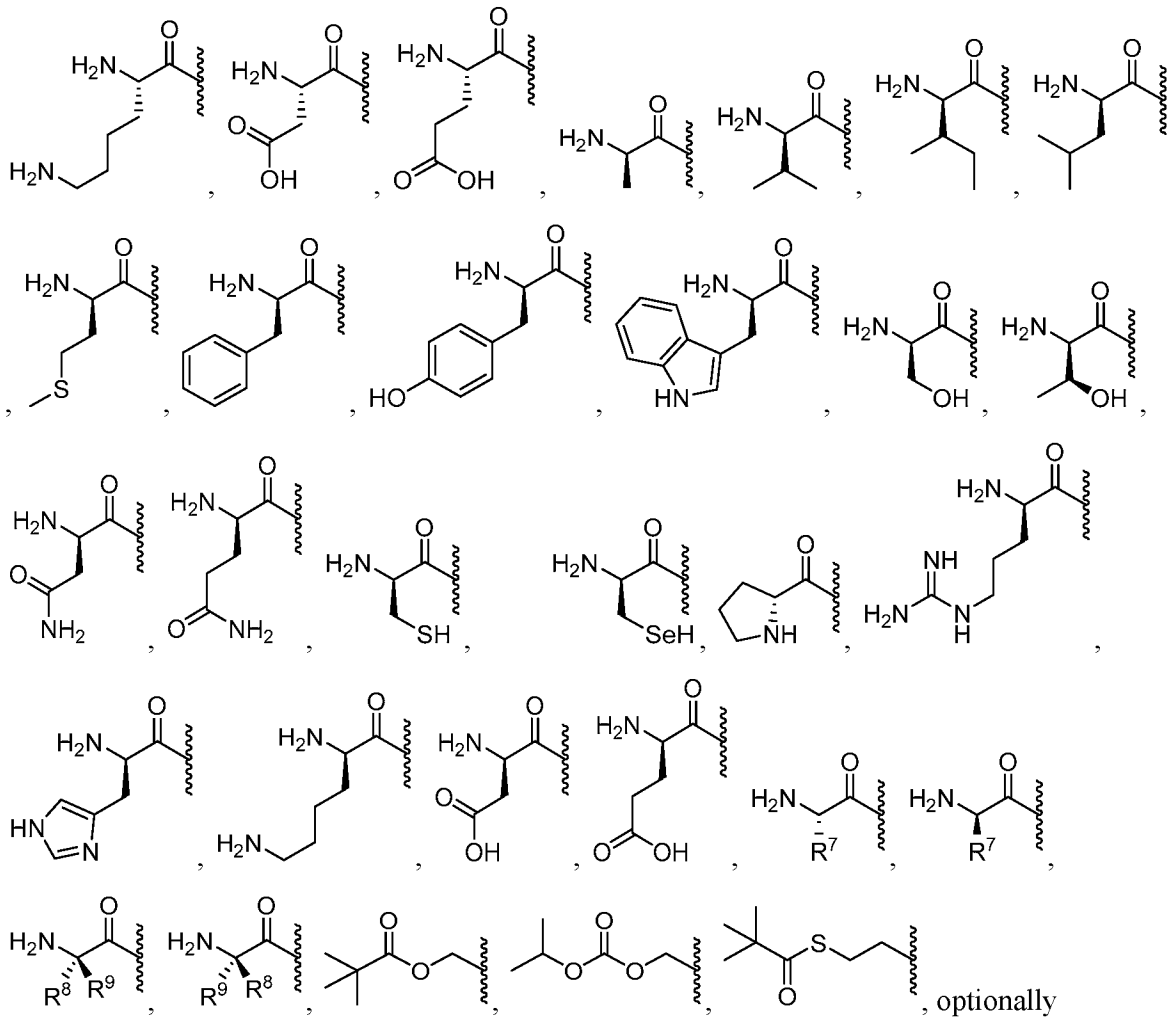


Formula XIX

or a pharmaceutical or physiological salt thereof, wherein

R^5 is selected from the following:





optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^5 are optionally substituted with one or more, the same or different, R^{10};

R^6 is hydrogen, C_2-C_7 n-alkyl, optionally substituted C_8 n-alkyl, C_9-C_{22} n-alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, C_3-C_9 cycloalkyl, C_{11}-C_{22} cycloalkyl, optionally substituted C_{10} cycloalkyl, cycloalkenyl, -O(C_1-C_6 n-alkyl), -O(optionally substituted C_7 n-alkyl), -O(C_8-C_{21} n-alkyl), -O(branched alkyl), carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, -N(C_2-C_{21} n-alkyl)$_2$, -N(optionally substituted C_1 alkyl)$_2$, -NH(optionally substituted C_1 alkyl), -NH(C_2-C_6 n-alkyl), -NH(optionally substituted C_7 n-alkyl), -NH(C_8-C_{15} n-alkyl), -NH(optionally substituted C_{16} n-alkyl), -NH(C_{17} n-alkyl), -NH(optionally substituted C_{18} n-alkyl), -NH(C_{19}-C_{21} n-alkyl), -NH(branched alkyl), -N(branched alkyl)$_2$, carbocyclamino, heterocarbocyclamino, optionally substituted arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio,

cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

In exemplified embodiments of Formula XIX, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

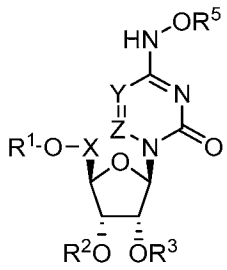
In exemplified embodiments of Formula XIX, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIX, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-

butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XIX, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In certain embodiments, the disclosure relates to a compound of Formula XX,



Formula XX

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

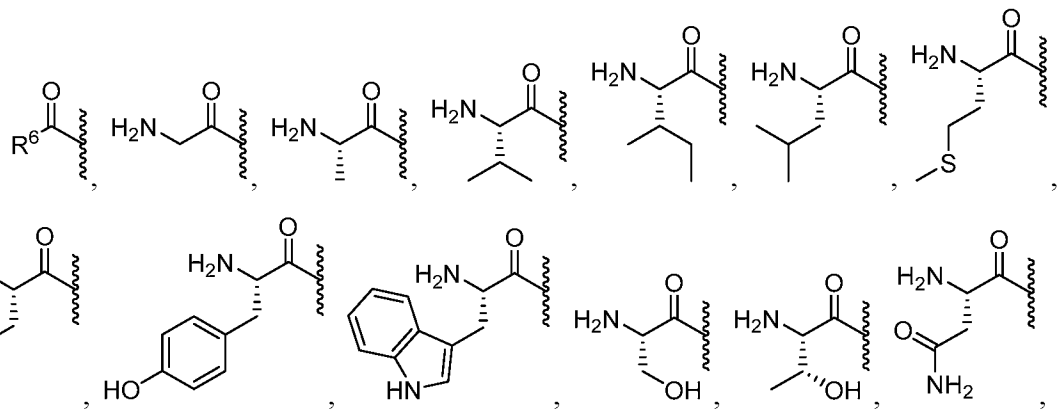
Y is N or CR';

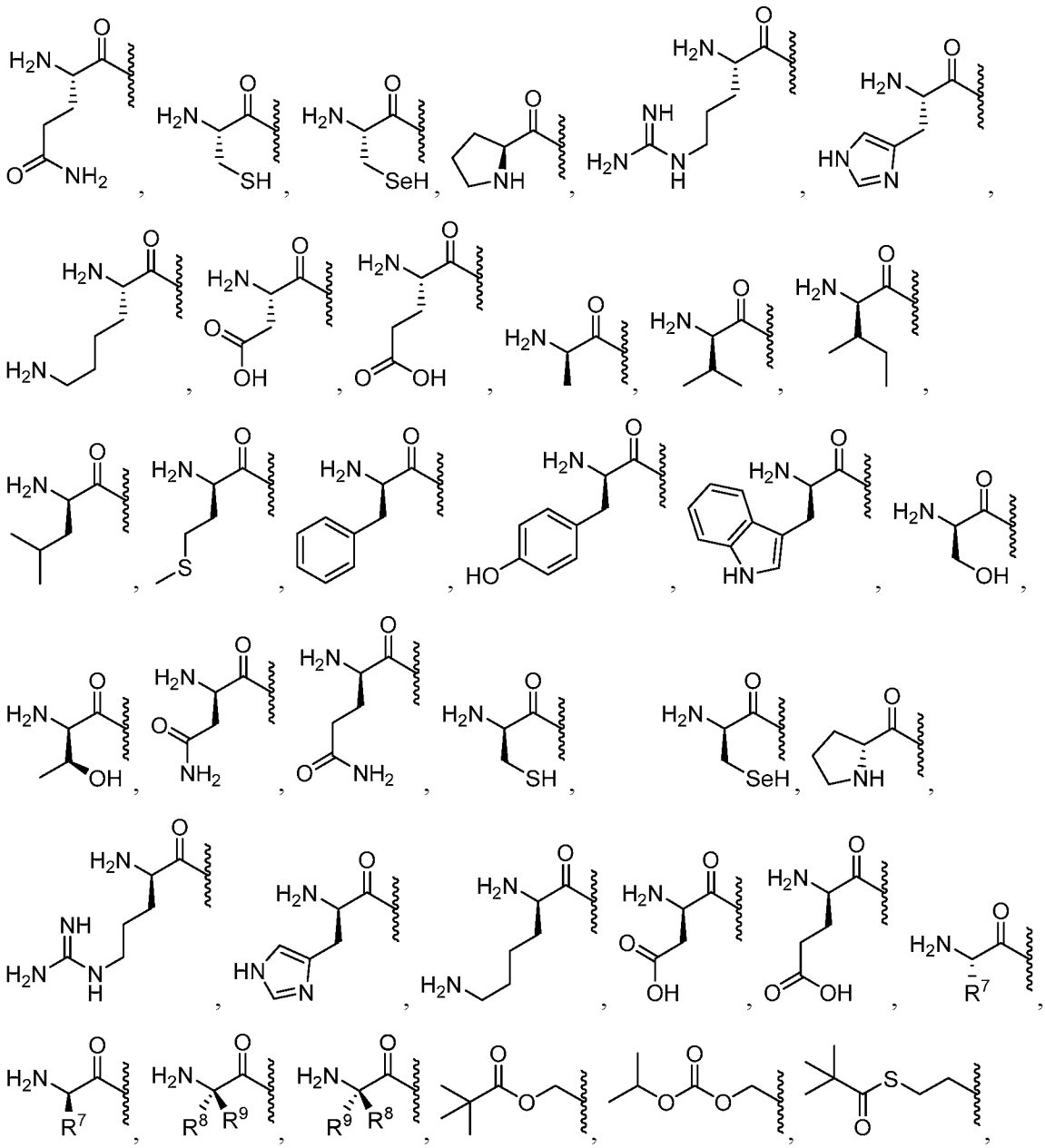
Z is N or CR";

R' is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R" is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H,





optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally

substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3 and R^5 are optionally substituted with one or more, the same or different, R^{10};

With the provisio that R^1, R^2, R^3 and R^5 are not all H;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino,

heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C_{11}-C_{22} higher alkyl, C_{11}-C_{22} higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

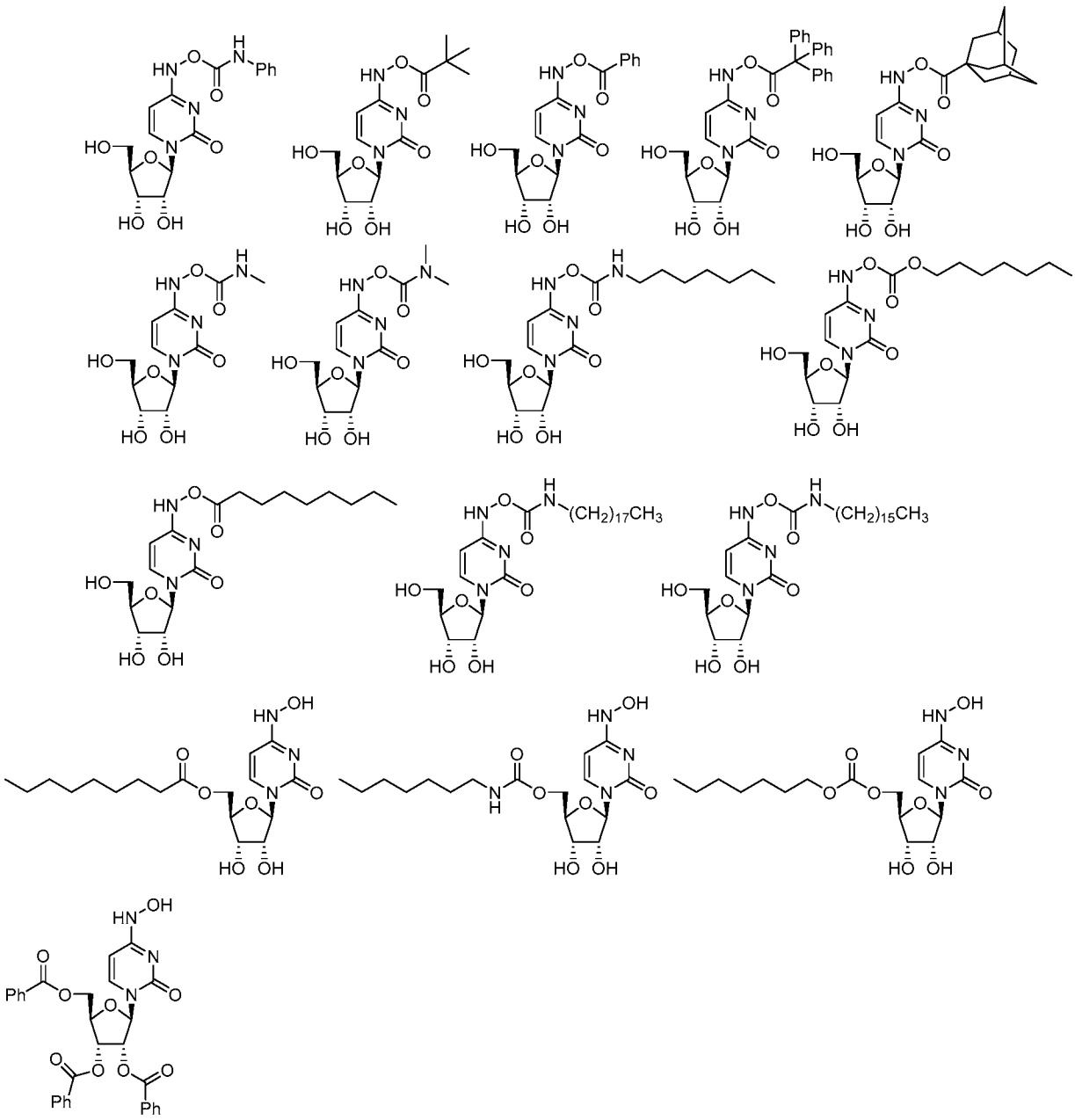
In exemplified embodiments of Formula XX, R^6 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, and N,N-dipropylamino.

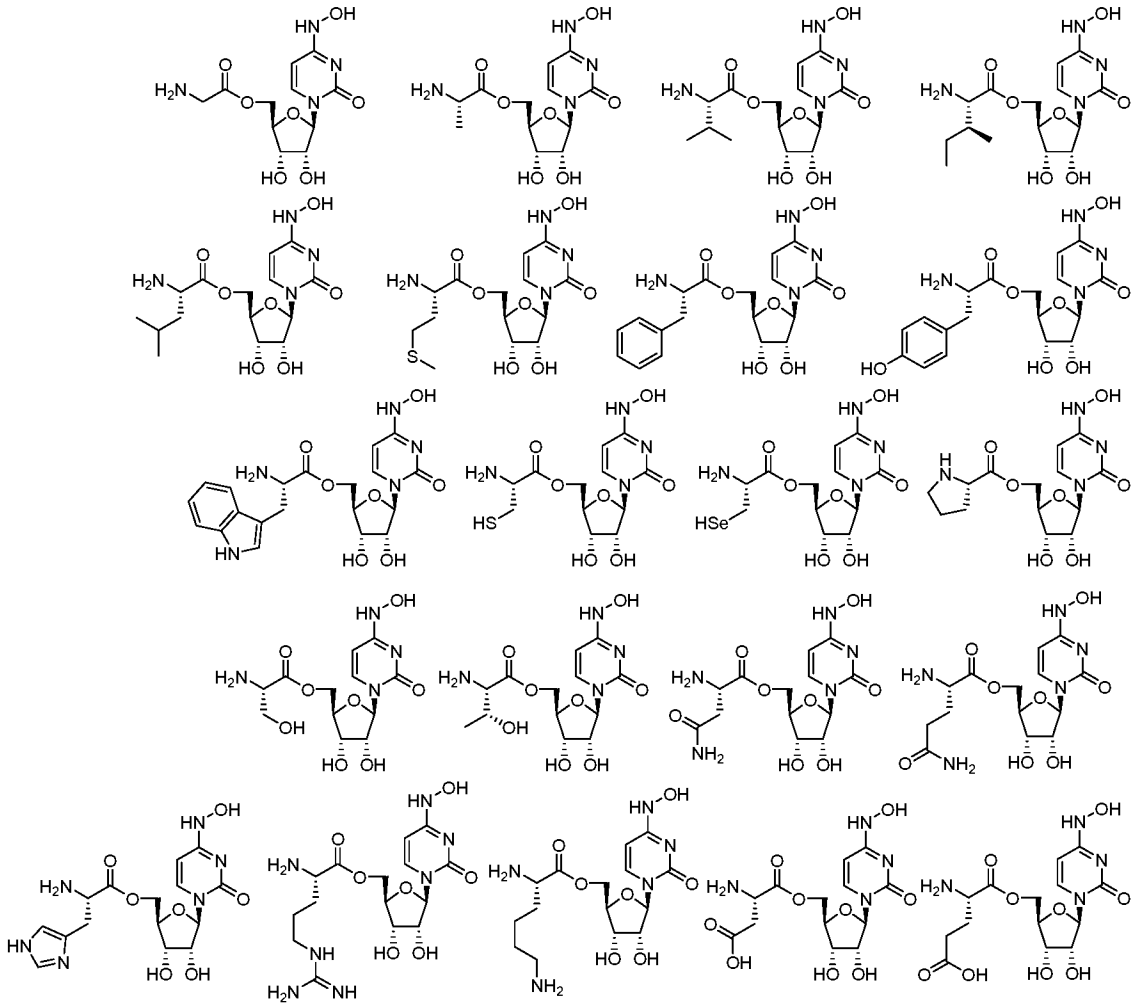
In exemplified embodiments of Formula XX, R^7 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In exemplified embodiments of Formula XX, R^8 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

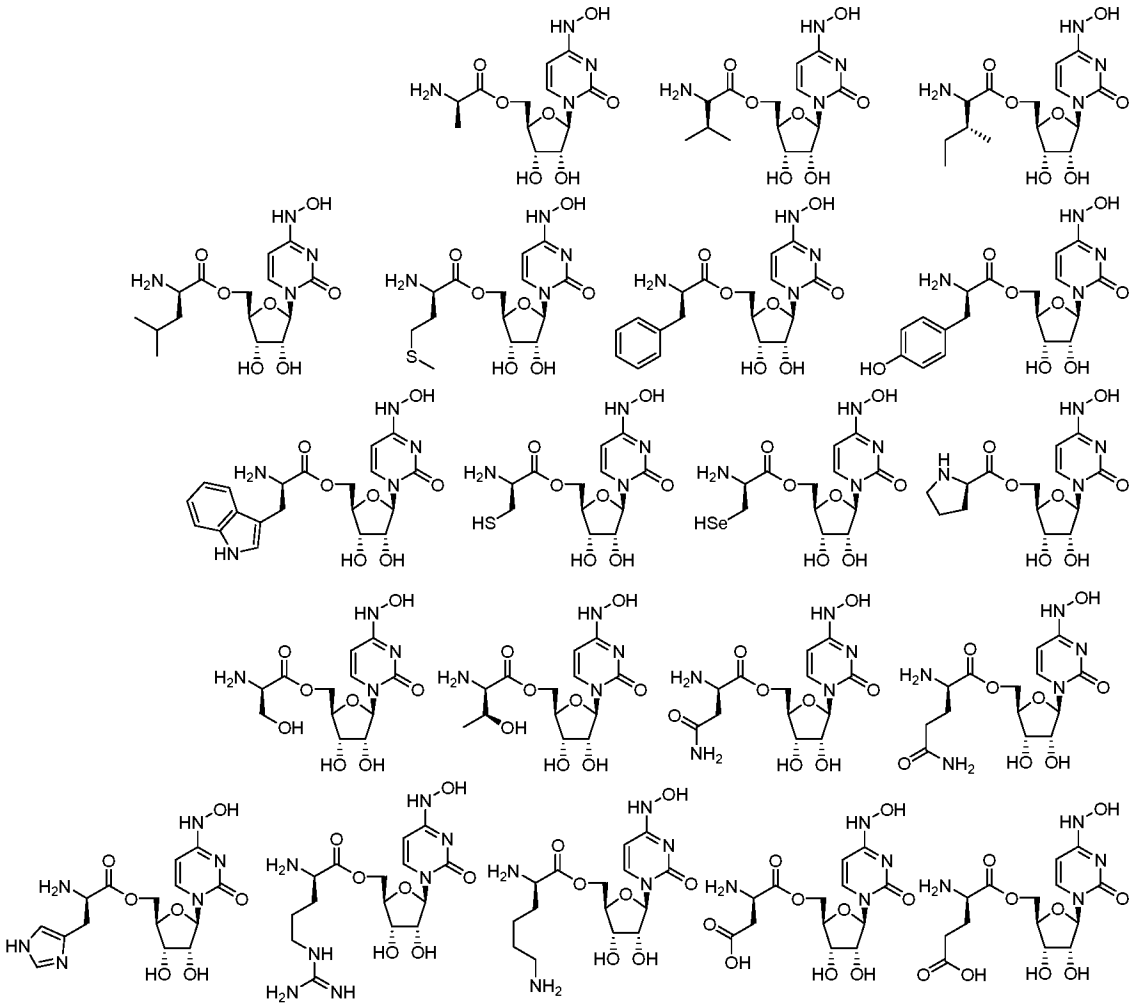
In exemplified embodiments of Formula XX, R^9 is methyl, ethyl, propyl, isopropyl, butyl, s-butyl, t-butyl, pentyl, s-pentyl, t-pentyl, neopentyl, 3-pentyl, hexyl, t-hexyl, 4-septyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl 2,6-dimethylphenyl, isopropoxide, tert-butoxide, N-propylamino, N-isopropylamino, N-tert-butylamino, N,N-dimethylamino, N,N-diethylamino, or N,N-dipropylamino.

In certain embodiments, a compound of Formula XX is not one of the following structures:

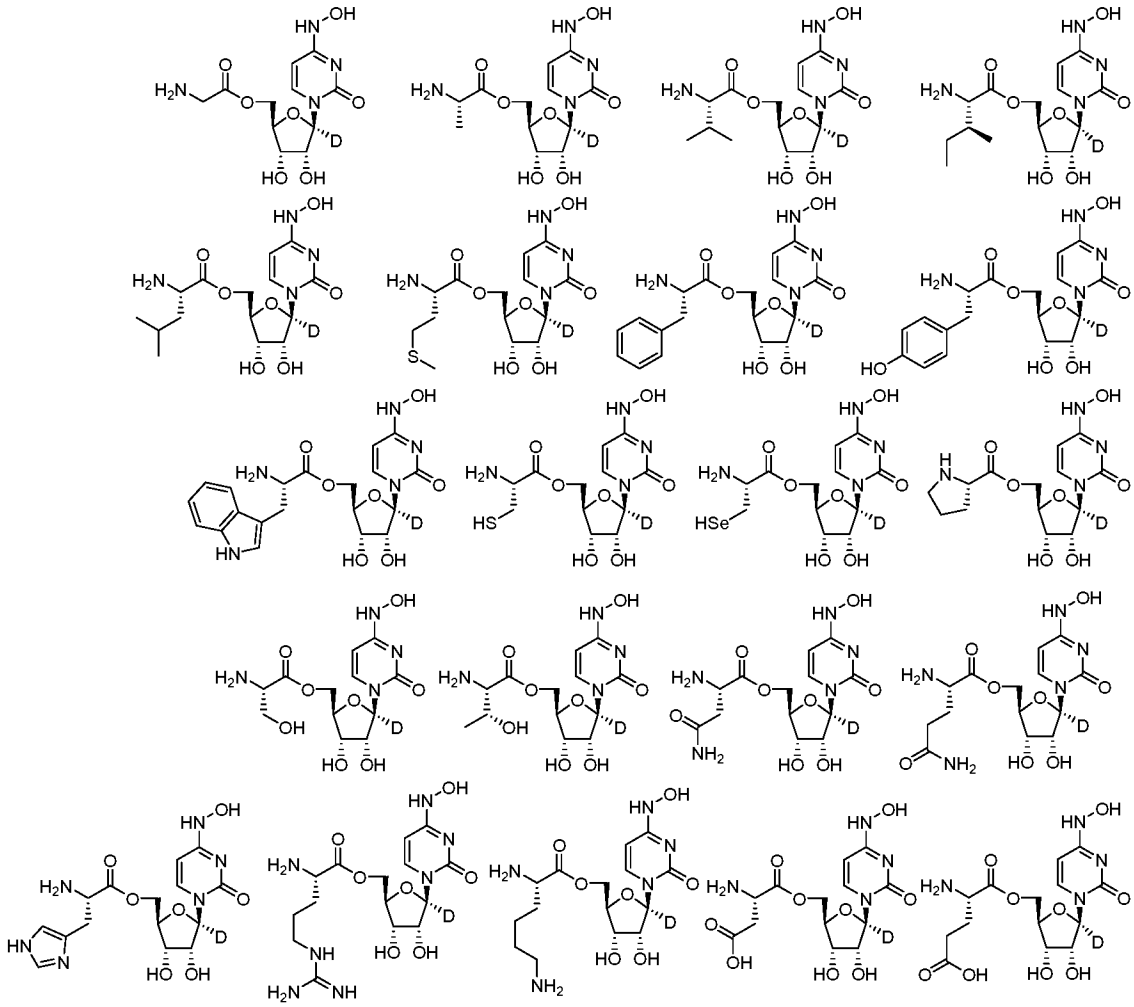




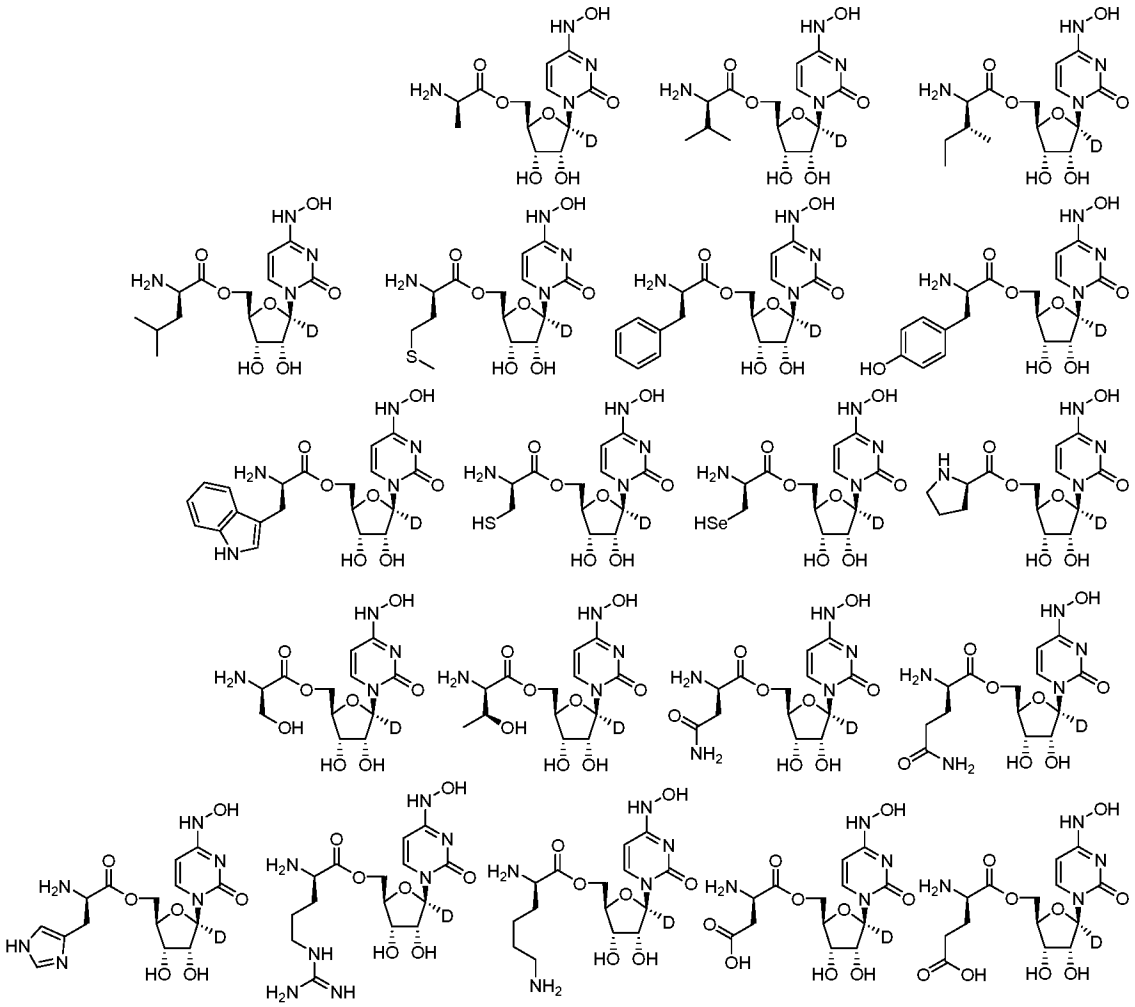
In exemplary embodiments, the compound is selected from:



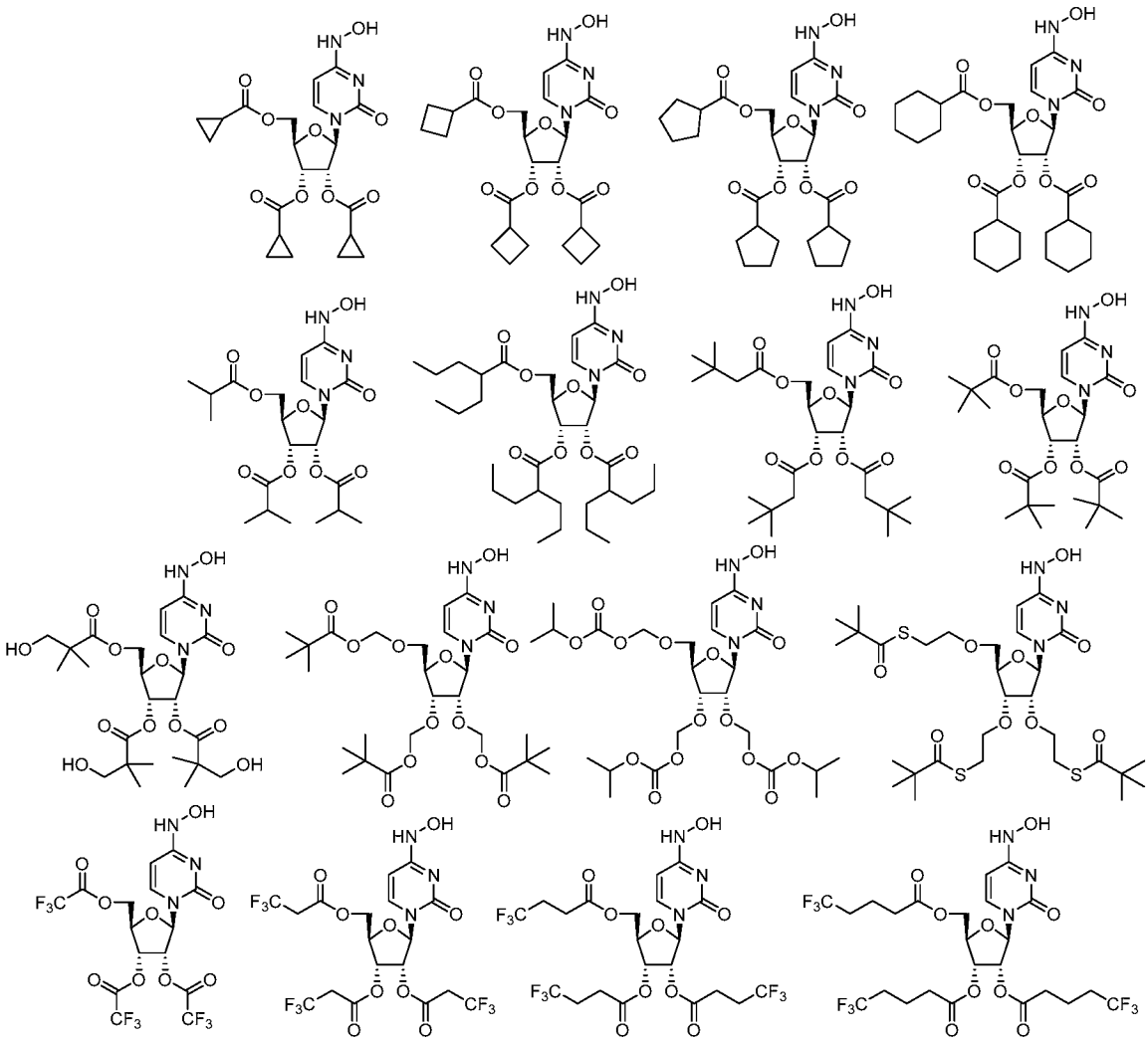
In exemplary embodiments, the compound is selected from:



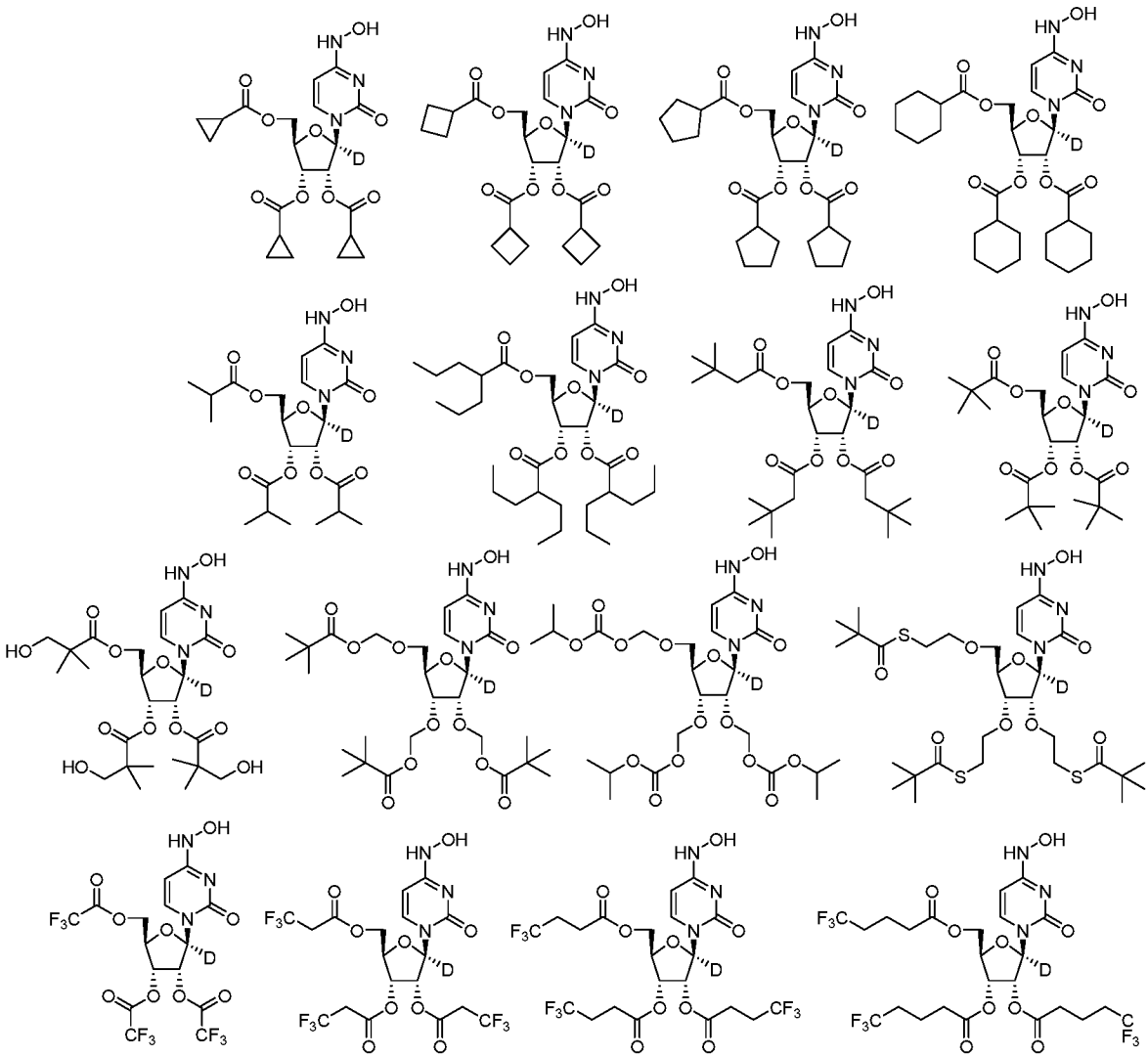
In exemplary embodiments, the compound is selected from:



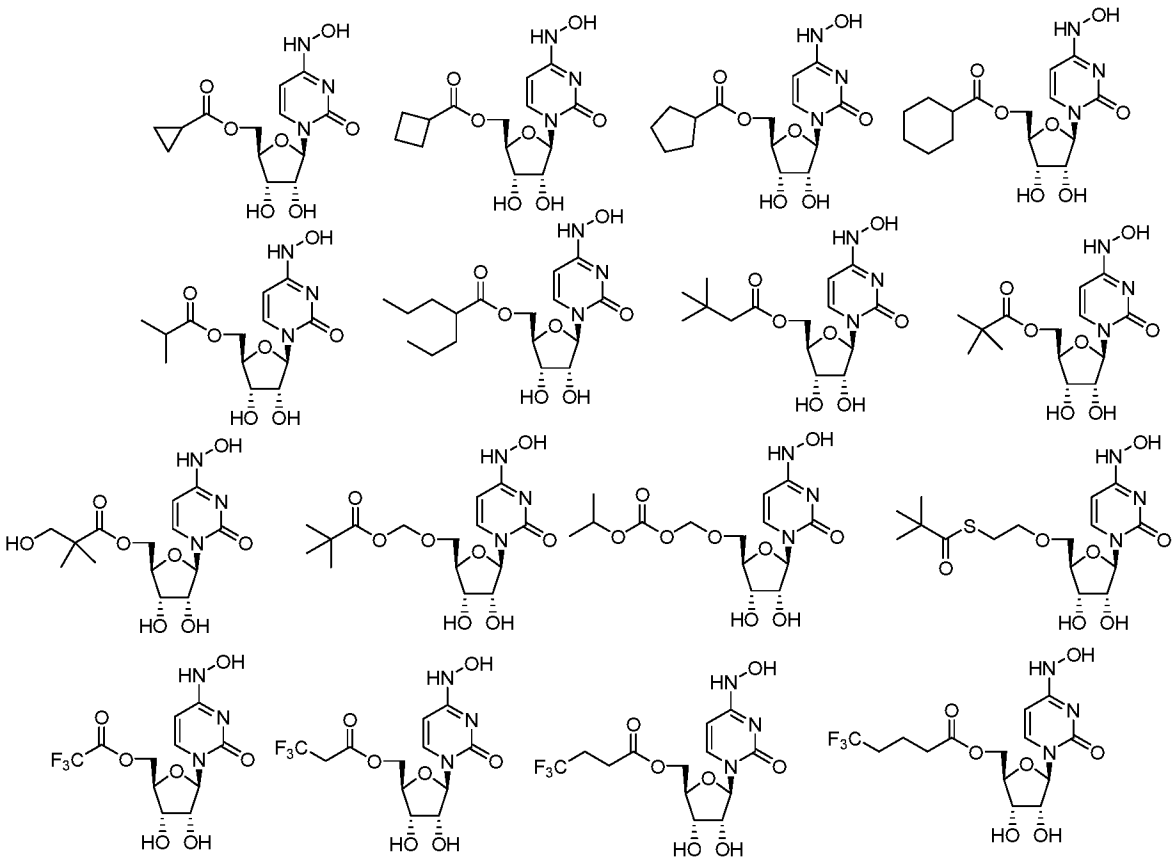
In exemplary embodiments, the compound is selected from:



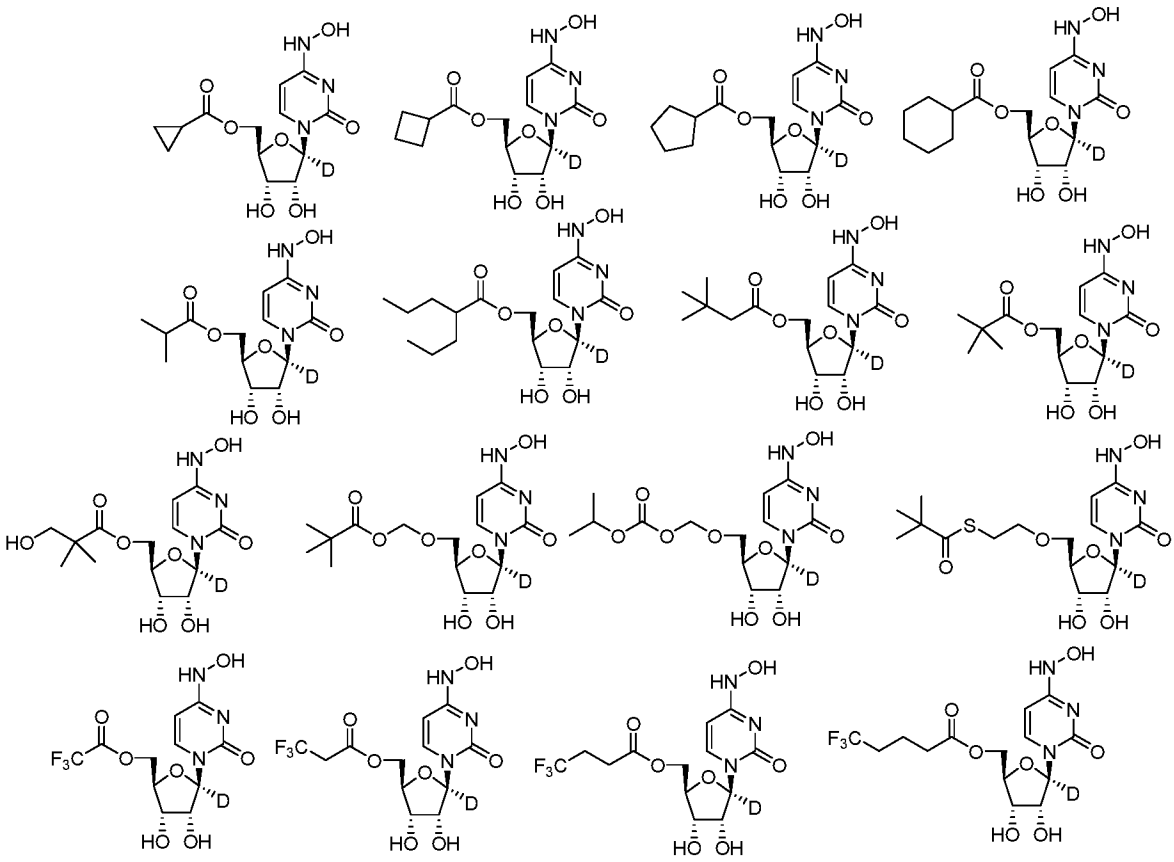
In exemplary embodiments, the compound is selected from:



In exemplary embodiments, the compound is selected from:



In exemplary embodiments, the compound is selected from:



Methods of Use

In certain embodiments, the disclosure relates to methods of treating or preventing a viral infection comprising administering an effective amount of a compound or pharmaceutical composition disclosed herein to a subject in need thereof. In certain exemplary embodiments, a method of treating or preventing a Zika virus infection is provided, the method comprising administering an effective amount of a compound or pharmaceutical composition disclosed herein to a subject in need thereof.

In certain embodiments, the viral infection is, or is caused by, an alphavirus, flavivirus or coronaviruses orthomyxoviridae or paramyxoviridae, or RSV, influenza, Powassan virus or filoviridae or ebola.

In certain embodiments, the viral infection is, or is caused by, a virus selected from MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, Barmah Forest virus, Powassan virus, Zika virus, and Chikungunya virus. In certain exemplary embodiments, the viral infection is, or is caused by, a Zika virus.

In certain embodiments, the compound is administered by inhalation through the lungs.

In some embodiments, the subject is at risk of, exhibiting symptoms of, or diagnosed with influenza A virus including subtype H1N1, H3N2, H7N9, or H5N1, influenza B virus, influenza C virus, rotavirus A, rotavirus B, rotavirus C, rotavirus D, rotavirus E, human coronavirus, SARS coronavirus, MERS coronavirus, human adenovirus types (HAdV-1 to 55), human papillomavirus (HPV) Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, parvovirus B19, molluscum contagiosum virus, JC virus (JCV), BK virus, Merkel cell polyomavirus, coxsackie A virus, norovirus, Rubella virus, lymphocytic choriomeningitis virus (LCMV), Dengue virus, Zika virus, chikungunya, Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV), Ross River virus, Barmah Forest virus, yellow fever virus, measles virus, mumps virus, respiratory syncytial virus, rinderpest virus, California encephalitis virus, hantavirus, rabies virus, ebola virus, marburg virus, herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes lymphotropic virus, roseolovirus, or Kaposi's sarcoma-associated herpesvirus, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E or human immunodeficiency virus (HIV), The Human T-lymphotropic virus Type I (HTLV-1), Friend spleen focus-forming virus (SFFV) or Xenotropic MuLV-Related Virus (XMRV). In some embodiments, the subject is at risk of, exhibiting symptoms of, or diagnosed with a Zika virus infection.

In certain embodiments, the subject is diagnosed with influenza A virus including subtypes H1N1, H3N2, H7N9, H5N1 (low path), and H5N1 (high path) influenza B virus, influenza C virus, rotavirus A, rotavirus B, rotavirus C, rotavirus D, rotavirus E, SARS coronavirus, MERS-CoV, human adenovirus types (HAdV-1 to 55), human papillomavirus (HPV) Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, parvovirus B19, molluscum contagiosum virus, JC virus (JCV), BK virus, Merkel cell polyomavirus, coxsackie A virus, norovirus, Rubella virus, lymphocytic choriomeningitis virus (LCMV), yellow fever virus, measles virus, mumps virus, respiratory syncytial virus, parainfluenza viruses 1 and 3, rinderpest virus, chikungunya, eastern equine encephalitis virus (EEEV), Venezuelan equine encephalitis virus (VEEV), western equine encephalitis virus (WEEV), California encephalitis virus, Japanese encephalitis virus, Rift Valley fever virus (RVFV), hantavirus, Dengue virus serotypes 1, 2, 3 and 4, Zika virus, West Nile virus, Tacaribe virus, Junin, rabies virus, ebola virus, marburg virus, adenovirus, herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes lymphotropic virus, roseolovirus, or Kaposi's sarcoma-associated herpesvirus, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E or human immunodeficiency virus (HIV). In certain embodiments, the subject is diagnosed with a Zika virus infection.

In certain embodiments, the subject is diagnosed with gastroenteritis, acute respiratory disease, severe acute respiratory syndrome, post-viral fatigue syndrome, viral hemorrhagic fevers, acquired immunodeficiency syndrome or hepatitis.

Formulations

In exemplary embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable excipient, such as a pharmaceutically acceptable carrier, and an exemplary compound described herein.

In certain exemplary embodiments, the pharmaceutical composition comprises, or is in the form of, a pharmaceutically acceptable salt, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the references referred to below).

When the exemplary compounds contain an acidic group as well as a basic group, the compounds can form internal salts, which can also be used in the compositions and methods described herein. When an exemplary compound contains a hydrogen-donating heteroatom

(e.g., NH), salts are contemplated to cover isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

Pharmaceutically acceptable salts of the exemplary compounds include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002), incorporated herein by reference.

Physiologically acceptable salts of the exemplary compounds are those that are formed internally in a subject administered compound for the treatment or prevention of disease. Suitable salts include those of lithium, sodium, potassium, magnesium, calcium, manganese, bile salts.

The exemplary compounds can be administered in the form of prodrugs. A prodrug can include a covalently bonded carrier which releases the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include, for example, compounds wherein a hydroxyl group is bonded to any group that, when administered to a subject, cleaves to form a free hydroxyl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol functional groups in the compounds. Methods of structuring a compound as prodrugs can be found in the book of Testa and Mayer, Hydrolysis in Drug and Prodrug Metabolism, Wiley (2006). Typical prodrugs form the active metabolite by transformation of the prodrug by hydrolytic enzymes, the hydrolysis of amide, lactams, peptides, carboxylic acid esters, epoxides or the cleavage of esters of inorganic acids.

In exemplary embodiments, the pharmaceutical composition comprises an effective amount of an exemplary compound and a pharmaceutically acceptable carrier. Generally, for

pharmaceutical use, the compounds can be formulated as a pharmaceutical preparation comprising at least one compound and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds. The preparations can be prepared in a manner known per se, which usually involves mixing the at least one compound according to the disclosure with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to U.S. Pat. No. 6,372,778, U.S. Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences. The disclosed pharmaceutical compositions can be in a unit dosage form, and can be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which can be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain from 1 and 1000 mg, and usually from 5 and 500 mg, of the at least one compound of the disclosure, e.g., about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, ocular, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used. The compound will generally be administered in an "effective amount", by which is meant any amount of a compound that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the subject to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be from 0.01 to 1000 mg per kilogram body weight of the patient per day, more often from 0.1 and 500 mg, such as from 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight of the patient per day, which can be administered as a single daily dose, divided over one or more daily doses. The amount(s) to be administered, the route of administration and the further treatment regimen can be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to U.S. Pat. No. 6,372,778, U.S. Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Depending upon the manner of introduction, the compounds described herein can be formulated in a variety of ways. Formulations containing one or more compounds can be

prepared in various pharmaceutical forms, such as granules, tablets, capsules, suppositories, powders, controlled release formulations, suspensions, emulsions, creams, gels, ointments, salves, lotions, or aerosols and the like. In certain embodiments, the formulations are employed in solid dosage forms suitable for simple, and preferably oral, administration of precise dosages. Solid dosage forms for oral administration include, but are not limited to, tablets, soft or hard gelatin or non-gelatin capsules, and caplets. However, liquid dosage forms, such as solutions, syrups, suspension, shakes, etc. can also be utilized. In another embodiment, the formulation is administered topically. Suitable topical formulations include, but are not limited to, lotions, ointments, creams, and gels. In a preferred embodiment, the topical formulation is a gel. In another embodiment, the formulation is administered intranasally.

Formulations containing one or more of the compounds described herein can be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and can be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, pH modifying agents, preservatives, antioxidants, solubility enhancers, and coating compositions.

Carrier also includes all components of the coating composition, which can include plasticizers, pigments, colorants, stabilizing agents, and glidants. Delayed release, extended release, and/or pulsatile release dosage formulations can be prepared as described in standard references such as "Pharmaceutical dosage form tablets", eds. Liberman et al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These references provide information on carriers, materials, equipment and process for preparing tablets and capsules and delayed release dosage forms of tablets, capsules, and granules.

Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name EUDRAGIT™ (Roth Pharma, Westerstadt, Germany), zein, shellac, and polysaccharides.

Additionally, the coating material can contain conventional carriers such as plasticizers, pigments, colorants, glidants, stabilization agents, pore formers and surfactants.

Optional pharmaceutically acceptable excipients present in the drug-containing tablets, beads, granules or particles include, but are not limited to, diluents, binders, lubricants, disintegrants, colorants, stabilizers, and surfactants. Diluents, also referred to as "fillers," are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

Disintegrants are used to facilitate dosage form disintegration or "breakup" after administration, and generally include, but are not limited to, starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, alginine, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone XL from GAF Chemical Corp).

Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions.

Surfactants can be anionic, cationic, amphoteric or nonionic surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited

to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, POLOXAMER™ 401, stearoyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl-β-alanine, sodium N-lauryl-β-iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

If desired, the tablets, beads, granules, or particles can also contain minor amount of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, or preservatives.

The concentration of the exemplary compound to pharmaceutically acceptable carrier, excipient and/or other substances can vary from about 0.5 to about 100 wt. % (weight percent). For oral use, the pharmaceutical composition can generally contain from about 5 to about 100% by weight of the active material. For other uses, the pharmaceutical composition can generally have from about 0.5 to about 50 wt. % of the active material.

The compositions described herein can be formulated for modified or controlled release. Examples of controlled release dosage forms include extended release dosage forms, delayed release dosage forms, pulsatile release dosage forms, and combinations thereof.

The extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington – The science and practice of pharmacy" (20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000). A diffusion system typically consists of two types of devices, a reservoir and a matrix, and is well known and described in the art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkylcelluloses such as hydroxypropyl-cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and CARBOPOL™ 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain preferred embodiments, the plastic material is a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one preferred embodiment, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name EUDRAGIT. In further preferred embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names EUDRAGIT RL30D and EUDRAGIT RS30D, respectively. EUDRAGIT RL30D and EUDRAGIT RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in EUDRAGIT RL30D and 1:40 in EUDRAGIT RS30D. The mean molecular weight is about 150,000. EUDRAGIT S-100 and EUDRAGIT L-100 are also preferred. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. EUDRAGIT RL/RS mixtures are insoluble in water and in digestive fluids. However,multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as EUDRAGIT RL/RS can be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release multiparticulate systems can be obtained, for instance, from 100% EUDRAGIT RL, 50% EUDRAGIT RL and 50% EUDRAGIT RS, and 10% EUDRAGIT RL and 90% EUDRAGITRS. One skilled in the art will recognize that other acrylic polymers can also be used, such as, for example, EUDRAGIT L.

Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable proportion.

The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include, but are not limited to, multilayer tablets andcapsules containing tablets, beads, or granules An immediate release portion can be added to the extended release system by means of either applying an immediate release layer on top of the extended release core using a coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

Extended release tablets containing hydrophilic polymers are prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation. Their formulations usually incorporate polymers, diluents, binders, and lubricants as well as the active pharmaceutical ingredient. The usual diluents include inert powdered substances such as starches, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders include substances such as starch, gelatin and sugars such as lactose, fructose, and glucose. Natural and synthetic gums, including acacia, alginates, methylcellulose, and polyvinylpyrrolidone can also be used. Polyethylene glycol, hydrophilic polymers, ethylcellulose and waxes can also serve as binders. A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Extended release tablets containing wax materials are generally prepared using methods known in the art such as a direct blend method, a congealing method, and an aqueous dispersion method. In the congealing method, the drug is mixed with a wax material and either spray-congealed or congealed and screened and processed.

Delayed release formulations are created by coating a solid dosage form with a polymer film, which is insoluble in the acidic environment of the stomach, and soluble in the neutral environment of the small intestine.

The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition can be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into either a tablet or capsule. Preferred coating materials include bioerodible, gradually hydrolyzable, gradually water-soluble, and/or enzymatically degradable polymers, and

can be conventional "enteric" polymers. Enteric polymers, as will be appreciated by those skilled in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, and other methacrylic resins that are commercially available under the trade name EUDRAGIT™ (Rohm Pharma; Westerstadt, Germany), including EUDRAGIT™ L30D-55 and L100-55 (soluble at pH 5.5 and above), EUDRAGIT™ L-100 (soluble at pH 6.0 and above), EUDRAGIT™ S (soluble at pH 7.0 and above, as a result of a higher degree of esterification), and EUDRAGIT™ NE, RL and RS (water-insoluble polymers having different degrees of permeability and expandability); vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different coating materials can also be used. Multi-layer coatings using different polymers can also be applied.

The preferred coating weights for particular coating materials can be readily determined by those skilled in the art by evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and formof application that produce the desired release characteristics, which one can determine only from the clinical studies.

The coating composition can include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizers include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film

formation and drying, and will generally represent approximately 25 wt. % to 100 wt. % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates can also be used. Pigments such as titanium dioxide can also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), can also be added to the coating composition.

The formulation can provide pulsatile delivery of the one or more compounds. By "pulsatile" is meant that a plurality of drug doses are released at spaced apart intervals of time. Generally, upon ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release "pulse" occurs within about one hour of ingestion. This initial pulse is followed by a first time interval (lag time) during which very little or no drug is released from the dosage form, after which a second dose is then released. Similarly, a second nearly drug release-free interval between the second and third drug release pulses can be designed. The duration of the nearly drug release-free time interval will vary depending upon the dosage form design e.g., a twice daily dosing profile, a three times daily dosing profile, etc. For dosage forms providing a twice daily dosage profile, the nearly drug release-free interval has a duration of approximately 3 hours to 14 hours between the first and second dose. For dosage forms providing a three times daily profile, the nearly drug release-free interval has a duration of approximately 2 hours to 8 hours between each of the three doses.

In one embodiment, the pulsatile release profile is achieved with dosage forms that are closed and preferably sealed capsules housing at least two drug-containing "dosage units" wherein each dosage unit within the capsule provides a different drug release profile. Control of the delayed release dosage unit(s) is accomplished by a controlled release polymer coating on the dosage unit, or by incorporation of the active agent in a controlled release polymer matrix. Each dosage unit can comprise a compressed or molded tablet, wherein each tablet within the capsule provides a different drug release profile. For dosage forms mimicking a twice a day dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, while a second tablet releases drug approximately 3 hours to less than 14 hours following ingestion of the dosage form. For dosage forms mimicking a three times daily dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, a second tablet releases drug approximately 3 hours to less than 10 hours following ingestion of the dosage form, and the third tablet releases drug at least 5 hours to approximately 18 hours following ingestion of the dosage form. It is possible that the dosage form includes more than three tablets. While the dosage form will not generally include more than a third tablet, dosage forms housing more than three tablets can be utilized.

Alternatively, each dosage unit in the capsule can comprise a plurality of drug-containing beads, granules or particles. As is known in the art, drug-containing "beads" refer to beads made with drug and one or more excipients or polymers. Drug-containing beads can be produced by applying drug to an inert support, e.g., inert sugar beads coated with drug or by creating a "core" comprising both drug and one or more excipients. As is also known, drug-containing "granules" and "particles" comprise drug particles that can or can not include one or more additional excipients or polymers. In contrast to drug-containing beads, granules and particles do not contain an inert support. Granules generally comprise drug particles and require further processing. Generally, particles are smaller than granules, and are not further processed. Although beads, granules and particles can be formulated to provide immediate release, beads and granules are generally employed to provide delayed release.

In one embodiment, the compound is formulated for topical administration. Suitable topical dosage forms include lotions, creams, ointments, and gels. A "gel" is a semisolid system containing a dispersion of the active agent, i.e., compound, in a liquid vehicle that is rendered semisolid by the action of a thickening agent or polymeric material dissolved or suspended in the liquid vehicle. The liquid can include a lipophilic component, an aqueous component or both. Some emulsions can be gels or otherwise include a gel component. Some gels, however, are not emulsions because they do not contain a homogenized blend of immiscible components. Methods for preparing lotions, creams, ointments, and gels are well known in the art.

Combination Therapies

The compound described herein can be administered adjunctively with other active compounds. These compounds include but are not limited to analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxioltyics, sedatives, hypnotics, antipsychotics, bronchodilators, anti-asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics, anti-narcoleptics, and antiviral agents. In a particular embodiment, the antiviral agent is a non-CNS targeting antiviral compound. “Adjunctive administration”, as used herein, means the compound can be administered in the same dosage form or in separate dosage forms with one or more other active agents. The additional active agent(s) can be formulated for immediate release, controlled release, or combinations thereof.

Specific examples of compounds that can be adjunctively administered with the compounds include, but are not limited to, aceclofenac, acetaminophen, adomexetine, almotriptan, alprazolam, amantadine, amcinonide, aminocyclopropane, amitriptyline, amolodipine, amoxapine, amphetamine, aripiprazole, aspirin, atomoxetine, azasetron, azatadine,

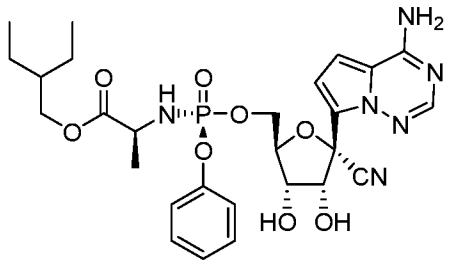
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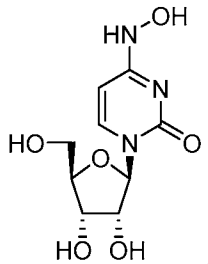
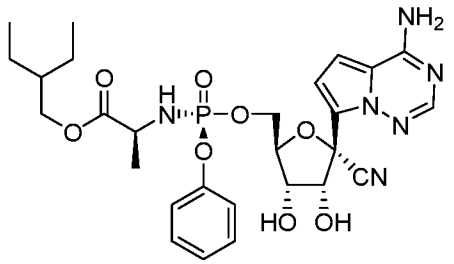
In certain embodiments, the exemplary compounds and pharmaceutical compositions can be administered in combination with another antiviral agent(s) such as abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, balapiravir, BCX4430, boceprevir, cidofovir, combivir, daclatasvir, darunavir, dasabuvir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, favipiravir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, GS-5734, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, ledipasvir, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, NITD008, ombitasvir, oseltamivir, paritaprevir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin , raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, simeprevir, sofosbuvir, stavudine, telaprevir, telbivudine, tenofovir, tenofovir disoproxil, Tenofovir Exalidex, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine zalcitabine, zanamivir, or zidovudine and combinations thereof.

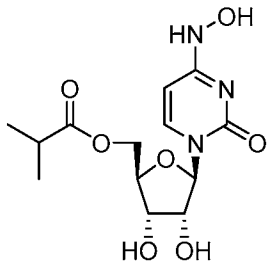
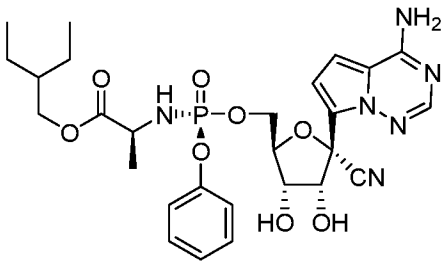
In certain embodiments, the exemplary compounds and pharmaceutical compositions disclosed herein can be administered in combination with any of the compounds disclosed in: WO2003090690A2, WO2003090690A3, WO2003090691A2, WO2003090691A3, WO2004005286A2, WO2004005286A3, WO2004006843A2, WO2004006843A3, WO2004031224A2, WO2004031224A3, WO2004035576A2, WO2004035576A3, WO2004035577A2, WO2004035577A3, WO2004050613A2, WO2004050613A3, WO2004064845A1, WO2004064846A1, WO2004096286A2, WO2004096286A3, WO2004096287A2, WO2004096287A3, WO2004096818A2, WO2004096818A3, WO2004100960A2, WO2005002626A2, WO2005002626A3, WO2005012324A2, WO2005012324A3, WO2005028478A1, WO2005039552A2, WO2005039552A3, WO2005042772A1, WO2005042773A1, WO2005047898A2, WO2005047898A3, WO2005063744A2, WO2005063744A3, WO2005063751A1, WO2005064008A1, WO2005064008A9, WO2005066189A1, WO2005070901A2, WO2005070901A3, WO2005072748A1, WO2005117904A2, WO2005117904A3, WO2006015261A2, WO2006015261A3, WO2006017044A2, WO2006017044A3, WO2006020276A2, WO2006020276A3, WO2006033703A1, WO2006047661A2, WO2006047661A3, WO2006069193A2, WO2006069193A3, WO2006091905A1, WO2006110157A2, WO2006110157A3, WO2006110157A9, WO2006125048A2, WO2006125048A3, WO2007009109A2, WO2007009109A3, WO2007011658A1, WO2007014174A2, WO2007014174A3, WO2007014352A2, WO2007014352A3, WO2007079260A1, WO2007079260A9, WO2007126812A2, WO2007126812A3, WO2008003149A2,

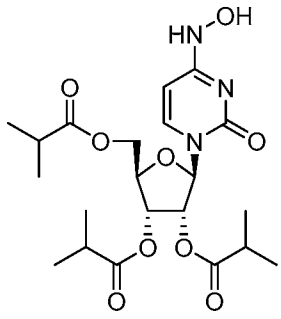
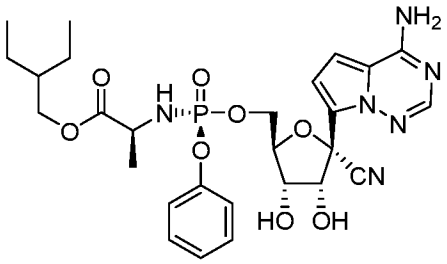
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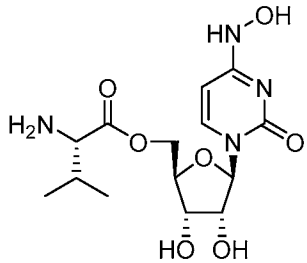
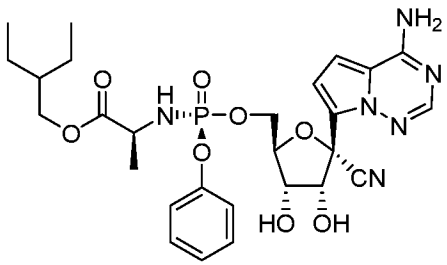
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In exemplified embodiments, the exemplary compounds and pharmaceutical compositions can be administered in combination with  and derivities and prodrugs thereof.

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In exemplified embodiments,  can be administered in comination with  and derivities and prodrugs thereof.

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EXAMPLES

The following examples are set forth below to illustrate the compositions, methods, and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods, compositions, and results. These examples are not intended to exclude equivalents and variations of the present invention, which are apparent to one skilled in the art.

Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated

otherwise, parts are parts by weight. There are numerous variations and combinations of reaction conditions, e.g., component concentrations, temperatures, pressures, and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process. Only reasonable and routine experimentation will be required to optimize such process conditions.

All chemical reactions were performed in oven-dried glassware under a nitrogen atmosphere, except where noted. Chemicals and solvents were reagent-grade and purchased from commercial suppliers (typically Aldrich, Fisher, Acros, Carbosynth Limited, and Oakwood Chemical) and used as received, excepting where noted. In particular, EIDD-1910, EIDD-1993, and EIDD-2003 were purchased from Carbosynth Limited. Solvents used for reactions (tetrahydrofuran, methanol, acetonitrile, dichloromethane, toluene, pyridine, dimethylformamide) were ≥99.9% anhydrous in all cases. All reactions were followed by thin layer chromatography (TLC) to completion, unless stated otherwise. TLC analysis was performed on silica gel, using illumination with a UV lamp (254 nm) or staining with $KMnO_4$ and heating. Manual flash column chromatography was performed with 40-60 micron (60 Å particle size) RediSep R_f silica gel, purchased from Teledyne Isco, as the stationary phase. Automated gradient flash column chromatography was performed on a Teledyne Isco CombiFlash Companion; normal phase separations were performed with pre-packed RediSep R_f silica gel as the stationary phase, and reverse phase separations were performed with pre-packed RediSep R_f C_{18} High Performance Gold stationary phase. Triphosphate purifications were performed using ion-exchange chromatography, with DEAE (diethylaminoethyl) Sephadex A-25 as the stationary phase, and aqueous TEAB (triethylammonium bicarbonate) as the mobile phase.

^{1}H NMR spectra were measured on a Varian 400 MHz instrument, and processed using MestReNova software, version 9.0.1. Chemical shifts were measured relative to the appropriate solvent peak: $CDCl_3$ (δ 7.27), DMSO-d_6 (δ 2.50), CD_3OD (δ 3.31), D_2O (δ 4.79). The following abbreviations were used to describe coupling: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. ^{13}C NMR spectra were measured on a Varian instrument at 100 MHz with chemical shifts relative to the appropriate solvent peak: $CDCl_3$ (δ 77.0), DMSO-d_6 (δ 39.5), CD_3OD (δ 49.0). ^{19}F spectra were measured on a Varian instrument at 376 MHz, and ^{31}P spectra were measured on a Varian instrument at 162 MHz. Chemical shifts for ^{19}F spectra, ^{31}P spectra, and ^{13}C spectra (in D_2O only) were calibrated by MestReNova software using an absolute reference function to the corresponding ^{1}H NMR spectrum in the same solvent.

Nominal (low resolution) liquid chromatography / mass spectrometry was performed using an Agilent 1200 series LC (UV absorption detector at 254 nm), using a Zorbax Eclipse

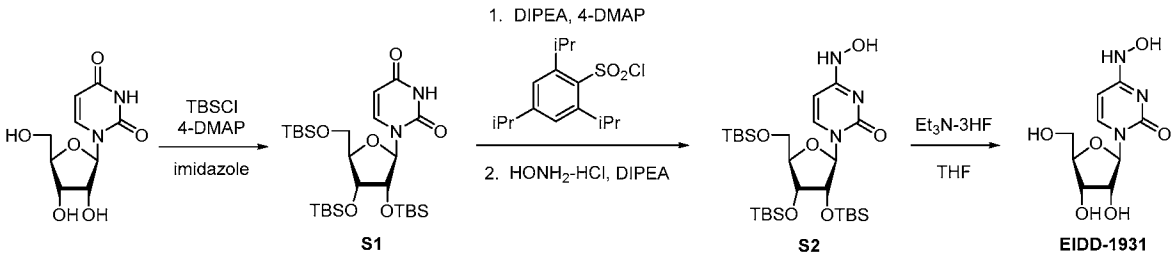
XDB C_{18} 4.6x50 mm, 3.5 micron column, eluting with a MeOH/water mixture (typically 95/5 isocratic) and an Agilent 6120 LCMS quadrupole instrument. High resolution mass spectrometry was performed by the Emory University Mass Spectrometry Center with a Thermo LTQ-FTMS using either APCI or ESI.

Example 1: Synthesis of N4-hydroxycytidine or 1-(3,4-dihydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-4-(hydroxyamino)pyrimidin-2-one (EIDD-1931)

Protection of uridine by persilylation is followed by activation of the 4-position of the nucleobase by a hindered arylsulfonyl group (see Figure 1). Displacement of this group with hydroxylamine installs the N-4-hydroxy moiety. Global deprotection using one of any number of fluoride sources available gives the desired product.

The compound can be made in one step from cytidine by heating in a pH-adjusted solution of hydroxylamine. Despite being shorter, this route tends to give lower yields and requires purification by reverse phase flash column chromatography, limiting its use to producing smaller quantities.

Another synthetic route is as shown below.

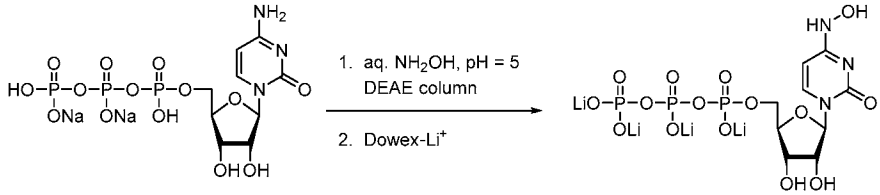


A 2 L 3-neck flask equipped with an overhead stirrer and nitrogen inlet was charged with uridine (25 g, 102 mmol) and 1 L of dichloromethane. The resulting solution was cooled to 0°C and 4-DMAP (1.251 g, 10.24 mmol) and imidazole (27.9 g, 409 mmol) were added sequentially. TBSCl (61.7 g, 409 mmol) was added over 10 minutes and the resulting mixture was warmed to ambient temperature and stirred for 18 hrs. Water (300 mL) was added to the reaction mixture and stirred at rt for 2 h, the layers were separated, and the aqueous layer was extracted with additional dichloromethane. The combined organic layers were washed with brine (1 x 300 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield 75 g of a clear colorless oil. Purification by flash chromatography (5 to 20% gradient of EtOAc in hexanes) to yield **S1** (45 g, 75%) as a clear, colorless oil, which solidified when dried *in vacuo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 5.67 (dd, J = 8.1, 2.2 Hz, 1H), 4.07 (q, J = 3.8, 3.3 Hz, 1H), 3.98 (dd, J = 11.7, 1.7 Hz, 1H), 3.75 (dd, J = 11.7, 1.1 Hz, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

A 1 L round bottom flask was charged with **S1** (28 g, 47.7 mmol) and dichloromethane (700 mL). The solution was cooled to 0°C using an ice bath; 4-DMAP (0.583 g, 4.77 mmol) and *N,N*-diisopropylethylamine (41.7 mL, 239 mmol) were added sequentially. 2,4,6-Triisopropylbenzene-1-sulfonyl chloride (28.9 g, 95 mmol) was slowly added to the flask, and after addition was complete, the flask was warmed to ambient temperature and stirred for 18 hrs. The dark orange solution was cooled to 0°C with an ice bath and *N,N*-diisopropylethylamine (24.66 g, 191 mmol) was added via syringe, followed by solid hydroxylamine hydrochloride (13.26 g, 191 mmol) all at once. The mixture was warmed to rt and stirred for 3 hrs. The reaction was quenched with water (200 mL) and the resulting layers were separated. The aqueous layer was extracted with dichloromethane (200 mL), and the combined organics were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to yield a dark orange oil. Purification by flash chromatography (15 to 50% gradient of EtOAc in hexanes) to yield **S2** (19.8 g, 69% over 2 steps) as an oil which solidified to a semi solid upon drying *in vacuo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 6.31 (s, 1H), 5.91 (d, *J* = 4.6 Hz, 1H), 5.56 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.07 (m, 2H), 4.02 (m, 1H), 3.91 (dd, *J*=11.6, 2.4 Hz, 1H), 3.73 (dd, *J*=11.6, 2.4 Hz, 1H), 0.95 (s, 9H), 0.92 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H), 0.098 (s, 3H), 0.083 (s, 3H), 0.063 (s, 3H), 0.057 (s, 3H); LRMS *m/z* 602.3 $[M+H]^+$.

A 50 mL round bottom flask was charged with **S2** (23.3 g, 38.7 mmol) and THF (50 mL). Triethylamine trihydrofluoride (6.30 mL, 38.7 mmol) was added all at once, and the mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved in a minimal amount of MeOH, and this solution was slowly added to an Erlenmeyer flask containing rapidly stirred dichloromethane (500 mL) to precipitate the product; the mixture was stirred at rt for 15 minutes. The triturated solid was collected by vacuum filtration and washed with dichloromethane, then ether. The solid was dried *in vacuo* to yield the title compound (7.10 g, 71%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (d, J = 8.2 Hz, 1H), 5.86 (d, *J* = 5.6 Hz, 1H), 5.59 (d, *J* = 8.2 Hz, 1H), 4.19 - 4.04 (m, 2H), 3.93 (q, J = 3.3 Hz, 1H), 3.77 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.68 (dd, *J* = 12.1, 2.9 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.46 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 5.71 (d, *J* = 6.3 Hz, 1H), 5.54 (d, *J* = 7.7 Hz, 1H), 5.23 (d, *J* = 6.0 Hz, 1H), 5.02 (d, *J* = 4.6 Hz, 1H), 4.98 (t, *J* = 5.1 Hz, 1H), 3.95 (q, *J* = 5.9 Hz, 1H), 3.89 (td, *J* = 4.9 Hz, 3.0 Hz, 1H), 3.75 (q, *J* = 3.4 Hz, 1H), 3.50 (qdd, *J* = 11.9 Hz, 5.2 Hz, 3.5 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.0, 143.9, 130.5, 98.89, 87.1, 85.0, 72.8, 70.8, 61.8. LRMS *m/z* 260.1 $[M+H]^+$.

Example 2: Synthesis of EIDD-2061

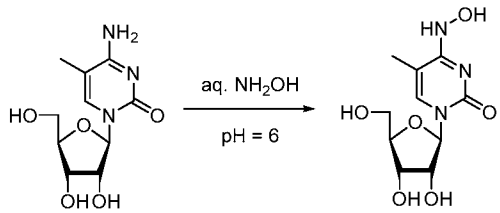


EIDD-2061

A sealable pressure tube was charged with a stir bar, cytidine triphosphate disodium salt (0.137 g, 0.260 mmol), and a 2 N aqueous hydroxylamine solution adjusted to pH = 5 (2.0 mL, 4.0 mmol). After mixing the reagents, the pH of the solution was measured (pH = 3) and additional drops of 10% w/w aq. NaOH solution were added to readjust the solution to pH = 5. The tube was sealed and heated with stirring at 55°C for 5 h. The mixture was cooled to rt, the sealed tube was opened, and a solution of 100 mM triethylammonium bicarbonate (TEAB) (2 mL) was added. The contents of the tube were transferred to a round bottom flask, and concentrated by rotary evaporation. The crude material was taken up in 100 mM TEAB, and chromatography on DEAE followed by lyophilization of the product gave a triethylammonium salt of the desired product.

An ion-exchange column (17 mL CV) of freshly prepared Dowex (Li^+ form) was rinsed with 5 CV water. The prepared triethylammonium salt was taken up in water and eluted through the ion-exchange column. Fractions containing product were combined and lyophilized to give the title compound (0.030 g, 22%) as a fluffy tan solid: ^{1}H NMR (400 MHz, D_2O) δ 7.19 (d, J = 8.3 Hz, 1H), 5.95 (d, J = 6.3 Hz, 1H), 5.82 (d, J = 8.3 Hz, 1H), 4.42-4.34 (m, 2H), 4.24-4.10 (m, 3H); ^{31}P NMR (162 MHz, D_2O) δ -8.5 (br s), -11.2 (d, J = 19.6 Hz), -22.0 (t, J = 19.3 Hz); LRMS m/z 498.0 $[M-H]^-$.

Example 3: Synthesis of EIDD-2101

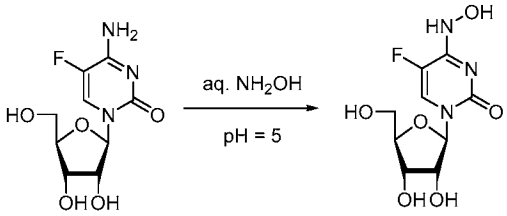


EIDD-2101

A solution of 5-methylcytidine (0.257 g, 1.00 mmol) in a 2N aq. hydroxylamine solution with pH 6 (8 mL, 16.0 mmol) was heated to 55°C in a sealed tube with stirring for 5 hrs. The solution was cooled to rt, transferred to a round bottom flask, concentrated by rotary evaporation, and coevaporated with MeOH (2 x 20 mL). The crude residue was taken up in MeOH and immobilized on silica gel. Flash chromatography (2 to 10% gradient of MeOH in DCM) provided the title compound (140 mg, 51%) as a light purple solid: ^{1}H NMR (400 MHz,

CD_3OD) δ 6.99 (s, 1H), 5.86 (d, J = 5.7 Hz, 1H), 4.23 - 4.06 (m, 2H), 3.93 (q, J = 3.2 Hz, 1H), 3.78 (dd, J = 12.1 Hz, 2.8 Hz, 1H), 3.70 (dd, J = 12.1 Hz, 3.4 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ152.0, 146.6, 128.4, 108.4, 89.4, 86.1, 74.4, 71.8, 62.8, 12.9; HRMS calcd. for $C_{10}H_{16}O_6N_3$ $[M+H]^+$: 274.10336, found: 274.10350.

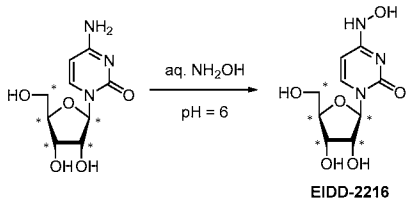
Example 4: Synthesis of EIDD-2103



EIDD-2103

A 2 N solution of hydroxylamine hydrochloride (1.11 g, 16.0 mmol) in water (8 mL) was prepared, and adjusted to pH = 5 with a small amount of aq. NaOH (10% w/w). A sealable pressure tube was charged with this solution and 5-fluorocytidine (0.261 g, 1.00 mmol), the flask was sealed, and heated with stirring at 55°C for 16 h. The mixture was cooled to rt, transferred to a round bottom flask, and concentrated by rotary evaporation. The crude material was suspended in MeOH and immobilized on Celite. Automated flash chromatography (40 g column, 0 to 20% gradient of MeOH in DCM) gave 600 mg of a semipure pink solid. This solid was dissolved in 2 mL water, and automated reverse phase chromatography (43 g column, 5 to 100% gradient of MeOH in water) gave the desired product free from organic and inorganic impurities. The solid was dissolved in water, frozen in a dry ice/acetone bath, and lyophilized to provide the title compound (0.066 g, 0.238 mmol, 24% yield) as a white flocculent solid. ^1H NMR (400 MHz, D_2O) δ 7.31 (d, J = 7.6 Hz, 1H), 5.87 (dd, J = 5.5 Hz, 1.8 Hz, 1H), 4.26 (t, J = 5.5 Hz, 1H), 4.19 (t, J = 4.8 Hz, 1H), 4.07 (q, J = 3.8 Hz, 1H), 3.85 (dd, J = 12.8 Hz, 3.1 Hz, 1H), 3.77 (dd, J = 12.7 Hz, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 150.0, 139.7, 137.4, 115.6 (d, J = 36.1 Hz), 88.0, 84.2, 72.8, 69.8, 61.0; ^{19}F NMR (376 MHz, D_2O) δ -164.70 (d, J = 7.6 Hz); HRMS calcd. for $C_9H_{13}FN_3O_6$ $[M+H]^+$: 278.07829, found: 278.07848.

Example 5: Synthesis of EIDD-2216

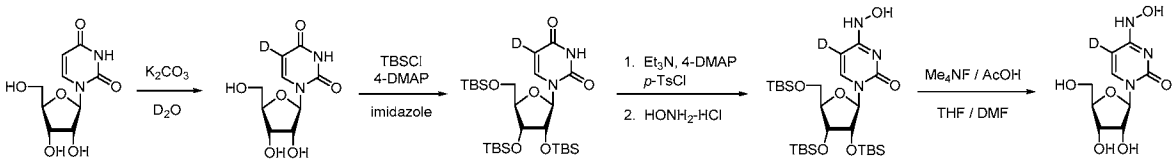


EIDD-2216

A 5 N solution of hydroxylamine hydrochloride (4.71 g, 67.8 mmol) in water (13.5 mL) was prepared, and adjusted to pH = 6 with a small amount of aq. NaOH (10% w/w). A sealable pressure tube was charged with this solution and [1',2',3',4',5'-$^{13}C_5$]cytidine (0.661 g, 2.26

mmol), the flask was sealed, and heated with stirring at 37°C for 16 h. The mixture was cooled to room temperature (rt), transferred to a round bottom flask, and concentrated by rotary evaporation. The crude material was taken up in water, and automated reverse phase flash chromatography (240 g C_{18} column, 0 to 100% gradient of acetonitrile in water) removed bulk impurities to give 1.4 g of a wet solid. This solid was dissolved in water, and a second automated reverse phase chromatography (240 g C_{18} column, 0 to 100% gradient of acetonitrile in water) removed more impurities to give 400 mg semipure material. The material was dissolved in MeOH and immobilized on Celite. Automated flash chromatography (24 g column, 5 to 25% gradient of MeOH in dichloromethane) gave 200 mg of nearly pure product. The solid was dissolved in water, and a final automated reverse phase chromatography (48 g C_{18} column, 0 to 100% gradient of acetonitrile in water) gave the desired product free from organic and inorganic impurities. The solid was dissolved in water, frozen in a dry ice/acetone bath, and lyophilized to provide the title compound (0.119 g, 20%) as a pale purple flocculent solid, about 95% pure by NMR/LCMS analysis: ^{1}H NMR (400 MHz, D_2O) δ 7.03 (dd, J = 8.2 Hz, 2.2 Hz, 1H), 5.82 (ddd, J = 167.5 Hz, 5.3 Hz, 2.9 Hz, 1H), 5.70 (d, J = 8.2 Hz, 1H), 4.47-4.30 (br m, 1H), 4.23-4.03 (br m, 1H), 4.00-3.80 (br m, 2H), 3.65-3.50 (br m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 151.3, 146.6, 131.3, 98.7, 87.9 (dd, J = 43.1 Hz, 4.0 Hz), 84.0 (dd, J = 41.5 Hz, 38.0 Hz), 72.5 (dd, J = 43.3 Hz, 37.8 Hz), 69.8 (td, J = 37.9 Hz, 3.9 Hz), 61.1 (d, J = 41.5 Hz); LRMS *m/z* 265.1 $[M+H]^+$.

Example 6: Synthesis of EIDD-2261



A sealable pressure tube was charged with uridine (1.00 g, 4.09 mmol), K_2CO_3 (0.679 g, 4.91 mmol), and deuterium oxide (8.2 mL). The mixture was purged with nitrogen for 15 minutes, the tubed was sealed, and the contents were heated with stirring at 95°C for 16 h. The mixture was cooled to rt, the tube was unsealed, and the mixture was transferred to a round-bottom flask and concentrated by rotary evaporation. The resulting crude was coevaporated with MeOH (x 3) to remove water. NMR analysis showed > 95% deuterium incorporation at the 5-position on the nucleobase. The light brown solid **S28** (1.00 g, 100%) was used in the next step without further purification: ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (s, 1H), 5.88 (d, J = 4.2 Hz, 1H), 4.17-4.12 (m, 2H), 4.00-3.96 (m, 1H), 3.84 (dd, J = 12.3 Hz, 2.8 Hz, 1H), 3.72 (dd, J = 12.3 Hz, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 185.6, 177.4, 160.4, 141.1, 91.8, 85.8, 75.9, 71.2, 62.4.

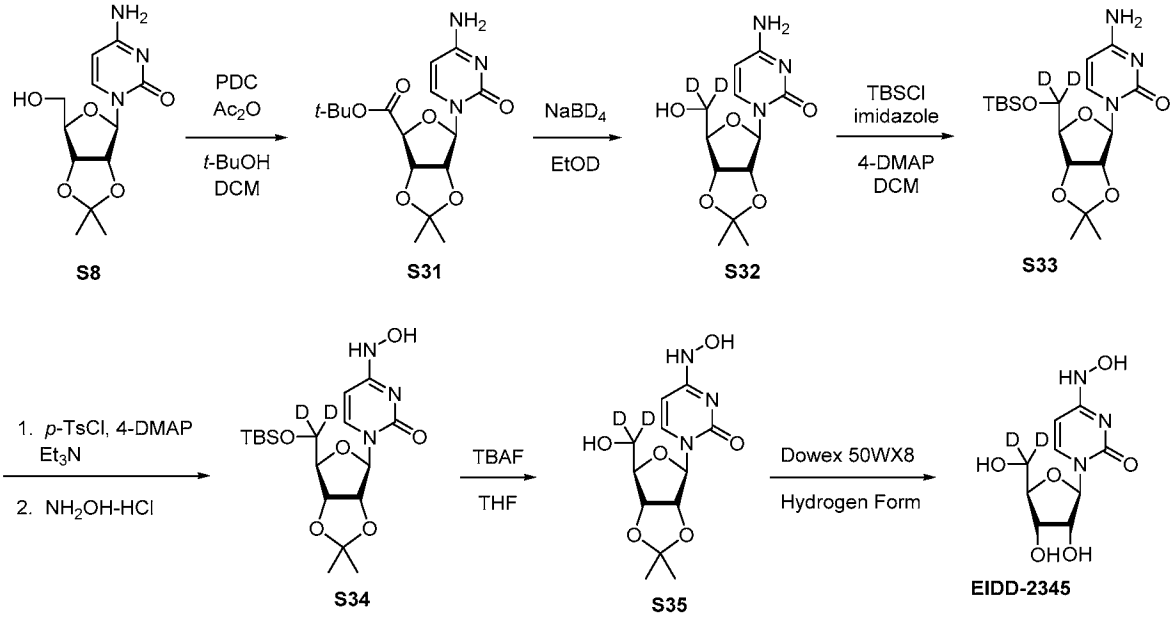
A round bottom flask was charged with **S28** (1.00 g, 4.09 mmol) and dichloromethane (8 mL) under nitrogen. The resulting mixture was cooled to 0°C and 4-DMAP (0.050 g, 0.408 mmol) and imidazole (1.11 g, 16.3 mmol) were added all at once. TBSCl (2.15 g, 14.3 mmol) was added all at once as a solid, the mixture was warmed to ambient temperature, and stirred for 16 hours. Water (25 mL) was added to the reaction mixture, the layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine (1 x 25 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Automated flash chromatography (40 g column, 0 to 35% gradient of EtOAc in hexanes) gave **S29** (2.52 g, 84%) as an off-white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 8.03 (s, 1H), 5.89 (d, J = 3.6 Hz, 1H), 4.12-4.06 (m, 3H), 3.99 (dd, J = 11.5 Hz, 1.8 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 0.96 (s, 9H), 0.92 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.3, 140.3, 89.0, 84.3, 76.1, 70.5, 61.6, 26.0 (3C), 25.8 (3C), 25.7 (3C), 18.4, 18.3, 17.9, -4.2, -4.6, -4.8, -4.9, -5.4, -5.6; HRMS calcd. for $C_{27}H_{54}DN_2NaO_6Si$ $[M+Na]^+$: 610.32446, found: 610.32482.

To a stirred solution of **S29** (0.840 g, 1.43 mmol) in acetonitrile (14.3 mL) at 0°C under nitrogen, were added sequentially *p*-toluenesulfonyl chloride (0.545 g, 2.86 mmol), 4-DMAP (0.175 g, 1.43 mmol), and triethylamine (0.80 mL, 5.71 mmol). The mixture was stirred at 0°C for 2.5 h, at which time hydroxylamine hydrochloride (0.993 g, 14.3 mmol) was added all at once as a solid. The mixture was heated at 50°C for 3 days, then cooled to rt. The reaction mixture was diluted with EtOAc (100 mL), then washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Automated flash chromatography (40 g column, 5 to 35% gradient of EtOAc in hexanes) produced a mixture of starting material and desired product. A second automated flash chromatography (24 g column, 10 to 40% gradient of EtOAc in hexanes), gave **S30** (0.332 g, 39%) as an off-white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 5.92 (d, J = 4.6 Hz, 1H), 4.10-4.05 (m, 2H), 4.04-4.00 (m, 1H), 3.91 (dd, J = 11.6 Hz, 2.4 Hz, 1H), 3.73 (dd, J = 11.6 Hz, 1.8 Hz, 1H), 0.95 (s, 9H), 0.92 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

A round bottom flask was charged with **S30** (0.332 g, 0.551 mmol), tetramethylammonium fluoride (0.196 g, 2.64 mmol), THF (8.25 mL), and DMF (2.75 mL) under nitrogen at 0°C. Acetic acid (0.157 mL, 2.75 mmol) was added all at once via syringe. The mixture was warmed to 45°C and heated with stirring for 4 days, then concentrated by rotary evaporation. Automated flash chromatography (40 g column, 0 to 20% gradient of MeOH in DCM) gave the title compound (0.106 g, 74%) as a white solid. Final NMR analysis showed

> 95% deuterium incorporation at the 5-position of the nucleobase: ^{1}H NMR (400 MHz, D_2O) δ 7.16 (s, 1H), 5.85 (d, J = 5.6 Hz, 1H), 4.14 (t, J = 5.5 Hz, 1H), 4.10 (dd, J = 5.6 Hz, 3.8 Hz, 1H), 3.93 (q, J = 3.4 Hz, 1H), 3.77 (dd, J = 12.2 Hz, 2.9 Hz, 1H), 3.68 (dd, J = 12.2 Hz, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.8, 146.3, 132.1, 89.7, 86.1, 74.6, 71.8, 62.8; HRMS calcd. for $C_9H_{13}DN_3O_6$ $[M+H]^+$: 261.09399, found: 261.09371.

Example 7: Synthesis of EIDD-2345



A round bottom flask was charged with **S8** (3.13 g, 11.0 mmol) and dichloromethane (75 mL) under nitrogen at rt. To this stirred mixture was added sequentially pyridinium dichromate (8.28 g, 22.0 mmol), acetic anhydride (10.4 mL, 110 mmol) and *t*-butanol (21.1 mL, 220 mmol) at rt. The mixture was stirred for 22 hours at rt, then washed with water (1 x 75 mL). The aqueous layer was extracted with dichloromethane (2 x 75 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The obtained residue was taken up in EtOAc and filtered through a Celite plug, followed by washing with EtOAc. The filtrate was concentrated by rotary evaporation, and automated flash chromatography (120 g column, 40 to 80% gradient of EtOAc in hexanes) gave **S31** (3.10 g, 72%) as an off-white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 5.76 (dd, J = 8.0 Hz, 2.3 Hz, 1H), 5.59 (s, 1H), 5.27 (dd, J = 6.0 Hz, 1.8 Hz, 1H), 5.19 (d, J = 6.0 Hz, 1H), 4.62 (d, J = 1.8 Hz, 1H), 1.56 (s, 3H), 1.48 (s, 9H), 1.39 (s, 3H).

To a stirred solution of **S31** (2.61 g, 7.37 mmol) in EtOD (75 mL) at rt under nitrogen, was added $NaBD_4$ (1.234 g, 29.5 mmol) in one portion. The mixture was stirred at rt for 1 hour, heated to 55°C for 6 hours, then overnight at rt. The mixture was cooled to 0°C and excess

reagent was quenched with AcOD. The mixture was concentrated by rotary evaporation to give crude **S32** (2.57 g) which was taken directly on to the next step without further purification.

To a stirred suspension of crude **S32** (2.00 g impure material, 5.74 mmol) in dichloromethane (70 mL) at 0°C, was added solid imidazole (1.90 g, 27.9 mmol) and 4-DMAP (0.171 g, 1.40 mmol). Solid *t*-butyldimethylsilyl chloride (2.11 g, 14.0 mmol) was added, and the mixture was warmed to rt and stirred for 4 days. The mixture was washed sequentially with water and brine (1 x 70 mL each), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Automated flash chromatography (120 g column, 0 to 35% gradient of EtOAc in hexanes) gave **S33** (1.42 g, 66% over 2 steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.72 (m, 1H), 5.99 (d, J = 2.8 Hz, 1H), 5.69 (dd, J = 8.2 Hz, 2.3 Hz, 1H), 4.77 (dd, J = 6.1 Hz, 2.9 Hz, 1H), 4.69 (dd, J = 6.2 Hz, 2.8 Hz, 1H), 4.33 (d, J = 3.0 Hz, 1H), 1.60 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 149.9, 140.5, 114.1, 102.1, 91.9, 86.5, 85.4, 80.3, 27.4, 25.9 (3C), 25.4, 18.4, -5.4, -5.5; HRMS calcd. for $C_{18}H_{29}D_2N_2O_6Si$ $[M+H]^+$: 401.20714, found: 401.20663.

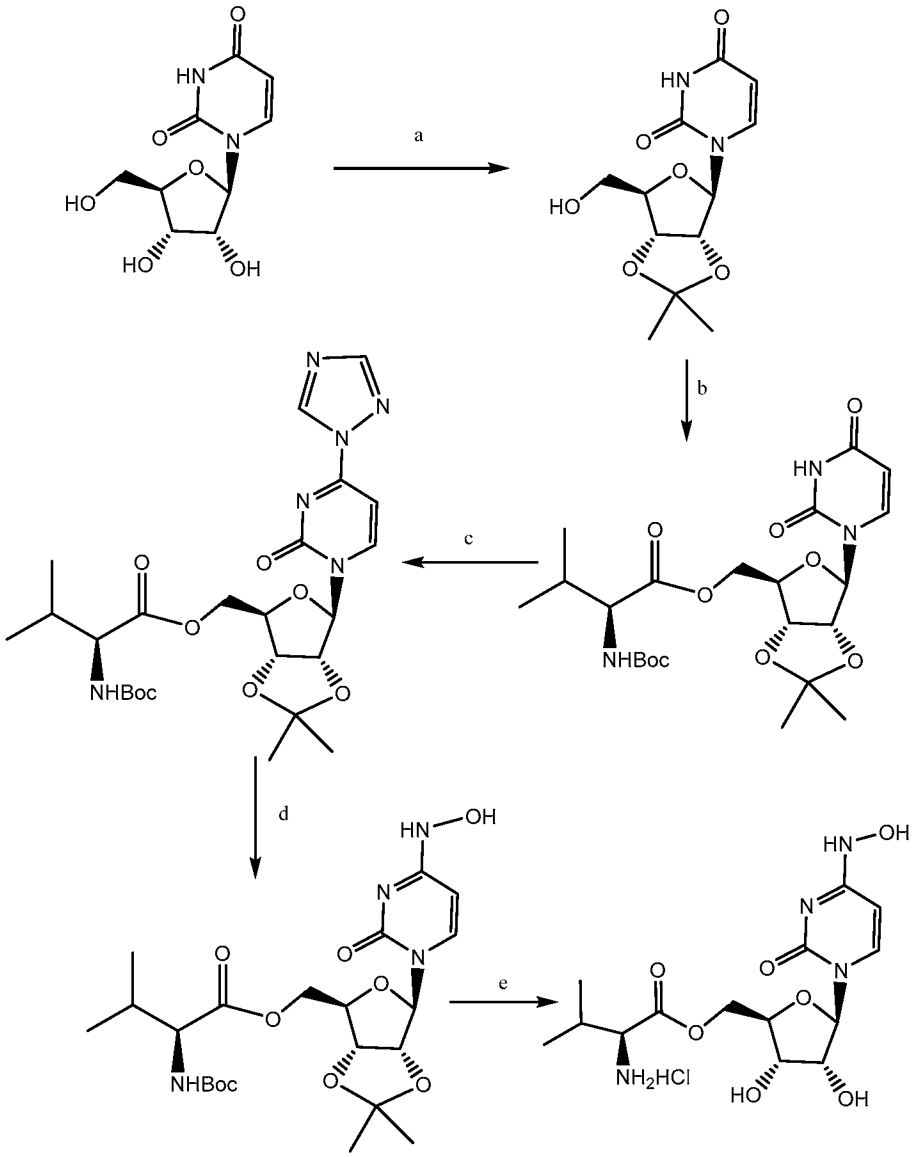
To a stirred solution of **S33** (1.42 g, 3.55 mmol) in acetonitrile (35 mL) at 0°C under nitrogen, was added sequentially *p*-toluenesulfonyl chloride (1.35 g, 7.09 mmol), 4-DMAP (0.433 g, 3.55 mmol), and triethylamine (9.88 mL, 70.9 mmol). The resulting mixture was stirred at 0°C for 2.5 hours. Hydroxylamine hydrochloride (2.46 g, 35.5 mmol) was added, and the mixture was heated with stirring at 50°C for 2 days. The mixture was recooled to rt and diluted with EtOAc (100 mL), then washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Automated flash chromatography (120 g column, 1 to 3.5% gradient of methanol in dichloromethane) gave **S34** (0.416 g, 28%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 7.00 (m, 1H), 5.97 (d, J = 3.1 Hz, 1H), 5.58 (d, J = 8.2 Hz, 1H), 4.77 (dd, J = 6.2 Hz, 3.2 Hz, 1H), 4.68 (dd, J = 6.3 Hz, 3.2 Hz, 1H), 4.22 (d, J = 3.2 Hz, 1H), 1.59 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 145.4, 131.4, 114.1, 98.3, 90.8, 85.5, 84.5, 80.2, 27.4, 25.9 (3C), 25.5, 18.4, -5.4, -5.5; HRMS calcd. for $C_{18}H_{29}D_2N_3O_6Si$ $[M+H]^+$: 416.21804, found: 416.21827.

To a stirred solution of **S34** (0.416 g, 1.00 mmol) in THF (5 mL) at 0°C under nitrogen, was added a 1.0 M THF solution of TBAF (1.50 mL, 1.5 mmol), and the resulting mixture was kept at 0°C for 24 hours. The reaction mixture was concentrated by rotary evaporation, and automated flash chromatography (40 g column, 0 to 8% gradient of methanol in dichloromethane) gave **S35** (0.257 g, 85%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (m, 1H), 5.81 (d, J = 3.2 Hz, 1H), 5.58 (d, J = 8.2 Hz, 1H), 4.86 (dd, J = 6.4 Hz, 3.2 Hz,

1H), 4.79 (dd, J = 6.5 Hz, 3.6 Hz, 1H), 4.09 (d, J = 3.7 Hz, 1H), 1.54 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.3, 146.2, 133.4, 115.2, 99.4, 92.9, 87.2, 84.9, 82.1, 27.6, 25.6; HRMS calcd. for $C_{12}H_{16}D_2N_3O_6$ $[M+H]^+$: 302.13157, found: 302.13130.

To a stirred solution of **S35** (0.140 g, 0.465 mmol) in methanol (8.4 mL) and water (0.93 mL) at rt, was added Dowex 50WX8 hydrogen form (0.30 g), and the mixture was stirred at rt for 24 hours. The reaction mixture was filtered, and the filtrate was concentrated by rotary evaporation. Automated flash chromatography (40 g column, 5 to 20% gradient of methanol in dichloromethane) gave the title compound (0.050 g, 41%) as an off-white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (m, 1H), 5.86 (d, J = 5.6 Hz, 1H), 5.60 (d, J = 8.2 Hz, 1H), 4.15 (t, J = 5.5 Hz, 1H), 4.11 (dd, J = 5.6 Hz, 3.5 Hz, 1H), 3.94 (d, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.8, 146.3, 132.2, 99.3, 89.7, 86.0, 74.6, 71.7, HRMS calcd. for $C_9H_{10}D_2N_3O_6$ $[M+H]^+$: 260.08571, found: 260.08578.

Example 8: Synthesis of EIDD-2898



Reagents and conditions; a) Acetone, H_2SO_4, 2,2-DMP, RT, 12 hr, 80-85%; b) Boc-L-Val-OH, DCC, DMAP, DCM, RT 5-6 hr; c) 1,2,4-triazole, POCl3, triethylamine, MeCN; d) 50%NH2OH in water, MeCN; e) conc.HCl, MeOH, RT, 24 hr

A 2L 3-neck RBF was charged with 1-[(3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]pyrimidine-2,4-dione (61.4g, 251.43 mmol) and acetone (1400 mL). The resulting slurry was stirred at RT and sulfuric acid (2 mL was added. Stirring was continued overnite. The clear colorless solution was quenched/adjusted to basic pH with 100 mL of trimethylamine. The crude solution was concentrated under reduced pressure to yield a pale yellow oil. The residue was dissolved in 600 mL of EtOAc and washed with water x 2, bicarb x 2, water, brine x 2 and dried over sodium sulfate. The colorless solution was

concentrated under reduced pressure to yield 1-[(3aR,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pyrimidine-2,4-dione (45 g) as a white solid.

A 200 mL RBF was charged with 1-[(3aR,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl]pyrimidine-2,4-dione (2.36 g, 8.3 mmol) and DCM (50 mL). The reaction was stirred until a solution was formed. Next, (2S)-2-(tert-butoxycarbonylamino)-3-methyl-butanoic acid (2.16 g, 9.96 mmol) and N,N-dimethylpyridin-4-amine (0.1 g, 0.8300 mmol) were added. The reaction was cooled to 0°C with an ice bath. A DCM solution of N,N'-dicyclohexylcarbodiimide (2.06 g, 9.96 mmol) was added slowly. The reaction mixture was allowed to warm to rt. Monitored by TLC (EtOAc).

A precipitate (DCU) formed after about 1 hr and no starting material was detected after 3 hrs. The solids were filtered off and rinsed with EtOAc. The filtrate was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure to yield white, gooey solid. The gummy solid was triturated with ether and filtered to remove the solid. The filtrate was concentrated under reduced pressure to yield about 8 g of thick viscous oil. The product was purified by SGC, pooled fractions 6-25 and concentrated under reduced pressure to yield [(3aR,6R,6aR)-4-(2,4-dioxopyrimidin-1-yl)-2,2-dimethyl-3a,4,6,6a-tetrahydrofuro[3,4-d][1,3]dioxol-6-yl]methyl (2S)-2-(tert-butoxycarbonylamino)-3-methyl-butanoate (3.8 g,7.8592 mmol, 94.667% yield) as a foamy white solid after drying *in vacuo*.

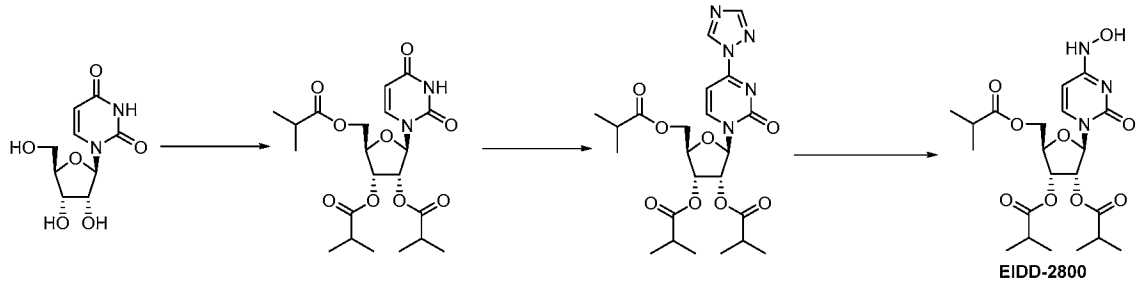
1,2,4-triazole was taken in anhydrous acetonitrile and stirred at RT after 30 min, the reaction mixture was cooled to 0°C and $POCl_3$ was added dropwise and continued stirring for 2 hr. After 2 hr triethylamine was added added dropwise and continue stirring for 1 hr, the reaction mixture was slowly brought to RT, and the uridine derived substrate from the above reaction was added as solution in acetonitrile. The reaction mixture stirred at RT overnight. After completion of the reaction, the solvent was removed under reduced pressure and taken in DCM and extracted with water. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

To a solution of the substrate in acetonitrile (10 mL/gm), 50% hydroxylamine in water was added dropwise and stirred at rt for 2-3 hrs. After completion of the reaction, solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using hexane and EtOAc as eluent.

1 g of substrate was taken in 20 mL of methanol and treated with 2 mL of conc.HCl (36%) and after 3-4 hr 30% completion was obsereved. Another 5 mL of conc.HCl was added and stirred overnight. After completion of the reaction, solvent was removed and the crude product was taken in minimum methanol and added dropwise to excess diethylether with

stirring, product was crashed out of solution and allowed to settle, ether was decanted and fresh ether was added, stirred, settled and decanted, the same process was repeated two times. After ether was decanted, solid was dried over a rotavap and high vaccum to get free flowing white solid. Ether was trapped in the solid and was difficult to remove. The solid was dissolved in methanol, evaporated and dried to get colorless foam, which still holds methanol. The foam was taken in water and a purple solution was observed. The purple solution was purified by reverse phase ISCO column chromatography using water and acetonitrile. The fractions containing product were evaporated under reduced pressure and lyophilized to get colorless solid.

Example 9: Synthesis of EIDD-2800



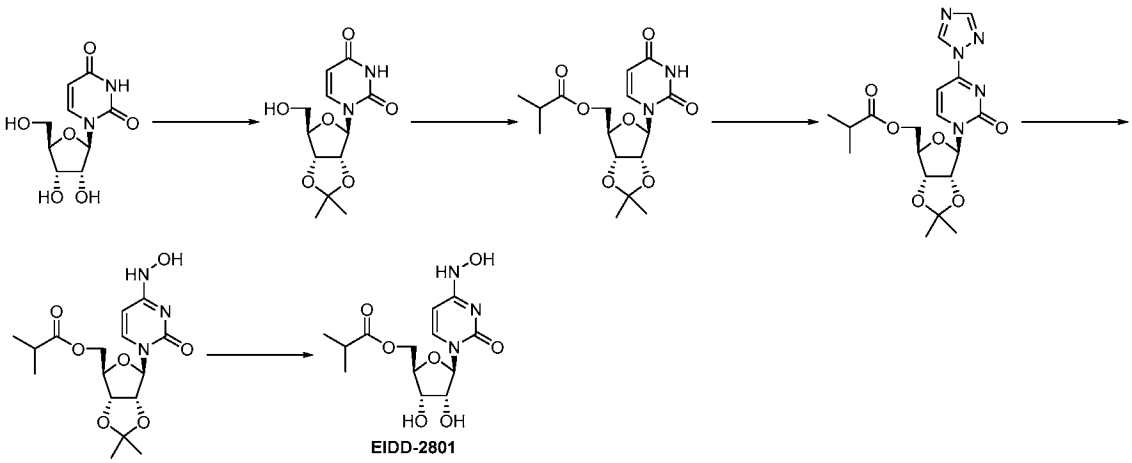
A 3-neck 1L round bottom flask equipped with an overhead stirrer, temperature probe and addition funnel was charged with uridine (25 g, 102.38 mmol) and ethyl acetate (500 mL). The white slurry was stirred at ambient temperature while triethylamine (71.39 mL, 511.88 mmol) and DMAP (0.63 g, 5.12 mmol) were added to the mixture. The slurry was cooled in an ice bath and isobutyric anhydride (56.02 mL, 337.84 mmol) was slowly added to the reaction mixture over a 5 minute period. The temperature rose 25°C during the addition. The resulting slurry was stirred at ambient temperature and monitored by TLC. After 1 hour, a clear colorless solution had formed and TLC showed no starting material. The reaction was quenched with 200mL of water, stirred at rt for 20 minutes. The layers were separated, and the organics were washed with water (2 x 100 mL), saturated aqueous bicarbonate solution (100 mL x 2), 100 mL of water, brine (100 mL x 2), and then dried over sodium sulfate. The organics were filtered and the filtrate was concentrated under reduced pressure at 45°C to yield a yellow oil. The oil was used in the next step without any further purification.

A 2L 3-neck flask equipped with an argon inlet, overhead stirrer and temperature probe was charged with 1H-1,2,4-triazole (50.88 g, 736.68 mmol), triethylamine (114.17 mL, 818.54 mmol) and MeCN (350 mL). The reaction mixture was stirred at rt for 20 minutes. An ethyl acetate (350 mL) solution of [(2R,3R,4R)-5-(2,4-dioxopyrimidin-1-yl)-3,4-bis(2-methylpropanoyloxy)tetrahydrofuran-2-yl]methyl 2-methylpropanoate (46.5 g, 102.32 mmol) was added and the mixture was cooled to <5°C using an ice bath. Stirring continued for 20 minutes. Next, phosphorous(V)oxychloride (14.35 mL, 153.48 mmol) was added slowly under

argon at less than 20°C over 15 minutes. The reaction was monitored by TLC (100% EtOAc), starting material (R_f = 0.89) consumed in less than 2 hours and a new spot due to product (R_f = 0.78) present. The reaction was quenched with 500 mL of water and 400 mL of EtOAc. The quenched reaction was allowed to stir at rt for 15 minutes. The layers were separated and the organic layer was washed with water (2 x 100 mL), 200mL of 0.5N HCl, and brine (2 x 100 mL). The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure to yield [(2R,3R,4R)-3,4-bis(2-methylpropanoyloxy)-5-[2-oxo-4-(1,2,4-triazol-1-yl)pyrimidin-1-yl]tetrahydrofuran-2-yl]methyl 2-methylpropanoate (49 g, 96.93 mmol, 94.735% yield) as a yellow oil. The crude material was used in the next step without further purification.

A 500mL round bottom flask was charged with [(2R,3R,4R)-3,4-bis(2-methylpropanoyloxy)-5-[2-oxo-4-(1,2,4-triazol-1-yl)pyrimidin-1-yl]tetrahydrofuran-2-yl]methyl 2-methylpropanoate (48.9 g, 96.73 mmol), ethyl acetate (400 mL), and isopropyl alcohol (100 mL). The reaction mixture was stirred at rt until all of the starting material was dissolved. The orange solution was treated with hydroxylamine (6.52 mL, 106.41 mmol), and the resulting pale yellow solution was stirred at rt and monitored by TLC (EtOAc). No starting material was observed after 1 hour. The reaction was quenched with 500mL of water, and the layers were separated. The organics were washed with 100mL of water, 100 mL x 2 of brine, and then dried over sodium sulfate. The organics were filtered and concentrated under reduced pressure to yield the crude product. The crude product was dissolved in 180 mL of hot MTBE and allowed to cool to rt. Seed crystals were added, and the flask was placed in the freezer. The white solid that formed was collected by filtration, washed with a minimal amount of MTBE and dried *in vacuo* to yield the desired product.

Example 10: Synthesis of EIDD-2801



A 1L round bottom flask was charged with uridine (25 g, 102.38 mmol) and acetone (700 mL). The reaction mixture was allowed to stir at rt. The slurry was then treated with sulfuric acid (0.27 mL, 5.12 mmol). Stirring was allowed to continue at rt for 18 hours. The reaction

was quenched with 100 mL of trimethylamine and was used in the next step without further pruficication.

A 1L round bottom flask was charged with the reaction mixture from the previous reaction. Triethylamine (71.09 mL, 510.08 mmol) and 4-dimethylaminopyridine (0.62 g, 5.1 mmol) were then added. The flask was cooled using an ice bath and then 2-methylpropanoyl 2-methylpropanoate (17.75 g, 112.22 mmol) was slowly added. The reaction mixture was allowed to stir at rt until the reaction was complete. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 600 mL ethyl acetate and washed with saturated aqueous bicarbonate solution x 2, water x 2 and brine x 2. The organics were dried over sodium sulfate and concentrated under reduced pressure to yield a clear colorless oil. The crude product was used in the next step without further purification.

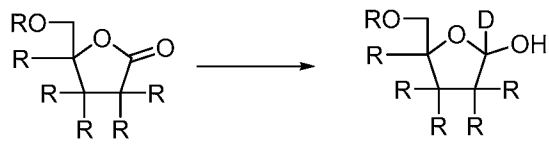
A 1L round bottom flask was charged with the crude product from above (36 g, 101.59 mmol) and MeCN (406.37 mL). The reaction mixture was allowed to stir until all the starting material was dissolved. Next, 1,2,4-triazole (50.52 g, 731.46 mmol) was added followed by the addition of N,N-diethylethanamine (113.28 mL, 812.73 mmol). The reaction mixture was allowed to stir at rt until all solids dissolved. The reaction was then cooled to 0°C using an ice bath. Phosphorous oxychloride (24.44 mL, 152.39 mmol) was added slowly. The slurry that formed was allowed to stir under argon while slowly warming to rt. The reaction was then allowed to stir until complete by TLC (EtOAc). The reaction was then quenched by the addition of 100mL of water. The slurry then became a dark colored solution, which was then concentrated under reduced pressure. The residue was dissolved in DCM and washed with water and brine. The organics were then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by silica gel chromatography (2 x 330 g columns). All fractions containing product were collected and concentrated under reduced pressure.

A 500 mL round bottom flask was charged with the product from the previous step (11.8 g, 29.11 mmol) and isopropyl alcohol (150 mL). The reaction mixture was allowed to stir at rt until all solids dissolved. Next, hydroxylamine (1.34 mL, 43.66 mmol) was added and stirring continued at ambient temperature. When the reaction was complete (HPLC) some solvent was removed under high vacuum at ambient temperature. The remaining solvent was removed under reduced pressure at 45°C. The resulting residue was dissolved in EtOAc and was washed with water and brine. The organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield oil. Crystals formed upon standing at rt. The crystals were collected by filtration, washed with ether x 3, and dried *in vacuo* to provide the product as a white solid.

A 200 mL round bottom flask was charged with the product from the previous step (6.5 g, 17.6 mmol) and formic acid (100 mL, 2085.6 mmol). The reaction mixture was allowed to stir at rt overnight. The progress of the reaction was monitored by HPLC. The reaction mixture was concentrated under reduced pressure at 42°C to yield a clear, pale pink oil. Next, 30 mL of ethanol was added. Solvent was then removed under reduced pressure. MTBE (50 mL) was added to the solid and heated. Next, isopropyl alcohol was added and heating was continued until all solid material dissolved (5 mL). The solution was then allowed to cool and stand at rt. A solid started to form after about 1hr. The solids were collected by filtration, washed with MTBE, and dried *in vacuo* to yield the EIDD-2801 as a white solid. The filtrate was concentrated under reduced pressure to yield a sticky solid, which was dissolved in a small amount of isopropyl alcohol with heating. The solution was allowed to stand at rt overnight. A solid formed in the flask, which was collected by filtration, rinsed with isopropyl alcohol and MTBE, and dried *in vacuo* to an additional crop of desired product.

EIDD-2801 (25 g) was dissolved in 250 mL of isopropyl alcohol by heating to 70°C to give a clear solution. The warm solution was polish filtered and filtrate transferred to 2L three neck flask with overhead stirrer. It was warmed back to 70°C and MTBE (250 mL) was slowly added into the flask. The clear solution was seeded and allowed to cool slowly to rt with stirring for 18 hrs. The EIDD-2801 solid that formed was filtered and washed with MTBE and dried at 50°C under vacuum for 18hours. The filtrate was concentrated, redissolved in 50 mL isopropyl alcohol and 40 mL MTBE by warming to give clear solution and allowed to stand at rt to give a second crop of EIDD-2801.

Example 11: General synthesis for Deuteration



389 **390**

The lactone **389** (0.0325 mol) was added to a dry flask under an argon atmosphere and was then dissolved in dry THF (250 mL). The solution as then cooled to -78°C and a DIBAL-D solution in toluene (0.065 mol) was dropwise. The reaction was allowed to stir at -78°C for 3-4 hours. The reaction was then quenched with the slow addition of water (3 mL). The reaction was then allowed to stir while warming to rt. The mixture was then diluted with two volumes of diethyl ether and was then poured into an equal volume of saturated sodium potassium tartrate solution. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on silica eluting with hexanes/ethyl acetate. The

resulting lactol **390** was then converted to an acetate or benzolyate and subjected to cytosine coupling conditions and then further elaborated to N-hydroxycytidine.

Example 12: Assay Protocols

Screening Assays for DENV, JEV, POWV, WNV, YFV, PTV, RVFV, CHIKV, EEEV, VEEV, WEEV, TCRV, PCV, JUNV, MPRLV

Primary cytopathic effect (CPE) reduction assay.

Four-concentration CPE inhibition assays are performed. Confluent or near-confluent cell culture monolayers in 96-well disposable microplates are prepared. Cells are maintained in MEM or DMEM supplemented with FBS as required for each cell line. For antiviral assays the same medium is used but with FBS reduced to 2% or less and supplemented with 50 μg/mL gentamicin. The test compound is prepared at four $\log_{10}$ final concentrations, usually 0.1, 1.0, 10, and 100 μg/mL or μM. The virus control and cell control wells are on every microplate. In parallel, a known active drug is tested as a positive control drug using the same method as is applied for test compounds. The positive control is tested with each test run. The assay is set up by first removing growth media from the 96-well plates of cells. Then the test compound is applied in 0.1 mL volume to wells at 2X concentration. Virus, normally at <100 50% cell culture infectious doses ($CCID_{50}$) in 0.1 mL volume, is placed in those wells designated for virus infection. Medium devoid of virus is placed in toxicity control wells and cell control wells. Virus control wells are treated similarly with virus. Plates are incubated at 37°C with 5% CO_2 until maximum CPE is observed in virus control wells. The plates are then stained with 0.011% neutral red for approximately two hours at 37°C in a 5% CO_2 incubator. The neutral red medium is removed by complete aspiration, and the cells can be rinsed 1X with phosphate buffered solution (PBS) to remove residual dye. The PBS is completely removed and the incorporated neutral red is eluted with 50% Sorensen's citrate buffer/50% ethanol (pH 4.2) for at least 30 minutes. Neutral red dye penetrates into living cells, thus, the more intense the red color, the larger the number of viable cells present in the wells. The dye content in each well is quantified using a 96-well spectrophotometer at 540 nm wavelength. The dye content in each set of wells is converted to a percentage of dye present in untreated control wells using a Microsoft Excel computer-based spreadsheet. The 50% effective (EC_{50}, virus-inhibitory) concentrations and 50% cytotoxic (CC_{50}, cell-inhibitory) concentrations are then calculated by linear regression analysis. The quotient of CC_{50} divided by EC_{50} gives the selectivity index (SI) value.

Secondary CPE/Virus yield reduction (VYR) assay.

This assay involves similar methodology to what is described in the previous paragraphs using 96-well microplates of cells. The differences are noted in this section. Eight half-$\log_{10}$ concentrations of inhibitor are tested for antiviral activity and cytotoxicity. After sufficient virus

replication occurs, a sample of supernatant is taken from each infected well (three replicate wells are pooled) and held for the VYR portion of this test, if needed. Alternately, a separate plate can be prepared and the plate can be frozen for the VYR assay. After maximum CPE is observed, the viable plates are stained with neutral red dye. The incorporated dye content is quantified as described above. The data generated from this portion of the test are neutral red EC_{50}, CC_{50}, and SI values. Compounds observed to be active above are further evaluated by VYR assay. The VYR test is a direct determination of how much the test compound inhibits virus replication. Virus that was replicated in the presence of test compound is titrated and compared to virus from untreated, infected controls. Titration of pooled viral samples (collected as described above) is performed by endpoint dilution. This is accomplished by titrating log_{10} dilutions of virus using 3 or 4 microwells per dilution on fresh monolayers of cells by endpoint dilution. Wells are scored for presence or absence of virus after distinct CPE (measured by neutral red uptake) is observed. Plotting the log_{10} of the inhibitor concentration versus log_{10} of virus produced at each concentration allows calculation of the 90% (one log_{10}) effective concentration by linear regression. Dividing EC_{90} by the CC_{50} obtained in part 1 of the assay gives the SI value for this test.

Example 13: Screening Assays for Lassa fever virus (LASV)

Primary Lassa fever virus assay.

Confluent or near-confluent cell culture monolayers in 12-well disposable cell culture plates are prepared. Cells are maintained in DMEM supplemented with 10% FBS. For antiviral assays the same medium is used but with FBS reduced to 2% or less and supplemented with 1% penicillin/streptomycin. The test compound is prepared at four log_{10} final concentrations, usually 0.1, 1.0, 10, and 100 μg/mL or μM. The virus control and cell control will be run in parallel with each tested compound. Further, a known active drug is tested as a positive control drug using the same experimental set-up as described for the virus and cell control. The positive control is tested with each test run. The assay is set up by first removing growth media from the 12-well plates of cells, and infecting cells with 0.01 MOI of LASV strain Josiah. Cells will be incubated for 90 min: 500 μL inoculum/M12 well, at 37°C, 5% CO_2 with constant gentle rocking. The inoculums will be removed and cells will be washed 2X with medium. Then the test compound is applied in 1 mL of total volume of media. Tissue culture supernatant (TCS) will be collected at appropriate time points. TCS will then be used to determine the compounds inhibitory effect on virus replication. Virus that was replicated in the presence of test compound is titrated and compared to virus from untreated, infected controls. For titration of TCS, serial ten-fold dilutions will be prepared and used to infect fresh monolayers of cells. Cells will be overlaid with 1% agarose mixed 1:1 with 2X MEM supplemented with 10%FBS and 1%

penecillin, and the number of plaques determined. Plotting the log_{10} of the inhibitor concentration versus log_{10} of virus produced at each concentration allows calculation of the 90% (one log_{10}) effective concentration by linear regression.

Secondary Lassa fever virus assay.

The secondary assay involves similar methodology to what is described in the previous paragraphs using 12-well plates of cells. The differences are noted in this section. Cells are being infected as described above but this time overlaid with 1% agarose diluted 1:1 with 2X MEM and supplemented with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. Cells will be incubated at 37oC with 5% CO_2 for 6 days. The overlay is then removed and plates stained with 0.05% crystal violet in 10% buffered formalin for approximately twenty minutes at rt. The plates are then washed, dried and the number of plaques counted. The number of plaques is in each set of compound dilution is converted to a percentage relative to the untreated virus control. The 50% effective (EC_{50}, virus-inhibitory) concentrations are then calculated by linear regression analysis.

Example 14: Screening Assays for Ebola virus (EBOV) and Nipah virus (NIV)

Primary Ebola/Nipah virus assay.

Four-concentration plaque reduction assays are performed. Confluent or near-confluent cell culture monolayers in 12-well disposable cell culture plates are prepared. Cells are maintained in DMEM supplemented with 10% FBS. For antiviral assays the same medium is used but with FBS reduced to 2% or less and supplemented with 1% penicillin/streptomycin. The test compound is prepared at four log_{10} final concentrations, usually 0.1, 1.0, 10, and 100 μg/mL or μM. The virus control and cell control will be run in parallel with each tested compound. Further, a known active drug is tested as a positive control drug using the same experimental set-up as described for the virus and cell control. The positive control is tested with each test run. The assay is set up by first removing growth media from the 12-well plates of cells. Then the test compound is applied in 0.1 mL volume to wells at 2X concentration. Virus, normally at approximately 200 plaque-forming units in 0.1 mL volume, is placed in those wells designated for virus infection. Medium devoid of virus is placed in toxicity control wells and cell control wells. Virus control wells are treated similarly with virus. Plates are incubated at 37°C with 5% CO_2 for one hour. Virus-compound inoculums will be removed, cells washed and overlaid with 1.6% tragacanth diluted 1:1 with 2X MEM and supplemented with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. Cells will be incubated at 37°C with 5% CO_2 for 10 days. The overlay is then removed and plates stained with 0.05% crystal violet in 10% buffered formalin for approximately twenty minutes at rt. The plates are then washed, dried and the number of plaques counted. The

number of plaques is in each set of compound dilution is converted to a percentage relative to the untreated virus control. The 50% effective (EC_{50}, virus-inhibitory) concentrations are then calculated by linear regression analysis.

Secondary Ebola/NIpah virus assay with VYR component.

The secondary assay involves similar methodology to what is described in the previous paragraphs using 12-well plates of cells. The differences are noted in this section. Eight half-log_{10} concentrations of inhibitor are tested for antiviral activity. One positive control drug is tested per batch of compounds evaluated. For this assay, cells are infected with virus. Cells are being infected as described above but this time incubated with DMEM supplemented with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. Cells will be incubated for 10 days at 37°C with 5% CO_2, daily observed under microscope for the number of green fluorescent cells. Aliquots of supernatant from infected cells will be taken daily and the three replicate wells are pooled. The pooled supernatants are then used to determine the compounds inhibitory effect on virus replication. Virus that was replicated in the presence of test compound is titrated and compared to virus from untreated, infected controls. For titration of pooled viral samples, serial ten-fold dilutions will be prepared and used to infect fresh monolayers of cells. Cells are overlaid with tragacanth and the number of plaques determined. Plotting the log_{10} of the inhibitor concentration versus log_{10} of virus produced at each concentration allows calculation of the 90% (one log_{10}) effective concentration by linear regression.

Example 15: Anti-Dengue Virus Cytoprotection Assay

Cell Preparation -BHK21 cells (Syrian golden hamster kidney cells, ATCC catalog # CCL-I 0), Vero cells (African green monkey kidney cells, ATCC catalog# CCL-81), or Huh-7 cells (human hepatocyte carcinoma) were passaged in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin in T-75 flasks prior to use in the antiviral assay. On the day preceding the assay, the cells were split 1:2 to assure they were in an exponential growth phase at the time of infection. Total cell and viability quantification was performed using a hemocytometer and Trypan Blue dye exclusion. Cell viability was greater than 95% for the cells to be utilized in the assay. The cells were resuspended at 3×10^3 (5×10^5 for Vero cells and Huh-7 cells) cells per well in tissue culture medium and added to flat bottom microtiter plates in a volume of 100 μL. The plates were incubated at 37°C/5% CO_2 overnight to allow for cell adherence. Monolayers were observed to be approximately 70% confluent.

Virus Preparation-The Dengue virus type 2 New Guinea C strain was obtained from ATCC (catalog# VR-1584) and was grown in LLC-MK2 (Rhesus monkey kidney cells; catalog

#CCL-7.1) cells for the production of stock virus pools. An aliquot of virus pretitered in BHK21 cells was removed from the freezer (-80°C) and allowed to thaw slowly to rt in a biological safety cabinet. Virus was resuspended and diluted into assay medium (DMEM supplemented with 2% heat-inactivated FBS, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin) such that the amount of virus added to each well in a volume of 100 µL was the amount determined to yield 85 to 95% cell killing at 6 days post-infection.

Plate Format-Each plate contains cell control wells (cells only), virus control wells (cells plus virus), triplicate drug toxicity wells per compound (cells plus drug only), as well as triplicate experimental wells (drug plus cells plus virus).

Efficacy and Toxicity XTT-Following incubation at 37°C in a 5% CO_2 incubator, the test plates were stained with the tetrazolium dye XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide). XTT-tetrazolium was metabolized by the mitochondrial enzymes of metabolically active cells to a soluble formazan product, allowing rapid quantitative analysis of the inhibition of virus-induced cell killing by antiviral test substances. XTT solution was prepared daily as a stock of 1 mg/mL in RPMI 1640. Phenazine methosulfate (PMS) solution was prepared at 0.15mg/mL in PBS and stored in the dark at -20°C. XTT/PMS stock was prepared immediately before use by adding 40 µL of PMS per mL of XTT solution. Fifty microliters ofXTT/PMS was added to each well of the plate and the plate was reincubated for 4 hours at 37°C. Plates were sealed with adhesive plate sealers and shaken gently or inverted several times to mix the soluble formazan product and the plate was read spectrophotometrically at 450/650 nm with a Molecular Devices Vmax plate reader.

Data Analysis -Raw data was collected from the Softmax Pro 4.6 software and imported into a Microsoft Excel spreadsheet for analysis. The percent reduction in viral cytopathic effect compared to the untreated virus controls was calculated for each compound. The percent cell control value was calculated for each compound comparing the drug treated uninfected cells to the uninfected cells in medium alone.

Example 16: Anti-RSV Cytoprotection Assay:

Cell Preparation-HEp2 cells (human epithelial cells, A TCC catalog# CCL-23) were passaged in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin 1 mM sodium pyruvate, and 0.1 mM NEAA, T-75 flasks prior to use in the antiviral assay. On the day preceding the assay, the cells were split 1:2 to assure they were in an exponential growth phase at the time of infection. Total cell and viability quantification was performed using a hemocytometer and Trypan Blue dye exclusion. Cell viability was greater than 95% for the cells to be utilized in the assay. The cells were resuspended at 1 x 10^4 cells per well in tissue culture medium and added to flat bottom microtiter plates in a volume of 100 µL.

The plates were incubated at 37°C/5% CO_2 overnight to allow for cell adherence. Virus Preparation -The RSV strain Long and RSV strain 9320 were obtained from ATCC (catalog# VR-26 and catalog #VR-955, respectively) and were grown in HEp2 cells for the production of stock virus pools. A pretitered aliquot of virus was removed from the freezer (-80°C) and allowed to thaw slowly to rt in a biological safety cabinet. Virus was resuspended and diluted into assay medium (DMEMsupplemented with 2% heat-inactivated FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin, 1 mM sodium pyruvate, and 0.1 mM NEAA) such that the amount of virus added to each well in a volume of 100 µL was the amount determined to yield 85 to 95% cell killing at 6 days post-infection. Efficacy and Toxicity XTT-Plates were stained and analyzed as previously described for the Dengue cytoprotection assay.

Example 17: Anti-Influenza Virus Cytoprotection Assay

Cell Preparation-MOCK cells (canine kidney cells, ATCC catalog# CCL-34) were passaged in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin 1 mM sodium pyruvate, and 0.1 mM NEAA, T-75 flasks prior to use in the antiviral assay. On the day preceding the assay, the cells were split 1:2 to assure they were in an exponential growth phase at the time of infection. Total cell and viability quantification was performed using a hemocytometer and Trypan Blue dye exclusion. Cell viability was greater than 95% for the cells to be utilized in the assay. The cells were resuspended at 1 x 10^4 cells per well in tissue culture medium and added to flat bottom microtiter plates in a volume of 100 µL. The plates were incubated at 37°C/5% CO_2 overnight to allow for cell adherence.

Virus Preparation-The influenza A/PR/8/34 (A TCC #VR-95), A/CA/05/09 (CDC), A/NY/18/09 (CDC) and A/NWS/33 (ATCC #VR-219) strains were obtained from ATCC or from the Center of Disease Control and were grown in MDCK cells for the production of stock virus pools. A pretitered aliquot of virus was removed from the freezer (-80°C) and allowed to thaw slowly to rt in a biological safety cabinet. Virus was resuspended and diluted into assay medium (DMEM supplemented with 0.5%BSA, 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin, 1 mM sodium pyruvate, 0.1 mM NEAA, and 1 µg/mL TPCK-treated trypsin) such that the amount of virus added to each well in a volume of 100 µL was the amount determined to yield 85 to 95% cell killing at 4 days post-infection. Efficacy and Toxicity XTT-Plates were stained and analyzed as previously described for the Dengue cytoprotection assay.

Example 18: Anti-Hepatitis C Virus Assay

Cell Culture -The reporter cell line Huh-luc/neo-ET was obtained from Dr. Ralf Bartenschlager (Department of Molecular Virology, Hygiene Institute, University of Heidelberg, Germany) by ImQuest BioSciences through a specific licensing agreement. This cell line harbors the persistently replicating I_{389}luc-ubi-neo/NS3-3'/ET replicon containing the firefly

luciferase gene-ubiquitin-neomycin phosphotransferase fusion protein and EMCV IRES driven NS3-5B HCV coding sequences containing the ET tissue culture adaptive mutations (E1202G, Tl2081, and K1846T). A stock culture of the Huh-luc/neo-ET was expanded by culture in DMEM supplemented with I 0% FCS, 2 mM glutamine, penicillin (100 μU/mL)/streptomycin (100 μg/mL) and I X nonessential amino acids plus 1 mg/mL G418. The cells were split 1:4 and cultured for two passages in the same media plus 250 μg/mL G418. The cells were treated with trypsin and enumerated by staining with trypan blue and seeded into 96-well tissue culture plates at a cell culture density 7.5 x 10^3 cells per well and incubated at 37°C/5% CO_2 for 24 hours. Following the 24 hour incubation, media was removed and replaced with the same media minus theG418 plus the test compounds in triplicate. Six wells in each plate received media alone as a no-treatment control. The cells were incubated an additional 72 hours at 37°C/5% CO_2 then anti-HCV activity was measured by luciferase endpoint. Duplicate plates were treated and incubated in parallel for assessment of cellular toxicity by XTT staining.

Cellular Viability- The cell culture monolayers from treated cells were stained with the tetrazolium dye XTT to evaluate the cellular viability of the Huh-luc/neo-ET reporter cell line in the presence of the compounds.

Measurement of Virus Replication-HCV replication from the replicon assay system was measured by luciferase activity using the britelite plus luminescence reporter gene kit according to the manufacturer's instructions (Perkin Elmer, Shelton, CT). Briefly, one vial of britelite plus lyophilized substrate was solubilized in 10 mL of britelite reconstitution buffer and mixed gently by inversion. After a 5 minute incubation at rt, the britelite plus reagent was added to the 96 well plates at 100 μL per well. The plates were sealed with adhesive film and incubated at rt for approximately 10 minutes to lyse the cells. The well contents were transferred to a white 96-well plate and luminescence was measured within 15 minutes using the Wallac 1450 Microbeta Trilux liquid scintillation counter. The data were imported into a customized Microsoft Excel 2007 spreadsheet for determination of the 50% virus inhibition concentration (EC_{50}).

Example 19: Anti-Parainfluenza-3 Cytoprotection Assay

Cell Preparation- HEp2 cells (human epithelial cells, ATCC catalog# CCL-23) were passaged in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin 1 mM sodium pyruvate, and 0.1 mM NEAA, T-75 flasks prior to use in the antiviral assay. On the day preceding the assay, the cells were split 1:2 to assure they were in an exponential growth phase at the time of infection. Total cell and viability quantification was performed using a hemocytometer and Trypan Blue dye exclusion. Cell viability was greater than 95% for the cells to be utilized in the assay. The cells were resuspended at 1 x 10^4 cells per

well in tissue culture medium and added to flat bottom microtiter plates in a volume of 100 µL. The plates were incubated at 37°C/5% CO_2 overnight to allow for cell adherence.

Virus Preparation - The Parainfluenza virus type 3 SF4 strain was obtained from ATCC (catalog# VR-281) and was grown in HEp2 cells for the production of stock virus pools. A pretitered aliquot of virus was removed from the freezer (-80°C) and allowed to thaw slowly to rt in a biological safety cabinet. Virus was resuspended and diluted into assay medium (DMEM supplemented with 2% heat-inactivated FBS, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin) such that the amount of virus added to each well in a volume of 100 µL was the amount determined to yield 85 to 95% cell killing at 6 days post-infection.

Plate Format - Each plate contains cell control wells (cells only), virus control wells (cells plus virus), triplicate drug toxicity wells per compound (cells plus drug only), as well a triplicate experimental wells (drug plus cells plus virus). Efficacy and Toxicity XTT- Following incubation at 37°C in a 5% CO_2 incubator, the test plates were stained with the tetrazolium dye XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazol hydroxide). XTT-tetrazolium was metabolized by the mitochondrial enzymes of metabolically active cells to a soluble formazan product, allowing rapid quantitative analysis of the inhibition of virus-induced cell killing by antiviral test substances. XTT solution was prepared daily as a stock of 1 mg/mL in RPMI1640. Phenazine methosulfate (PMS) solution was prepared at 0.15 mg/mL in PBS and stored in the dark at -20°C. XTT/PMS stock was prepared immediately before use by adding 40 µL of PMS per mL of XTT solution. Fifty microliters of XTT/PMS was added to each well of the plate and the plate was reincubated for 4 hours at 37°C. Plates were sealed with adhesive plate sealers and shaken gently or inverted several times to mix the soluble fom1azan product and the plate was read spectrophotometrically at 450/650 nm with a Molecular Devices Vmax plate reader.

Data Analysis - Raw data was collected from the Softmax Pro 4.6 software and imported into a Microsoft Excel spreadsheet for analysis. The percent reduction in viral cytopathic effect compared to the untreated virus controls was calculated for each compound. The percent cell control value was calculated for each compound comparing the drug treated uninfected cells to the uninfected cells in medium alone.

Example 20: Influenza Polymerase Inhibition Assay

Virus Preparation - Purified influenza virus A/PR/8/34 (1 mL) was obtained from Advanced Biotechnologies, Inc. (Columbia, MD), thawed and dispensed into five aliquots for storage at -80°C until use. On the day of assay set up, 20 µL of 2.5% Triton N-101 was added to 180 µL of purified virus. The disrupted virus was diluted 1:2 in a solution containing 0.25% Triton and PBS. Disruption provided the source of influenza ribonucleoprotein (RNP)

containing the influenza RNA-dependent RNA polymerase and template RNA. Samples were stored on ice until use in the assay.

Polymerase reaction - Each 50 µL polymerase reaction contained the following: 5 µL of the disrupted RNP, 100 mM Tris-HCl (pH 8.0), 100 mM KCl, 5 mM $MgCl_2$. 1 mM dithiothreitol, 0.25% Triton N-101, 5 µCi of [α-^{32}P] GTP, 100 µM ATP, 50 µM each (CTP, UTP), 1 µM GTP, and 200 µM adenyl (3'-5') guanosine. For testing the inhibitor, the reactions contained the inhibitor and the same was done for reactions containing the positive control (2'-Deoxy-2'-fluoroguanosine-5'-triphosphate). Other controls included RNP +reaction mixture, and RNP + I% DMSO. The reaction mixture without the ApG primer and NTPs was incubated at 30°C for 20 minutes. Once the ApG and NTPs were added to the reaction mixture, the samples were incubated at 30°C for 1 hour then immediately followed by the transfer of the reaction onto glass-fiber filter plates and subsequent precipitation with 10% trichloroacetic acid (TCA). The plate was then washed five times with 5% TCA followed by one wash with 95% ethanol. Once the filter had dried, incorporation of [α-^{32}P] GTP was measured using a liquid scintillation counter (Microbeta).

Plate Format - Each test plate contained triplicate samples of the three compounds (6 concentrations) in addition to triplicate samples of RNP + reaction mixture (RNP alone), RNP + 1% DMSO, and reaction mixture alone (no RNP).

Data Analysis - Raw data was collected from the Microbeta scintillation counter. The incorporation of radioactive GTP directly correlates with the levels of polymerase activity. The "percent inhibition values" were obtained by dividing the mean value of each test compound by the RNP + 1% DMSO control. The mean obtained at each concentration of 2DFGTP was compared to the RNP + reaction control. The data was then imported into Microsoft Excel spreadsheet to calculate the IC_{50} values by linear regression analysis.

Example 21: HCV Polymerase Inhibition Assay

Activity of compounds for inhibition of HCV polymerase was evaluated using methods previously described (Lam et al. *Antimicrob Agents Chemother* 2010, 54(8):3187-3196). HCV NS5B polymerase assays were performed in 20 µL volumes in 96 well reaction plates. Each reaction contained 40 ng/µL purified recombinant NS5BΔ22 genotype-1b polymerase, 20 ng/µL of HCV genotype-1b complimentary IRES template, 1 µM of each of the four natural ribonucleotides, 1 U/mL Optizyme RNAse inhibitor (Promega, Madison, WI), 1 mM $MgCl_2$, 0.75 mM $MnCl_2$, and 2 mM dithiothreitol (DTT) in 50 mM HEPES buffer (pH 7.5). Reaction mixtures were assembled on ice in two steps. Step 1 consisted of combining all reaction components except the natural nucleotides and labeled UTP in a polymerase reaction mixture. Ten microliters (10 µL) of the polymerase mixture was dispensed into individual wells of the 96

well reaction plate on ice. Polymerase reaction mixtures without NS5B polymerase were included as no enzyme controls. Serial half-logarithmic dilutions of test and control compounds, 2'-O-Methyl-CTP and 2'-O-Methyl-GTP (Trilink, San Diego, CA), were prepared in water and 5 µL of the serial diluted compounds or water alone (no compound control) were added to the wells containing the polymerase mixture. Five microliters of nucleotide mix (natural nucleotides and labeled UTP) was then added to the reaction plate wells and the plate was incubated at 27°C for 30 minutes. The reactions were quenched with the addition of 80 µL stop solution (12.5 mM EDTA, 2.25 M NaCl, and 225 mM sodium citrate) and the RNA products were applied to a Hybond-N+ membrane (GE Healthcare, Piscataway, N.J) under vacuum pressure using a dot blot apparatus. The membrane was removed from the dot blot apparatus and washed four times with 4X SSC (0.6 M NaCl, and 60 mM sodium citrate), and then rinsed one time with water and once with 100% ethanol. The membrane was air dried and exposed to a phosphoimaging screen and the image captured using a Typhoon 8600 Phospho imager. Following capture of the image, the membrane was placed into a Microbeta cassette along with scintillation fluid and the CPM in each reaction was counted on a Microbeta 1450. CPM data were imported into a custom Excel spreadsheet for determination of compound IC_{50}.

Example 22: NS5B RNA-dependent RNA polymerase reaction conditions

Compounds were assayed for inhibition of NS5B-δ21 from HCV GT-1b Con-1. Reactions included purified recombinant enzyme, 1 µg/µL negative-strand HCV IRES RNA template, and 1 µM NTP substrates including either [^{32}P]-CTP or [^{32}P]-UTP. Assay plates were incubated at 27°C for 1 hour before quench. [^{32}P] incorporation into macromolecular product was assessed by filter binding.

Example 23: Human DNA Polymerase Inhibition Assay

The human DNA polymerase alpha (catalog# 1075), beta (catalog# 1077), and gamma (catalog# 1076) were purchased from CHIMERx (Madison, WI). Inhibition of beta and gamma DNA polymerase activity was assayed in microtiter plates in a 50 uL reaction mixture containing 50 mM Tris-HCl (pH 8.7), KCl (10 mM for beta and 100mM for gamma), 10 mM $MgCl_2$, 0.4 mg/mL BSA, 1 mM DTT, 15% glycerol, 0.05 mM of dCTP, dTTP, and dATP, 10 uCi [^{32}P]-alpha-dGTP (800 Ci/mmol), 20 ug activated calf thymus DNA and the test compound at indicated concentrations. The alpha DNA polymerase reaction mixture was as follows in a 50 µL volume per sample: 20 mM Tris-HCl (pH 8), 5 mM magnesium acetate, 0.3 mg/mL BSA, 1 mM DTT, 0.1 mM spermine, 0.05 mM of dCTP, dTTP, and dATP, 10 µCi [^{32}P]-alpha-dGTP (800 Ci/mmol), 20 µg activated calf thymus DNA and the test compound at the indicated concentrations. For each assay, the enzyme reactions were allowed to proceed for 30 minutes at 37°C followed by the transfer onto glass-fiber filter plates and subsequent precipitation with

10% trichloroacetic acid (TCA). The plate was then washed with 5% TCA followed by one wash with 95% ethanol. Once the filter had dried, incorporation of radioactivity was measured using a liquid scintillation counter (Micro Beta).

Example 24: HIV infected PBMC assay

Fresh human peripheral blood mononuclear cells (PBMCs) were obtained from a commercial source (Biological Specialty) and were determined to be seronegative for HIV and HBV. Depending on the volume of donor blood received, the leukophoresed blood cells were washed several times with PBS. After washing, the leukophoresed blood was diluted 1:1 with Dulbecco's phosphate buffered saline (PBS) and layered over 15mL of Ficoll-Hypaque density gradient in a 50 mL conical centrifuge tube. These tubes were centrifuged for 30 minutes at 600 g. Banded PBMCs were gently aspirated from the resulting interface and washed three times with PBS. After the final wash, cell number was determined by Trypan Blue dye exclusion and cells were re-suspended at 1 x 10^6 cells/mL in RPMI 1640 with 15% Fetal Bovine Serum (FBS), 2 mmol/L L-glutamine, 2 µg/mL PHA-P, 100 U/mL penicillin and 100 µg/mL streptomycin and allowed to incubate for 48-72 hours at 37°C. After incubation, PBMCs were centrifuged and resuspended in tissue culture medium. The cultures were maintained until use by half-volume culture changes with fresh IL-2 containing tissue culture medium every 3 days. Assays were initiated with PBMCs at 72 hours post PHA-P stimulation.

To minimize effects due to donor variability, PBMCs employed in the assay were a mixture of cells derived from 3 donors. Immediately prior to use, target cells were resuspended in fresh tissue culture medium at 1 x 10^6 cells/mL and plated in the interior wells of a 96-well round bottom microtiter plate at 50 µL/well. Then, 100 µL of 2X concentrations of compound-containing medium was transferred to the 96-well plate containing cells in 50 µL of the medium. AZT was employed as an internal assay standard.

Following addition of test compound to the wells, 50 µL of a predetermined dilution of HIV virus (prepared from 4X of final desired in-well concentration) was added, and mixed well. For infection, 50-150 $TCID_{50}$ of each virus was added per well (final MOI approximately 0.002). PBMCs were exposed in triplicate to virus and cultured in the presence or absence of the test material at varying concentrations as described above in the 96-well microtiter plates. After 7 days in culture, HIV-1 replication was quantified in the tissue culture supernatant by measurement of reverse transcriptase (RT) activity. Wells with cells and virus only served as virus controls. Separate plates were identically prepared without virus for drug cytotoxicity studies.

Reverse Transcriptase Activity Assay – Reverse transcriptase activity was measured in cell-free supernatants using a standard radioactive incorporation polymerization assay. Tritiated

thymidine triphosphate (TTP; New England Nuclear) was purchased at 1 Ci/mL and 1 µL was used per enzyme reaction. A rAdT stock solution was prepared by mixing 0.5mg/mL poly rAand 1.7 U/mL oligo dT in distilled water and was stored at -20°C. The RT reaction buffer was prepared fresh daily and consists of 125 µL of 1 mol/L EGTA, 125 µL of dH_2O, 125 µL of 20% Triton X-100, 50 µL of 1 mol/L Tris (pH 7.4), 50 µL of 1 mol/L DTT, and 40 µL of 1 mol/L $MgCl_2$. For each reaction, 1 µL of TTP, 4 µL of dH_2O, 2.5 µL of rAdT, and 2.5 µL of reaction buffer were mixed. Ten microliters of this reaction mixture was placed in a round bottom microtiter plate and 15 µL of virus-containing supernatant was added and mixed. The plate was incubated at 37°C in a humidified incubator for 90 minutes. Following incubation, 10 µL of the reaction volume was spotted onto a DEAE filter mat in the appropriate plate format, washed 5 times (5 minutes each) in a 5% sodium phosphate buffer, 2 times (1 minute each) in distilled water, 2 times (1 minute each) in 70% ethanol, and then air dried. The dried filtermat was placed in a plastic sleeve and 4 mL of Opti-Fluor O was added to the sleeve. Incorporated radioactivity was quantified utilizing a Wallac 1450 Microbeta Trilux liquid scintillation counter.

Example 25: HBV

HepG2.2.15 cells (100 µL) in RPMI1640 medium with 10% fetal bovine serum was added to all wells of a 96-well plate at a density of 1 x 10^4 cells per well and the plate was incubated at 37°C in an environment of 5% CO_2 for 24 hours. Following incubation, six ten-fold serial dilutions of test compound prepared in RPMI1640 medium with 10% fetal bovine serum were added to individual wells of the plate in triplicate. Six wells in the plate received medium alone as a virus only control. The plate was incubated for 6 days at 37°C in an environment of 5% CO_2. The culture medium was changed on day 3 with medium containing the indicated concentration of each compound. One hundred microliters of supernatant was collected from each well for analysis of viral DNA by qPCR and cytotoxicity was evaluated by XTT staining of the cell culture monolayer on the sixth day.

Ten microliters of cell culture supernatant collected on the sixth day was diluted in qPCR dilution buffer (40 µg/mL sheared salmon sperm DNA) and boiled for 15 minutes. Quantitative real time PCR was performed in 386 well plates using an Applied Biosystems 7900HT Sequence Detection System and the supporting SDS 2.4 software. Five microliters (5 µL) of boiled DNA for each sample and serial 10-fold dilutions of a quantitative DNA standard were subjected to real time Q-PCR using Platinum Quantitative PCR SuperMix-UDG (Invitrogen) and specific DNA oligonucleotide primers (IDT, Coralville, ID) HBV-AD38-qF1 (5'-CCG TCT GTG CCT TCT CAT CTG-3') (SEQ ID NO.:1), HBV-AD38-qR1 (5'-AGT CCA AGA GTY CTC TTA TRY AAG ACC TT-3') (SEQ ID NO.:2), and HBV-AD38-qP1 (5'-FAM CCG TGT GCA

/ZEN/CTT CGC TTC ACC TCT GC-3'BHQ1) (SEQ ID NO.:3) at a final concentration of 0.2 μM for each primer in a total reaction volume of 15 μL. The HBV DNA copy number in each sample was interpolated from the standard curve by the SDS.24 software and the data were imported into an Excel spreadsheet for analysis.

The 50% cytotoxic concentration for the test materials are derived by measuring the reduction of the tetrazolium dye XTT in the treated tissue culture plates. XTT is metabolized by the mitochondrial enzyme NADPH oxidase to a soluble formazan product in metabolically active cells. XTT solution was prepared daily as a stock of 1 mg/mL in PBS. Phenazine methosulfate (PMS) stock solution was prepared at 0.15 mg/mL in PBS and stored in the dark at -20°C. XTT/PMS solution was prepared immediately before use by adding 40 μL of PMS per 1 mL of XTT solution. Fifty microliters of XTT/PMS was added to each well of the plate and the plate incubated for 2-4 hours at 37°C. The 2-4 hour incubation has been empirically determined to be within linear response range for XTT dye reduction with the indicated numbers of cells for each assay. Adhesive plate sealers were used in place of the lids, the sealed plate was inverted several times to mix the soluble formazan product and the plate was read at 450 nm (650 nm reference wavelength) with a Molecular Devices SpectraMax Plus 384 spectrophotometer. Data were collected by Softmax 4.6 software and imported into an Excel spreadsheet for analysis.

Example 26: Dengue RNA-dependent RNA polymerase reaction conditions

RNA polymerase assay was performed at 30°C using 100 μL reaction mix in 1.5 mL tube. Final reaction conditions were 50 mM Hepes (pH 7.0), 2 mM DTT, 1mM $MnCl_2$, 10 mM KCl, 100 nM UTR-Poly A (self-annealing primer), 10 μM UTP, 26 nM RdRp enzyme. The reaction mix with different compounds (inhibitors) was incubated at 30 °C for 1 hr. To assess amount of pyrophosphate generated during polymerase reaction, 30 μL of polymerase reaction mix was mixed with a luciferase coupled-enzyme reaction mix (70 μL). Final reaction conditions of luciferase reaction were 5mM $MgCl_2$, 50mM Tris-HCl (pH 7.5), 150 mM NaCl, 200 μU ATP sulfurylase, 5 μM APS, 10 nM Luciferase, 100 μM D-luciferin. White plates containing the reaction samples (100 μL) were immediately transferred to the luminometer Veritas (Turner Biosystems, CA) for detection of the light signal.

Example 27: Procedure for Cell Incubation and Analysis

Huh-7 cells were seeded at $0.5x10^6$ cells/well in 1 mL of complete media in 12 well tissue culture treated plates. The cells were allowed to adhere overnight at 37°/5% CO_2. A 40 μM stock solution of test article was prepared in 100% DMSO. From the 40 μM stock solution, a 20 μM solution of test article in 25 mL of complete DMEM media was prepared. For compound treatment, the media was aspirated from the wells and 1 mL of the 20 μM solution was added in complete DMEM media to the appropriate wells. A separate plate of cells with

"no" addition of the compound was also prepared. The plates were incubated at 37°/5% CO_2 for the following time points: 1, 3, 6 and 24 hours. After incubation at the desired time points, the cells were washed 2X with 1 mL of DPBS. The cells were extracted by adding 500 µL of 70% methanol/30% water spiked with the internal standard to each well treated with test article. The non-treated blank plate was extracted with 500 µL of 70% methanol/30% water per well. Samples were centrifuged at 16,000 rpm for 10 minutes at 4°C. Samples were analyzed by LC-MS/MS using an ABSCIEX 5500 QTRAP LC-MS/MS system with a Hypercarb (PGC) column.

Example 28: Procedure for Rodent Pharmacokinetic Experiment

DBA-1J mice (6-8 weeks old, female) were acclimated for $\geq$ 2 days after receipt. Mice were weighed the day before dosing to calculate dosing volumes. Mice were dosed by oral gavage with drug at 30 mg/kg, 100 mg/kg & 300 mg/kg. The mice were sampled at 8 time points: 0.5, 1, 2, 3, 4, 8 and 24 hrs (3 mice per time point for test drug). The mice were euthanized and their organs were collected (see below). In order to collected blood, mice with euthanized by CO_2 at the appropriate time point listed above. Blood was obtained by cardiac puncture (0.3 mL) at each time point. Following blood collection, the organs were removed from the mice (see below). The blood was processed by inverting Li-Heparin tube with blood gently 2 or 3 times to mix well. The tubes were then placed in a rack in ice water until able to centrifuge ($\leq$ 1 hour). As soon as practical, the blood was centrifuged at 2000 x g for 10 minutes in a refrigerated centrifuge to obtain plasma. Then, using a 200 µL pipette, the plasma was transferred to a labeled 1.5 mL Eppendorf tube in ice water. The plasma was then frozen in freezer or on dry ice. The samples were stored at -80°C prior to analysis. Organs were collected from euthanized mice. The organs (lungs, liver, kidney, spleen and heart) were removed, placed in a tube, and immediately frozen in liquid nitrogen. The tubes were then transferred to dry ice. The samples were saved in cryogenic tissue vials. Samples were analyzed by LC-MS/MS using an ABSCIEX 5500 QTRAP LC-MS/MS system with a Hypercarb (PGC) column.

Pharmacokinetic Parameters:

- T_{max} after oral dosing is 0.25 – 0.5hr
- C_{max}'s are 3.0, 7.7 and 11.7 ng/mL after PO dosing with 30, 100 and 300 mg/kg;
- Bioavailability (versus i.p. delivery) is 65% at 30 mg/kg and 39-46% at 100 and 300 mg/kg PO dosing;
- EIDD-1931 plasma $T_{1/2}$ is 2.2 hr after IV dosing and 4.1-4.7 hrs after PO dosing
- After 300 mg/kg P.O. dose, the 24 hr plasma levels are 0.4 µM; 0.1 µM after 100 mg/kg dose

Example 29: Protocol for Mouse Model of Chikungunya Infection

C57BL-6J mice were injected with 100 pfus CHIK virus in the footpad. The test groups comprised an unifected and untreated group, an infected and untreated group, an infected group receiving a high dose of 35 mg/kg i.p. of EIDD-01931, and an infected group receiving a low dose of 25 mg/kg i.p. of EIDD-01931. The two test groups receiving EIDD-01931 received compound 12 hours before challenge and then daily for 7 days. Footpads were evaluated for inflammation (paw thickness) daily for 7 days. CHIK virus induced arthritis (histology) was assessed in ankle joints using PCR after 7 days.

Example 30: N(4)-hydroxycytidine for the Prophylaxis and Treatment of Alphavirus Infections

Activity testing in Vero cell cytopathic effect (CPE) models of infection have shown that the ribonucleoside analog N(4)-hydroxycytidine (EIDD-01931) has activity against the Ross River, EEE, WEE, VEE and CHIK viruses with EC_{50} values of 2.45 μM, 1.08 μM, 1.36 μM, 1.00 μM and 1.28 μM, respectively. The cytotoxicity profile of the compound is acceptable, with selectivity indices ranging from a low of 8 in CEM cells to a high of 232 in Huh7 (liver) cells.

Example 31:

Given that high titers of VEE virus can develop in the brain within hours of aerosol exposure, a direct-acting antiviral agent is desirable if it is able to rapidly achieve therapeutic levels of drug in the brain. A pilot pharmacokinetic study was conducted in male SD rats dosed by oral gavage with 5 and 50 mg/kg of EIDD-01931, to determine pharmacokinetic parameters and the tissue distribution profile of the compound into key organ systems, including the brain. EIDD-01931 is orally available and dose-proportional with a calculated bioavailability (%F) of 28%. Organ samples (brain, lung, spleen, kidney and liver) were collected at 2.5 and 24 hours post-dose from the 50 mg/kg dose group. EIDD-01931 was well distributed into all tissues tested; of particular note, it was readily distributed into brain tissue at therapeutic levels of drug, based on estimates from cellular data. Once in the brain, EIDD-01931 was rapidly metabolized to its active 5′-triphosphate form to give brain levels of 526 and 135 ng/g at 2.5 and 24 hours, respectively. Even after 24 hours levels of EIDD-01931 and its 5′-triphosphate in the brain are considerable, suggesting that once-daily oral dosing can be adequate for treatment.

Alternatively, drug delivery by aerosol (nasal spray) administration can immediately achieve therapeutic levels of drug in the nasal mucosa and the brain. EIDD-01931 has an acceptable toxicology profile after 6 day q.d. intraperitoneal (IP) injections in mice, with the NOEL (NO Effect Level) to be 33 mg/kg; weight loss was observed at the highest dose tested (100 mg/kg), which reversed on cessation of dosing.

Example 32: N4-hydroxycytidine Arenaviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
Tacaribe virus	Vero	14.4		136
Tacaribe virus	Vero	18.8		104
Pichinde virus	Vero	18.4		184
Pichinde virus	Vero	21.6		128
Junin virus	Vero	18.4		136
Junin virus	Vero	20.8		124
Lassa fever virus	Vero	4.04		30
Lymphocytic choriomeningitis virus	Vero		25.2	>400

Example 33: N4-hydroxycytidine Togaviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
VEEV	Vero76	1.28		128
VEEV	Vero76	1		13.6
VEEV	Vero76		0.8	32.8
VEEV	Vero76	1.92		32.8
EEEV	Vero76	0.96		128
EEEV	Vero76	1.08		84
EEEV	Vero76		1.68	132
EEEV	Vero76	8		132
WEEV	Vero76	1.28		>400
WEEV	Vero76	1.36		288
WEEV	Vero76		<1.28	120
WEEV	Vero76	0.76		256
CHIKV	Vero76	1.28		76
CHIKV	Vero76	1.28		22.8
CHIKV	Vero76		0.72	96
CHIKV	Vero76	1.8		96

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Example 34: N4-hydroxycytidine Flaviviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
DENV2	Vero76	12.8		60
DENV2	Vero76	14		128
WNV	Vero76	>400		>400
WNV	Vero76	>400		>400
YFV	Vero76	1.88		224
YFV	Vero76	20.4		30
YFV	Vero76		26	52
YFV	Vero76	>52		52

JEV	Vero76	112		>400
JEV	Vero76	268		>400
POWV	BHK	11.2		30
POWV	BHK	8.8		19.2
ZIKV	Vero76	1.44		>400
ZIKV	Vero76	6.8		152
ZIKV	Vero76		2.36	80
ZIKV	Vero76	3.12		80
Usutu virus	Vero 76	228		>400
Usutu virus	Vero 76	100		212
ZIKV	Vero 76	1.46		400
ZIKV	Vero 76	3.04		16.4

Example 35: N4-hydroxycytidine Bunyaviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
RVFV	Vero76	1.48		60
RVFV	Vero76	1.44		48
RVFV	Vero76	6.8		96
RVFV	Vero76	7.6		96
RVFV	Vero		1	20.4
RVFV	Vero	1.68		20.4
Punta Toro virus	Vero76	20.4		184
Punta Toro virus	Vero76	20		160
La Crosse virus	Vero76	25.2		268
La Crosse virus	Vero76	15.2		188
La Crosse virus	Vero76		1	112
La Crosse virus	Vero76	1.96		112
Maporal virus	Vero76	84		140
Maporal virus	Vero76	>124		124
Heartland virus	Vero		7.84	>400
Lymphocytic choriomeningitis virus	Vero		25.2	>400
Severe fever thrombocytopenia syndrome virus	Vero		4.96	>400

Example 36: N4-hydroxycytidine Coronaviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
MERS	Vero E6	<0.80	<0.80	20
SARS	Vero76	<0.4		252
SARS	Vero76	<0.4		144
SARS	Vero76		0.56	76
SARS	Vero76	2.2		76

SARS	Vero E6	<0.80	<0.80	20
HCoV	HEL	1.28		100
HCoV	HEL	5.6		36
HCoV	HEL		<0.128	192
HCoV	HEL	0.228		192
HCoV	Vero76	<0.4		400
HCoV	Vero E6	<0.4		400
HCoV	HEL	1.28		100
HCoV	HEL	4		60
HCoV	HEL		0.4	232
HCoV	HEL	0.212		232
HCov	Vero76	12.8		400
HCoV	Vero76		0.32	44
HCov	Vero76	0.44		44

Example 37: N4-hydroxycytidine Influenza Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
Influenza A H1N1	MDCK	1.28		168
Influenza A H1N1	MDCK	1.16		136
Flu A H7N9 (High Path)	MDCK	>48		48
Flu A H7N9 (High Path)	MDCK	>44		44
Flu A H5N1 (High Path)	MDCK	>96		96
Flu A H5N1 (High Path)	MDCK	>88		88
Flu A H1N1	MDCK	1.44		76
Flu A H1N1	MDCK	1.24		68
Flu A H3N2	MDCK	0.96		60
Flu A H3N2	MDCK	0.88		52
Flu A H5N1 (Low Path)	MDCK	1.28		48
Flu A H5N1 (Low Path)	MDCK	1.28		27.6
Flu B	MDCK	<0.4		48
Flu B	MDCK	<0.4		30.4
Flu B	MDCK	<0.4		48
Flu B	MDCK	<0.4		76

Example 38: N4-hydroxycytidine Ebola Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
EBOV	Vero	4.7		>100
EBOV	Vero		25	>320

Example 39: N4-hydroxycytidine Norovirus Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
NV	HG23	>100	>100	>100

Example 40: N4-hydroxycytidine Picornaviridae Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC50 (□M)
Enterovirus-71	Vero76	3.44		>400
Enterovirus-71	Vero76	3.36		256
Enterovirus-68	RD	1.28		>400
Enterovirus-68	RD	1.16		25.6
Poliovirus -1	Vero76	12.8		128
Poliovirus -1	Vero76	10.4		76
Coxsackie virus B3	Vero 76	1.44		184
Coxsackie virus B3	Vero 76	1.4		76
HRV-14	HeLa-Ohio	1.28		>40
HRV-14	HeLa-Ohio	1.36		>40
Coxsackie virus B3	Vero 76		2.24	56
Coxsackie virus B3	Vero 76	2.12		56
Enterovirus-71	Vero76		0.76	48
Enterovirus-71	Vero76	2.32		48
Enterovirus-68	RD		0.92	52
Enterovirus-68	RD	2.28		52

Example 41: N4-hydroxycytidine Parainfluenza and RSV Activity

Virus	Cell Line	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
Parainfluenza virus 3	MA-104	212		272
Parainfluenza virus 3	MA-104	248		264
RSV	MA-104	14		>400
RSV	MA-104	27.6		>400

Example 42: Methods for Pharmacokinetic Studies in Cynomolgus Macaques

Eight cynomolgus macaques (4 males / 4 females) were dosed by oral gavage with a single dose of EIDD-1931 or a prodrug conjugate as shown in **Table 1**. One week washout periods were allowed between doses. Blood samples were collected after each dosing event at predose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 18 and 24 hrs post dose.

Table 1: Study design for pharmacokinetic evaluation of EIDD-1931 and 4 prodrug conjugates

Grp #	Compound	# Animals (M/F)	Dose level mmol/kg	Dose level (mg/Kg)	Feeding State
1	EIDD-1931	4/4	0.4	100	Fasted
2	EIDD-1931	4/4	0.4	100	Fed
3	EIDD-2800	4/4	0.4	180	Fed
4	EIDD-2801	4/4	0.4	130	Fed
5	EIDD-2776	4/4	0.4	175	Fed
6	EIDD-2898	4/4	0.4	160	Fed

Aliquots of Plasma were extracted with Acetonitrile that included $^{13}C_5$ EIDD-1931 as an Internal Standard. Samples were then vortexed and centrifuged in a Sorvall RT1 centrifuge (Thermo Fisher, Waltham, MA) at 3,500 RPM for 10 minutes. The supernatant was transferred to a microcentrifuge tube and centrifuged again in a Biofuge pico centrifuge (Heraeus, Hanau, Germany) for 10 minutes at 13,000 rpm. The remaining supernatant was then transferred to an HPLC vial for analysis.

LC-MS/MS conditions for EIDD-02898. HPLC separation was performed on an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA). An Atlantis HILIC Silica column, 50 x 4.6 mm, 5 µm particle size (Waters Corporation, Milford, MA, USA) was used for the separation of EIDD-1931, EIDD-2898 and $^{13}C_5$ EIDD-1931 (used as internal standard) with isocratic mode (70:30) with acetonitrile in 100 mM ammonium acetate buffer, pH 5.0 at a flow rate of 1.0 mL/min over 2 minutes. Mass Spectrometry analysis was performed on a QTrap 5500 Mass Spectrometer (AB Sciex, Farmingham, MA) using Positive Mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. An eight-point standard curve prepared in blank plasma covered concentrations range of 10 to 10,000 ng/mL. Separately prepared quality-control samples of 30, 500 and 5000 ng/mL in blank plasma were analyzed at the beginning of each sample set to ensure accuracy and precision within 20%. Calibration in each matrix showed linearity with an R^2 value of >0.99. Data analysis was performed using Analyst Software (AB Sciex, Farmingham).

LC-MS/MS conditions for EIDD-02800 and EIDD-02801. HPLC separation was performed on an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA). An Acclaim HILIC-1 Mixed Mode column, 150 x 4.6 mm, 5 µm particle size (Thermo Fisher, Waltham, MA) was used for the separation of EIDD-1931, EIDD-2800, EIDD-2801, and $^{13}C_5$ EIDD-1931 (used as internal standard) with isocratic mode (90:10) with acetonitrile in 100 mM

ammonium acetate buffer, pH 5.0 at a flow rate of 1.0 mL/min over 5 miminutes. Mass Spectrometry analysis was performed on a QTrap 5500 Mass Spectrometer (AB Sciex, Farmingham, MA) using Negative Mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. An eight-point standard curve prepared in blank plasma covered concentrations range of 10 to 10,000 ng/mL. Separately prepared quality-control samples of 30, 500 and 5000 ng/mL in blank plasma were analyzed at the beginning of each sample set to ensure accuracy and precision within 20%. Data analysis was performed using Analyst Software (AB Sciex, Farmingham).

Example 43: Parmacokinetic Parameters from Cynomolgus Macaques

As can be seen from Figures 11 through 15, these data show that after administration by oral gavage to cynomolgus macaques, the parent ribonucleoside is unexpectedly sequestered, largely unchanged, in the enterocytes of the gut. This results in the low apparent bioavailability of the compound in cynomolgus macaques. However, when administered via i.v. injection, the compound is widely distributed. As a result of these studies, it appears that EIDD-1931 has low bioavailability in cynomolgus monkeys as a result of inefficient transit/release from intestinal and stomach linings to circulating blood.

The low bioavailability of EIDD-1931 in cynomolgus macaques can be successfully addressed by utilizing chemically and/or enzymatically cleavable prodrug moieties that facilite the movement of EIDD-1931 across the gut wall into the circulating blood. Three prodrugs, EIDD-2800, EIDD-2801, and EIDD-2898, significantly improved the bioavailability if EIDD-1931 by 4 – 8 fold in cynomolgus macaques as can be seen from Figure 14 and 15.

Additional results are shown in **Tables 2** and **3**.

Table 2: Pharmacokinetic Parameters from Male Cynomolgus Macaques

Compound Dosed	t_{max} (h)	C_{max} (nmol/mL)	$AUC_{0->24h}$ (h·nmol/mL)	CL (L/h*kg)	$t_{1/2}$ (h)	F* (%)
EIDD-1931	0.75 ± 0.28	3.31 ± 1.82	5.75 ± 1.99	70.1 ± 18.7	1.2 ± 1.2	~ 3
EIDD-2800	0.37 ± 0.14	16.3 ± 13.2	38.9 ± 7.58	9.1 ± 1.3	5.5 ± 4.2	~ 27
EIDD-2801	2 ± 0.81	8.08 ± 1.32	31.7 ± 7.82	13 ± 3.7	1.8 ± 0.91	~ 22
EIDD-2898	2.3 ± 0.96	9.1 ± 2.7	26.1 ± 5.2	16.4 ± 3.1	0.53 ± 0.16	~ 18
EIDD-2776	5 ± 1.2	0.58 ± 0.21	2.6 ± 0.65	142 ± 37.3	0.97 ± 0.21	~ 2

Table 3: Pharmacokinetic Parameters from Female Cynomolgus Macaques

Compound Dosed	t_{max} (h)	C_{max} (nmol/mL)	$AUC_{0->24h}$ (h·nmol/mL)	CL (L/h*kg)	$t_{1/2}$ (h)	F (%)

EIDD-1931	0.87 ± 0.75	3.31 ± 1.99	7.21 ± 4.21	65.7 ± 31.6	0.78 ± 0.2	~ 3
EIDD-2800	0.31 ± 0.12	8.10 ± 5.06	27.4 ± 11.5	15.9 ± 7.7	4.4 ± 1.2	~ 16
EIDD-2801	1.25 ± 0.5	12.3 ± 2.33	43.8 ± 17.0	10.3 ± 5.6	1.9 ± 1.3	~ 26
EIDD-2898	1.3 ± 0.5	15.9 ± 8.1	26.9 ± 4.8	15.9 ± 3.2	0.55 ± 0.25	~ 15
EIDD-2776	3 ± 2.4	0.69 ± 0.26	3.3 ± 2.7	158 ± 85.5	1.2 ± 0.41	~ 2

Example 44: Methods for Pharmacokinetic Studies in Ferrets

EIDD-2801 and vehicle control were delivered via single oral gavage (P.O.). EIDD-2801 and vehicle control were delivered via oral gavage (P.O.) twice a day (BID). The first dose was at (-3 hrs) relative to virus challenge; the second dose at 0 hrs, and then every 12 hrs thereafter for 3.5 days; total 8 doses. The vehicle used consisted of 1% Methylcellulose in water (w/v). Female 6-8 month old outbred ferrets (*Mustela putorius furo*), acquired from Triple F Farms, weighing 0.8 – 1.0 kg, were used for PK and efficacy studies:

- *Pharmacokinetics*: 8 ferrets total (2 groups, 4 ferrets/group)
- *Efficacy testing*: Prophylactic dosing against A/Netherlands/602/2009 (H1N1) NL/09; $5x10^4$ $TCID_{50}$/animal intranasally – 12 ferrets total (3 groups, 4 ferrets/group)

Pharmacokinetic study: EIDD-2801 was administered as a suspension by oral gavage in 3.5 mL total volume, followed by catheter flushing with MIRACLEVET solution. Blood samples were collected from the anterior vena cava. At 72 hrs pre-dose, 0.5 mL of blood was collected from each animal. After dosing, blood samples (0.3 mL) were collected at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours in ice-cold Li Heparin tubes for plasma. Plasma was prepared within 1hr after blood collection and was stored for up to 12 hours on ice before being transferred to -80°C freezer. Samples were analyzed by LC/MS/MS.

Example 45: Parmacokinetic Parameters from Ferrets

Pharmacokinetic parameters for EIDD-1931 in ferrets after single doses of EIDD-2801.

Dose	C_{max}	AUC_{inf}	$t_{1/2}$
mg/kg	(nmol/mL)	(h·nmol/mL)	(h)
4	3.5 ± 1.5	13.2 ± 4.8	8.2 ± 1.7
20	15.4 ± 1.9	73 ± 32	4.7 ± 1.3
128	100 ± 22	322 ± 43	5.1 ± 0.8
512	209 ± 106	791 ± 391	4.2 ± 0.6

Example 46: Methods for Treatment with EIDD-2801 in a Ferret Model of Influenza Infection

A dose of $5x10^4$ $TCID_{50}$/animal of NL/09 was delivered intranasally in 0.2 ml (0.1 ml to each nare). Virus stocks were diluted in phosphate buffered saline (PBS). Ferrets were anaesthetized with a mixture of ketamine/dexmedetomidin prior to infection.

Endpoints: Fever, body weight, clinical signs (nasal discharge; activity levels; respiratory distress), and virus load in nasal lavages were assessed daily. Dosing commenced 3 hrs pre-infection, followed by dosing at 1 hr post-infection and then every 12 hrs until euthanasia of animals. Ferrets were sacrificed 3.5 days post-infection 12 hours post-last treatment dose, upper and lower respiratory tract tissue harvested separately, and a blood sample taken. Blood samples (0.3 mL) were collected, worked-up, and stored as described in the PK section above and analyzed for EIDD-1931 concentration. Virus load lower respiratory tissues was determined.
Dosing: EIDD-2801 was administered orally. The total gavage volume was 3.5 ml, followed by flushing of gavage catheters with 3.5 ml of MIRACLEVET.

Table 4. Study Design of EIDD-2801 Efficacy Finding with Influenza Challenge.

Exp	Grp	Virus	n	Sex	Compound	Total dose/Day	Dose Level	Dose Vol.	Treatment Regimen*
1	1	IAV (H1N1)	4	F	EIDD-2801	200 mg/kg/d	100 mg/kg BID	3.5 ml/kg	p.o. (bid), -3hr, +1 hr, and 6 doses every 12hrs PD; total 8 doses
1	2	IAV (H1N1)	4	F	EIDD-2801	1,000 mg/kg/d	500 mg/kg BID	3.5 ml/kg	p.o. (bid), -3hr, +1 hr, and 6 doses every 12hrs PD; total 8 doses
1	3	mock	4	F	Vehicle	0 mg/kg/d	0 mg/kg BID	3.5 ml/kg	p.o. (bid), -3hr, +1 hr, and 6 doses every 12hrs PD; total 8 doses

Example 47: Results of Treatment with EIDD-2801 in a Ferret Model of Influenza Infection

Results of EIDD-2801 treatment in a ferret model of influenza infection (A/California/07/2009 (H1N1)) can be found in Figure 16. Viral titers in nasal lavage samples

were greatly reduced with prophylaxis and 12 hour post infection treatment with EIDD-2801. Fever in ferrets was completely avoided with prohpylaxis and 12 hour post infection treatment with EIDD-2801. Even EIDD-2801 treatment at 24 hours post infection was able to rapidly reduce viral titers in nasal lavage samples as well as fever. Results of EIDD-2801 treatment in a ferret model of influenza infection (A/Wisconsin/67/2005 (H3N2)) can be found in Figure 17. Viral titers in nasal lavage, fever, and viral titers in turbinates was greatly reduced with EIDD-2801 (100mg/kg) treatment initiated 12 and 24 hours post infection. Even when the dose of EIDD-2801 was reduced from 100 mg/kg to 20 mg/kg and administered 24 hours post infection viral titers in nasal lavage and turbinates was greatly reduced.

Example 48: Methods for Pharmacokinetic Studies in Mice

ICR (CD-1), 7-8 weeks old mice were acclimated for ~1 week after receipt. The mice were weighed to ± 1 gram the day or morning before dosing to calculate dosing volumes. EIDD-2801 was completely dissolved in 5 mL of Solution A (PEG 400/Tween 80 (90%/10%)) with warming and vortexing and then was diluted with 5 mL of Solution B (30% Solutol/10% DMA). Mice were dosed p.o. There were 3 mice/group, to be sampled at 8 different time points: 0.25, 0.50, 1, 2, 3, 4, 8, and 24 hrs. Blood was collected at all 7 time points. Blood was obtained by retro-orbital bleeding under isoflurane anesthesia. Each mouse was sampled once (300 μL) and blood transferred immediately to Li heparin microtainers on ice water. The Li-Heparin tubes with blood were gently inverted 2 or 3 times to mix well; then placed in a rack in ice water until able to centrifuge (≤ 1 hour). Tubes were spun at ~ 2000 x g for 10 min in a refrigerated centrifuge to separate plasma from RBCs. Plasma was immediately transfered to Eppendorf tubes which were then placed in ice water. All samples were frozen on dry ice within ~1 hr. Samples were stored at -80 °C prior to analysis by LC/MS/MS.

Example 49: Methods for Pharmacokinetic Studies in Rats

Male Sprague Dawley (SD) rats, between 225-249 g in weight, were acclimated for at least two days before the experiment. The day before the experiment, the rats were weighed to determine average dosing volume of EIDD-2801. For dosing by oral gavage, EIDD-2801 was dissolved in 10% PEG 400, 2.5% Cremophor RH40 in water at 64 mg/mL and dosed at 5 mL/kg. Three rats were euthanized at each time by asphyxiation with carbon dioxide. Tissues and plasmas were collected 1, 2, 4, 6, 8, and 24 hours post-dose. One rat was dosed with the vehicle and euthanized by asphyxiation 6 hours post-dose. Plasma was collected from each animal by snipping the aorta to collect approximately 0.3 mL of whole blood into a lithium heparin tube. Blood was centrifuged at 2000 x g for 10 min at 5°C. Plasma was then transferred to a 1.5 mL micro-centrifuge tube and stored at -80°C until analysis. The Brain, Spleen, Lung, Kidney, Liver, and Heart were collected from each rat. Tissues were snap frozen in liquid nitrogen and

stored at -80°C. 30-70 mg pieces of frozen animal tissue were weighed in 2 mL reinforced tubes and the weights were recorded. Samples were homogenized in 70% Acetonitrile in water that included $^{13}C_5$-labelled-EIDD-1931 and $^{13}C_5$-labelled-EIDD-1931-TP as internal standards at 4°C using an Omni bead-ruptor (Omni International, Inc., Kennesaw, GA). Homogenates were transferred to 2 mL micro-centrifuge tubes and centrifuged for 5 minutes at 15,000 rpm in an Eppendorf 5415D centrifuge (Eppendorf, Hamburg, Germany) to remove large solids. The supernatant was then transferred to a new 2 mL micro-centrifuge tube and centrifuged again in an Eppendorf 5415D centrifuge for 10 minutes at 15,000 rpm to remove any remaining solids. The remaining supernatant was transferred to a LCMS vial and analyzed via LCMS-MS. Aliquots of rat plasma were extracted with acetonitrile that included $^{13}C_5$-labeled-EIDD-1931 as an Internal Standard. Samples were clarified by centrifugation in an Eppendorf 5415D centrifuge for 10 minutes at 15,000 rpm. The clarified supernatants were transferred to HPLC vials for analysis using qualified method BAM-106.

Samples were maintained at 4°C in a Leap Pal Autosampler (CTC Analytics AG, Zwingen, Switzerland). HPLC separation was performed on an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA) equipped with a column oven, UV lamp, and binary pump. For tissue samples, a SeQuant ZIC-pHILIC (100 x 4.6 mm, 5 µm) column (Merck Millipore, Burlington, MA, USA) was used for the separation of EIDD-1931, EIDD-2781, EIDD-2061, ATP, $^{13}C_5$-labelled-EIDD-1931, and $^{13}C_5$-labelled-EIDD-1931-TP. Mobile Phase A consisted of 25 mM ammonium bicarbonate buffer in HPLC grade water pH 9.8 and Mobile phase B consisted of pure Acetonitrile. An 8.5-minute isocratic HPLC method at 35% mobile phase A was performed to separate the analytes. Mass Spectrometry analysis was performed on a QTRAP 5500 Mass Spectrometer (AB Sciex, Framingham, MA, USA) using negative mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. An Acclaim Polar Advantage II (3.0 x 50 mm, 3 µm particle size) column (Thermo Fisher Scientific, Waltham, MA) was used for the analysis of EIDD-2801. Mobile phase A consisted of 100 mM Ammonium Formate buffer in HPLC grade water and mobile phase B consisted of pure acetonitrile. A gradient method was employed from 5-100% mobile phase B over 3 minutes. Mass Spectrometry analysis was performed on an QTRAP 5500 Mass Spectrometer (AB Sciex, Framingham, MA, USA) using positive mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. For plasma samples, a SeQuant ZIC-pHILIC (100 x 4.6 mm, 5 µm) column (Merck Millipore, Burlington, MA, USA) was used for the separation of EIDD-1931, EIDD-2801, and $^{13}C_5$-labelled-1931. Mobile Phase A consisted of 25 mM ammonium bicarbonate buffer in HPLC grade water pH 9.8 and Mobile phase B consisted of pure Acetonitrile. An 4.5-minute isocratic HPLC method at 35% mobile phase A was performed to

separate the analytes. Mass Spectrometry analysis was performed on a QTRAP 5500 Mass Spectrometer (AB Sciex, Framingham, MA, USA) using negative mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. Data analysis was performed using Analyst Software (AB Sciex, Framingham, MA, USA).

Example 50: Methods for Pharmacokinetic Studies in Dogs

Experimentally non-naïve dogs (from Marshall Biosciences) between the ages of 6.5 to 6.8 months, weighing between 7.1 to 7.95 kg were acclimated to their environment for at least three days prior to the first dosing event. Subsequent dosing events were executed after a 7-day washout period. Dogs were weighed at least once before each dose event to determine the dosing volume. EIDD-1931 was dissolved in sterile saline at 8 mg/mL for I.V. dosing. For oral dosing, EIDD-2801 was resuspended in 1% (v/v) methylcellulose in water at 6, 20, and 60 mg/mL. For I.V. dosing, dogs were dosed with a 1 mL/kg dose volume, and dogs dosed P.O. were dosed with a 5 mL/kg dose volume. Blood samples collected from dogs dosed by oral gavage were collected pre-dose, 0.25, 0.50, 1, 2, 3, 4, 8, 12, 18, and 24 hours post-dose. Blood samples collected from dogs dosed intravenously were collected pre-dose, 0.083, 0.25, 0.50, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. Blood samples were collected from the jugular and/or cephalic vein into lithium-heparin microtainer tubes, centrifuged at 2000 x g for 10 min at 5 °C, and the plasmas were transferred into fresh tubes and stored at -80°C before processing for quantitation by LC-MS/MS. 50 µL aliquots of dog plasma were extracted with 950 µL of acetonitrile that included $^{13}C_5$-labeled-EIDD-1931 as an Internal Standard. Samples were clarified by centrifugation at 20,000 x g at 4 °C for 5 min. The clarified supernatants were transferred to HPLC vials for analysis. Samples were maintained at 4 °C in a Leap Pal Autosampler (CTC Analytics AG, Zwingen, Switzerland). HPLC separation was performed on an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA) equipped with a column oven, UV lamp, and binary pump. A SeQuant ZIC-pHILIC (100 x 4.6 mm, 5 µm) column (Merck Millipore, Burlington, MA, USA) was used for the separation of EIDD-1931, EIDD-2801, and $^{13}C_5$-labeled-EIDD-1931. Mobile Phase A consisted of 25 mM Ammonium Bicarbonate buffer in HPLC grade Water pH 9.8 and Mobile phase B consisted of pure Acetonitrile. A 4-minute isocratic HPLC method at 35% mobile phase A was performed to separate the analytes. Mass Spectrometry analysis was performed on an QTRAP 5500 Mass Spectrometer (AB Sciex, Farmingham, MA, USA) using Negative Mode Electrospray Ionization (ESI) in Multiple Reaction Monitoring (MRM) Mode. Data analysis was performed using Analyst Software (AB Sciex, Farmingham, MA, USA). PK parameters are calculated using the Phoenix WinNonLin 6.4 (Build 6.4.0.768) Non-compartmental analysis tool (Certara, Princeton, NJ, USA). Bioavailability of EIDD-2801 is calculated by comparing the exposure (AUC-inf) of EIDD-1931

after EIDD-2801 oral dosing with the exposure of EIDD-1931 after intravenous dosing with EIDD-1931 using the formula below.

$$Oral\ Bioavailability = \frac{Dose_{I.V.}}{Dose_{P.O.}} \times \frac{AUC_{P.O.}}{AUC_{I.V.}}$$

Example 51: Plasma and Liver Microsome Stability for EIDD-2800, 2801, and 2898

Substrate	Species	Plasmat1/2 (min)	Liver Microsomes t1/2 (min)
EIDD-2800	Mouse	1	< 1
	Monkey	2	2
	Human	1	1
EIDD-2801	Mouse	1	2
	Rat	1	5
	Dog	192	1
	Monkey	24	1
	Human	63	73
EIDD-2898	Mouse	144	6
	Monkey	138	13
	Human	198	14

Example 52: Parmacokinetic Parameters from Mice

Plasma pharmacokinetic parameters for EIDD-1931 and EIDD-2898 in mice after single doses of EIDD-2898.

EIDD-2989 Dose	Analyte	t_{max}	C_{max}	AUC_{inf}	$t_{1/2}$
mg/kg		(h)	(nmol/mL)	(h·nmol/mL)	(h)
15	1931	0.25	11	10.2	2.9
	2898	0.08	23.1	8.23	0.34
225	1931	0.5	69.3	83.4	4.2
	2989	0.5	7.61	9.57	3.1
750	1931	0.5	71.3	228.9	5.2
	2989	0.25	7.3	21.9	6.7

Example 53: Parmacokinetic Parameters from Mice

Tissue pharmacokinetic parameters for EIDD-1931 and EIDD-2061 (EIDD-1931-5'-triphosphate) in mice after single doses of EIDD-2898.

EIDD-2898 Dose	Analyte	Spleen		Brain		Lung	
		$AUC_{0->t}$	C_{max}	$AUC_{0->t}$	C_{max}	$AUC_{0->t}$	C_{max}
mg/kg		(h·nmol/g)	(nmol/g)	(h·nmol/g)	(nmol/g)	(h·nmol/g)	(nmol/g)
225	1931	536.4	285.1	202.4	12.6	113.4	76.7
	2061	110.8	9.9	63.1	3.5	35.0	2.5
750	1931	1420.8	373.1	107.9	18.8	386.9	82.4
	2061	257.0	24.7	64.1	5.5	120.2	10.9

Example 54: Parmacokinetic Parameters from Mice

Plasma pharmacokinetic parameters for EIDD-1931 in mice after a single dose of EIDD-2800 (180 mg/kg). No EIDD-2800 (parent) was observed at any time point.

Analyte	t_{max}	C_{max}	AUC_{inf}	$t_{1/2}$
	(h)	(nmol/mL)	(h·nmol/mL)	(h)
EIDD-1931	0.5	11.4	42.5	1.86

Example 55: Parmacokinetic Parameters from Dogs

Plasma pharmacokinetic parameters for EIDD-1931 in dogs after a single dose of EIDD-2800 (140 mg/kg). No EIDD-2800 (parent) was observed at any time point.

Analyte	t_{max}	C_{max}	AUC_{inf}	$t_{1/2}$
	(h)	(nmol/mL)	(h·nmol/mL)	(h)
EIDD-1931	1.4 ± 0.5	112.8 ± 21.1	497.7 ± 40.4	4.8 ± 1

Example 56: Protocol for Evaluating EIDD-2801 in a Mouse Model of Intranasal VEEV Infection

CD-1 female mice 7-8 weeks old were used for this study. The Trinidad donkey strain of VEEV was originally obtained from Centers for Disease Control and was additionally passaged once on Vero cells to expand the virus and was titrated by a plaque assay. The residual inoculum used for the experiment was back titrated after the challenge to confirm the dose delivered. Mice were randomly assigned to groups of 10 animals. Virus challenge consisted of intranasal application of ~100 pfu of virus, corresponding to ~100 LD_{50}, in 25 µl volume of PBS split into two nostrils and delivered under ketamine-xylazine anesthesia. EIDD-2801 was administered PO by gavage feeding, twice a day for 6 days. The first treatment was administered 6 h post virus challenge and a follow-up treatment was then given every 12 hours (BID) starting 12 hours post infection (total 13 doses, 6 days of treatment). The inoculation virus was back-titrated after the challenge to confirm the dose.

Animals were dosed by gavage using a sterilized gavage needle. The virus titers in serum and brain were assayed using a standard double-overlay plaque assay where 0.1 ml volumes of serial dilutions of serum or brain homogenate were inoculated onto Vero cells cultured in 6-well plates. Plaques were counted ~48 hours after inoculation and titers calculated on the basis of mL of serum or gram of brain. The limit of detection of this assay was 100 plaques per mL or per gram. Animal survival were analyzed using a Log-rank (Mantel-Cox) test, a Logrank test for trend and Gehan-Breslow-Wilcox test for groups comparisons (all part of Prism 6, GraphPad Software, Inc.).

Example 57: Results of Dosing EIDD-2801 in a Mouse Model of Intranasal VEEV Infection

Mice infected with intranasal VEEV were treated with four different dose levels of EIDD-2801. Effect of treatment on survival can be found in Figure 18.

Example 58: Protocol for Evaluating Time of Treatment of EIDD-2801 in a Mouse Model of Intranasal VEEV Infection

ICR female mice 7-8 weeks old were used for this study. The Trinidad donkey strain of VEEV was passaged once on Vero cells to expand the virus and was titrated by a plaque assay. The residual inoculum used for the experiment was back titrated after the challenge to confirm the dose delivered. Mice were randomly assigned to groups of 10 animals. Virus challenge consisted of intranasal application of ~100 pfu of virus, corresponding to ~100 LD_{50}, in 25 µl volume of PBS split into two nostrils and delivered under ketamine-xylazine anesthesia. EIDD-2801 was administered PO by gavage feeding. The treatments were initiated either at 6, 24, 48 or 72 hrs post-infection, and were continued twice a day (every 12 hours; BID) for 6 days regardless of the start time. The vehicle control group (Group 6) was treated the same way with the vehicle only (10% PEG-400, 2.5% Cremophor RH 40 in water). The virus titers in serum and brain were assayed using a standard double-overlay plaque assay where 0.1 ml volumes of serial dilutions of serum or brain homogenate were inoculated onto Vero cells cultured in 6-well plates. Plaques were counted ~48 hours after inoculation and titers calculated on the basis of mL of serum or gram of brain. The limit of detection of this assay was 100 plaques per mL or per gram. Animal survival were analyzed using a Log-rank (Mantel-Cox) test for groups' comparison (Prism 6, GraphPad Software, Inc.).

Example 59: Results of Time of Treatment Dosing with EIDD-2801 in a Mouse Model of Intranasal VEEV Infection

Mice infected with intranasal VEEV were treated with EIDD-2801 (600 mg/kg). Effect of delay in treatment initiation on survival can be found in Figure 19.

Example 60: Protocol for Evaluating EIDD-2801 Prophylactic Treatment in a Mouse Model of SARS Infection

Female and male 20 week old C57BL/6J mice were used after a five day or greater acclimation period in BSL3. For each sex, animals were randomly assigned to treatment groups and individually marked with ear punches. The virus stock utilized for these studies was derived from the infectious clone of the mouse adapted SARS-CoV MA15 (MA15) strain. After electroporation of Vero E6 cells with viral genomic RNA from SARS MA15, supernatant was harvested when the monolayer exhibited >80% CPE. The resultant stock was passaged twice on Vero E6 cells to generate a working stock with a titer of $6.3x10^7$ pfu/ml.

The large left lung lobe of each mouse was harvested into a 2ml screw cap tube containing glass beads and 1ml PBS. This sample was frozen at -80°C until the plaque assay was performed. 24hr prior to performing the plaque assay, 6-well plates of Vero E6 cells were seeded at 500,000 cells/well/2ml. Cells were incubated at 37°C in 5% CO_2 for 24hr. On the day of the assay, lungs were homogenized using a Roche Magnalyzer, lung homogenates were clarified via centrifugation at >10,000 x g, serially diluted in PBS, added to monolayers of Vero E6 cells, and incubated at 37°C with 5% CO_2 for 1hr after which cells were overlayed with medium containing 0.8% agarose. Two days later, monolayers were stained with neutral red viability stain to aid in plaque visualization. The numbers of plaques per virus diluted were enumerated to generate the plaque forming units per lung lobe (pfu/lobe).

Equivalent numbers of male and female 20-25 week old SPF C57BL/6J (Stock 000664 Jackson Labs) were used for these studies. Mice were randomly assigned to each treatment group. Groups to be infected with SARS-CoV were comprised of 10 mice (5 male/5 female). To control for potential effects associated with oral dosing on animal weight or pulmonary function, as well as the effect of the tested compound, two smaller "sham" infected groups will also be included (n = 6, 3 males and 3 females each). EIDD-2801 or vehicle control was delivered via oral gavage (P.O.) twice a day (BID). The first dose was initiated at -2 hr relative to virus challenge; the second dose was at 12 hpi, and then every 12 hrs thereafter for 5 days; total 10 doses. Mice were anaesthetized with a mixture of ketamine/xylazine prior to intranasal infection with a dose of $1x10^4$ plaque forming units (PFU) of SARS-CoV MA15 strain in 0.05ml diluted in PBS at time 0hpi. All mice were weighed daily, and a subset of mice were assayed by whole body plethysmography (4 mice 2 males and 2 females per treatment group) to determine pulmonary function daily for 5 days post infection. Following sacrifice at Day 5 post infection, lungs were assessed for lung hemorrhage score. Tissue was then removed for virus lung titer and pathology. The large left lobe was harvested for virus lung titer and the lower right lobe was harvested for pathology. *Whole body plethysmography:* Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.). Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes.

Statistical analysis: All statistical data analysis was performed in Graphpad Prism 7. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. For percent starting weight and whole body plethysmography, we performed a two-way ANOVA and Dunnet's multiple comparison test. For lung hemorrhage and virus lung titer, we performed a one-way ANOVA with a Kruskall-Wallace multiple comparison test.

Example 61: Results of Prophylactic Dosing with EIDD-2801 in a Mouse Model of SARS Infection

Mice infected with SARS were treated prophylactically with EIDD-2801. Effect of treatment on lung viral titers can be found in Figure 20.

Example 62: Protocol for Evaluating EIDD-2801 Time of Treatment in a Mouse Model of SARS Infection

Femal and male 25-29 week old C57BL/6J mice were used after a five day or greater acclimation period in BSL3. For each sex, animals were randomly assigned to treatment groups and individually marked with ear punches. The virus stock utilized for these studies was derived from the infectious clone of the mouse adapted SARS-CoV MA15 (MA15) strain that was generated in the Baric laboratory. After electroporation of Vero E6 cells with viral genomic RNA from SARS MA15, supernatant was harvest when the monolayer exhibited >80% CPE. The resultant stock was passaged twice on Vero E6 cells to generate a working stock with a titer of $6.3x10^7$ pfu/ml. The lower right lung lobe of each mouse was harvested into a 2ml screw cap tube containing glass beads and 1ml PBS. This sample was frozen at -80°C until the plaque assay was performed. 24hr prior to performing the plaque assay, 6-well plates of Vero E6 cells were seeded at 500,000 cells/well/2ml. Cells were incubated at 37°C in 5% CO_2 for 24hr. On the day of the assay, lungs were homogenized using a Roche Magnalyzer, lung homogenates were clarified via centrifugation at >10,000 x g, serially diluted in PBS, added to monolayers of Vero E6 cells, and incubated at 37°C with 5% CO_2 for 1hr after which cells were overlayed with medium containing 0.8% agarose. Two days later, monolayers were stained with neutral red viability stain to aid in plaque visualization. The numbers of plaques per virus diluted were enumerated to generate the plaque forming units per lung lobe (pfu/lobe). Equivalent numbers of male and female 25-29 week old SPF C57BL/6J were used for these studies. Mice were randomly assigned to each treatment group. Groups to be infected with SARS-CoV were comprised of 10 mice (5 male/5 female). EIDD-2801 or vehicle control was delivered via oral gavage (P.O.) twice a day (BID). We initiated dosing at -2hr, +12hr, +24hr or +48hr relative to virus challenge. Mice were anaesthetized with a mixture of ketamine/xylazine prior to intranasal infection with a dose of $1x10^4$ plaque forming units (PFU) of SARS-CoV MA15 strain in 0.05ml diluted in PBS at time 0hpi. All mice were weighed daily, and a subset of mice were assayed by whole body plethysmography (4 females per treatment group) daily to determine pulmonary function. Following sacrifice at 5dpi, lungs were assessed for lung hemorrhage score. Tissue was then removed for virus lung titer and pathology. The large left lobe was harvested for pathology and the lower left lobe was harvested for virus titer. Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.).

Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes. All statistical data analysis was performed in Graphpad Prism 7. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. For percent starting weight and whole body plethysmography, we performed a two-way ANOVA and Dunnet's multiple comparison test. For lung hemorrhage and virus lung titer, we performed a one-way ANOVA with a Kruskall-Wallace multiple comparison test.

Example 63: Results of Therapeutic Dosing with EIDD-2801 in a Mouse Model of SARS Infection

Mice infected with SARS were treated with EIDD-2801. Effect of treatment on lung hemhorrage scores and lung viral titers can be found in Figures 21 and 22, respectively.

Example 64: Protocol for Evaluating EIDD-2801 Therapeutic Treatment in a Mouse Model of MERS Infection

Female and male 10-11 week old C57BL/6J 288/330 DPP4 mice created and bred by the Baric Laboratory were used after a five day or greater acclimation period in BSL3. For each sex, animals were randomly assigned to treatment groups and individually marked with ear punches. The virus stock utilized for these studies was derived from a plaque purified isolate of the mouse adapted MERS-CoV p35C4 (MERS) strain that was generated in the Baric laboratory. After plaque purification, virus was passaged twice on Vero CC81 cells. The resultant stock titer was of $1.1x10^8$ pfu/ml. The lower right lung lobe of each mouse was harvested into a 2ml screw cap tube containing glass beads and 1ml PBS. This sample was frozen at -80°C until the plaque assay was performed. 24hr prior to performing the plaque assay, 6-well plates of Vero CC81 cells were seeded at 500,000 cells/well/2ml. Cells were incubated at 37°C in 5% CO_2 for 24hr. On the day of the assay, lungs were homogenized using a Roche Magnalyzer, lung homogenates were clarified via centrifugation at >10,000 x g, serially diluted in PBS, added to monolayers of Vero CC81 cells, and incubated at 37°C with 5% CO_2 for 1hr after which cells were overlayed with medium containing 0.8% agarose. Three days later, monolayers were stained with neutral red viability stain to aid in plaque visualization. The number of plaques per virus diluted were enumerated to generate the plaque forming units per lung lobe (pfu/lobe). Equivalent numbers of 10-11 week old C57BL/6J 288/330 DPP4 mice were randomly assigned to each treatment group for these studies. Each group was comprised of 10 mice (5 male/5 female). EIDD-2801 or vehicle control was delivered via oral gavage (P.O.) twice a day (BID) beginning at -2hr and then every 12hr thereafter. Mice were anaesthetized with a mixture of ketamine/xylazine prior to intranasal infection with a dose of $5x10^4$ plaque forming units (PFU) of MERS strain in 0.05ml

diluted in PBS at time 0hpi. All mice were weighed daily, and a subset of mice were assayed by whole body plethysmography (4 females per treatment group) daily to determine pulmonary function. Following sacrifice at 5dpi, lungs were assessed for lung hemorrhage score. Tissue was then removed for virus lung titer and pathology. The large left lobe was harvested for pathology and the lower left lobe was harvested for virus titer. Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.). Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes.

All statistical data analysis was performed in Graphpad Prism 7. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. For percent starting weight and whole-body plethysmography, we performed a two-way ANOVA and Dunnet's multiple comparison test. For lung hemorrhage, we performed a one-way ANOVA with a Kruskall-Wallace multiple comparison test.

Example 65: Results of Therapeutic Dosing with EIDD-2801 in a Mouse Model of MERS Infection

Mice infected with MERS were treated with EIDD-2801. Effect of treatment on lung hemhorrage scores can be found in Figures 23.

Example 66: Method for Evaluating Cell Uptake and Metabolism of EIDD-2801 in Vero Cells

Three 24-well plates were plated with primary vero cells at a seeding density of 0.350 x 10^6/mL viable cells per well. The plates were incubated at 37°/5% CO_2 overnight to allow the cells to attach. A 40 mM solution of EIDD-2801 in 100% DMSO was prepared. From the 40 mM stock solution, a 20 µM solution of EIDD-2801 was preapred in 25 ml of complete DMEM media. For compound treatment plates, the media was aspirated and 1.0 mL of 20 µM EIDD-2801 in complete DMEM media was added to the appropriate wells. A separate plate of cells was prepared with no compound added. The plates were then incubated at 37°/5% CO_2 for the following time points: 1, 2, 3, 4, 6, 16 and 24 hours. The non-treated plate was sampled at 0 hrs. After incubation at the desired time points, cells were washed 2X with 1.0 mL of DPBS. Cells were extracted by adding 500 ul of 70% Acetonitrile/30% water spiked with the internal standard to each well treated with EIDD-2801. The non-treated blank plate was extracted with 500 ul of 70% Acetonitrile/30% water per well. The samples were pipetted up and down several times. The samples were transfered to labeled microcentrifuge tubes. The samples were centrifuged at 16,000 x g for 10 minutes at 4°C. 300 ul of supernatant was transferred to labeled

HPLC vials, and the samples were stored at -80°C or submitted to the BCDMPK group for LC-MS/MS analysis.

Example 67: Results for the Cell Uptake and Metabolism of EIDD-2801 in Vero Cells

Analyte	C_{max}	t_{max}	$AUC_{0->t}$
Analyte	(pmol/M Cells)	(h)	(pmol·h/M cells)
EIDD-1931 (Nuc)	13.5	24	228.6
EIDD-2061 (TP)	872.0	16	13850
EIDD-2801 (Parent)	121.2	3	1724

Example 68: Method for Evaluating Cell Uptake and Metabolism of EIDD-2801 in Huh-7 Cells

Four 24-well plates were plated with Huh-7 cells at a seeding density of 0.35 x 10^6/mL viable cells per well. The plates were incubated at 37°/5% CO_2 overnight to allow the cells to attach. A 40 mM stock solution of EIDD-2801 was prepared in 100% DMSO. From the 40 mM solution, a 20 µM solution of EIDD-2801 in 25 ml of complete DMEM media was prepared by pipetting 12.5 µL of EIDD-2801 into the media. For compound treatment plates, the media was aspirated and 1.0 mL of 20 µM EIDD-2801 solution in complete DMEM media was added to the appropriate wells. A separate plate of cells had no compound added and was aspirated and replaced with media without compound. The plates were incubated at 37°/5% CO2 for the following time points: 1, 2, 3, 4, 6, 16 and 24 hours. A non-treated plate was 0 hrs sample. After incubation at the desired time points, cells were washed 2X with 1.0 mL of DPBS. Cells were extracted by adding 500 ul of 70% acetonitrile/30% water spiked with the internal standard to each well treated with EIDD-2801. The non-treated blank plate was extracted with 500 ul of 70% acetonitrile/30% water per well without an internal standard. The samples were pipetted up and down several times. The samples were transfered to labeled microcentrifuge tubes. The samples were centrifuged at 16,000 x g for 10 minutes at 4°C. 350 ul of supernatant was transfered to labeled 5 mL tubes or if samples were not being dried down put in labeled HPLC vials. Samples were stored at -80°C or submitted to the BCDMPK group for LC-MS/MS analysis.

Example 69: Results for the Cell Uptake and Metabolism of EIDD-2801 in Huh-7 Cells

Analyte	C_{max}	t_{max}	$AUC_{0->t}$
Analyte	(pmol/M Cells)	(h)	(pmol·h/M cells)
EIDD-1931 (Nuc)	29.0	24	449.2
EIDD-2061 (TP)	1113.3	24	14640
EIDD-2801 (Parent)	77.5	2	1025

Example 70: Method for Evaluating Cell Uptake and Metabolism of EIDD-2801 in HepG2 Cells

Three 24-well plates were plated with primary vero cells at a seeding density of 0.350 x 10^6/mL viable cells per well. The plates were incubated at 37°/5% CO_2 overnight to allow the cells to attach. A 40 mM stock solution of EIDD-2801 in 100% DMSO was prepared. From the 40 mM solution, a 20 µM solution of EIDD-2801 was preapred in 25 ml of complete RPMI media. For compound treatment plates, the media was aspirated and 1.0 mL of 20 µM EIDD-2801 in complete RPMI media was added to the appropriate wells. A separate plate of cells was prepared with no compound added. The plates were then incubated at 37°/5% CO_2 for the following time points: 1, 2, 3, 4, 6, 16 and 24 hours. The non-treated plate was sampled at 0 hrs. After incubation at the desired time points, cells were washed 2X with 1.0 mL of DPBS. Cells were extracted by adding 500 ul of 70% Acetonitrile/30% water spiked with the internal standard to each well treated with EIDD-2801. The non-treated blank plate was extracted with 500 ul of 70% Acetonitrile/30% water per well. The samples were pipetted up and down several times. The samples were transfered to labeled microcentrifuge tubes. The samples were centrifuged at 16,000 x g for 10 minutes at 4°C. 300 ul of supernatant was transferred to labeled HPLC vials, and the samples were stored at -80°C or submitted to the BCDMPK group for LC-MS/MS analysis.

Example 71: Results for the Cell Uptake and Metabolism of EIDD-2801 in HepG2 Cells

Analyte	C_{max}	t_{max}	$AUC_{0->t}$
	(pmol/M Cells)	(h)	(pmol·h/M cells)
EIDD-1931 (Nuc)	13.4	16	249.8
EIDD-2061 (TP)	470.3	16	299.8
EIDD-2801 (Parent)	18.9	3	360.3

Example 72: Method for Evaluating Cell Uptake and Metabolism of EIDD-2801 in CEM Cells

Three 24-well plates were plated with primary vero cells at a seeding density of 2 x 10^6/mL viable cells per well. The plates were incubated at 37°/5% CO_2 overnight to allow the cells to attach. A 40 mM stock solution of EIDD-2801 in 100% DMSO was prepared. From the 40 mM solution, a 40 µM solution of EIDD-2801 was preapred in 25 ml of complete RPMI media. For compound treatment plates, the media was aspirated and 1.0 mL of 40 µM EIDD-2801 in complete RPMI media was added to the appropriate wells. A separate plate of cells was prepared with no compound added. The plates were then incubated at 37°/5% CO_2 for the

following time points: 1, 2, 3, 4, 6, 16 and 24 hours. The non-treated plate was sampled at 0 hrs. After incubation at the desired time points, cells were washed 2X with 1.0 mL of DPBS. Cells were extracted by adding 500 ul of 70% Acetonitrile/30% water spiked with the internal standard to each well treated with EIDD-2801. The non-treated blank plate was extracted with 500 ul of 70% Acetonitrile/30% water per well. The samples were pipetted up and down several times. The samples were transfered to labeled microcentrifuge tubes. The samples were centrifuged at 16,000 x g for 10 minutes at 4°C. 300 ul of supernatant was transferred to labeled HPLC vials, and the samples were stored at -80°C or submitted to the BCDMPK group for LC-MS/MS analysis.

Example 73: Results for the Cell Uptake and Metabolism of EIDD-2801 in CEM Cells

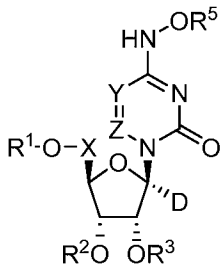
Analyte	C_{max}	t_{max}	$AUC_{0->t}$
	(pmol/M Cells)	(h)	(pmol·h/M cells)
EIDD-1931 (Nuc)	0.3	3	5.8
EIDD-2061 (TP)	171.3	24	2355
EIDD-2801 (Parent)	5.4	4	85.3

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula I,



Formula I

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

Y is N or CR';

Z is N or CR";

R' is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R" is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H, optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

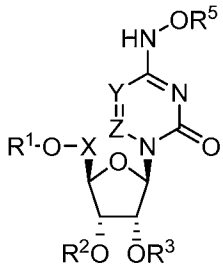
hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

2. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula II,



Formula II

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

Y is N or CR';

Z is N or CR";

R' is deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R" is hydrogen, deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H, optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and

BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

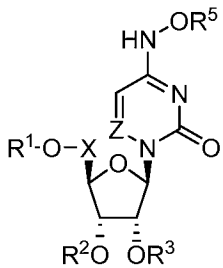
with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

3. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula III,



Formula III

or a pharmaceutical or physiological salt thereof, wherein

X is CH_2, $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

Z is N or CR";

R" is deuterium, halogen, hydroxyl, amino, thiol, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, heterocarbocyclyl, cycloalkyl, heterocyclyl, hydroxyl, thiol, or carbonyl, wherein R' is optionally substituted with one or more, the same or different, R^{10};

R^1, R^2, R^3, and R^5 are each independently selected from H, optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

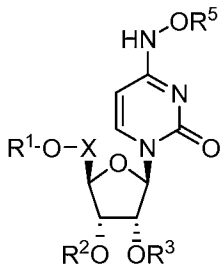
with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

4. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula IV,



Formula IV

or a pharmaceutical or physiological salt thereof, wherein

X is $CHCH_3$, $C(CH_3)_2$, CHF, CF_2, or CD_2;

R^1, R^2, R^3, and R^5 are each independently selected from H, optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

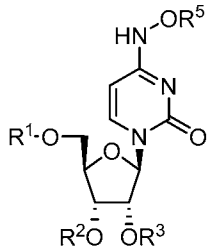
with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

5. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula V,



Formula V

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, R^3, and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

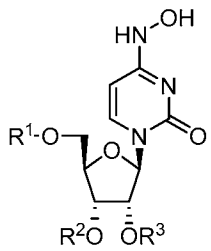
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

6. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula VI,



Formula VI

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^3 are each independently selected from the following: optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal,

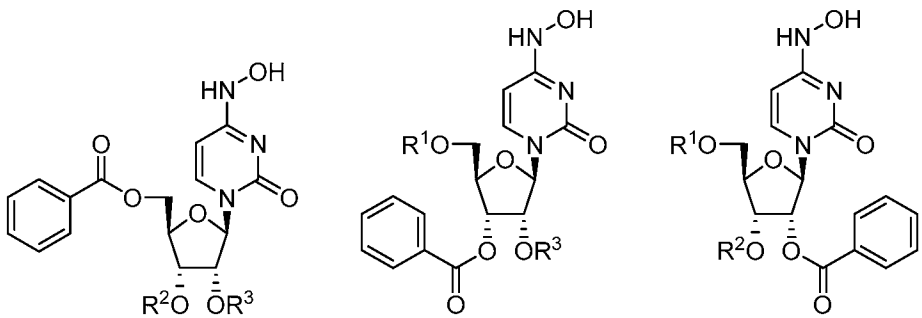
optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

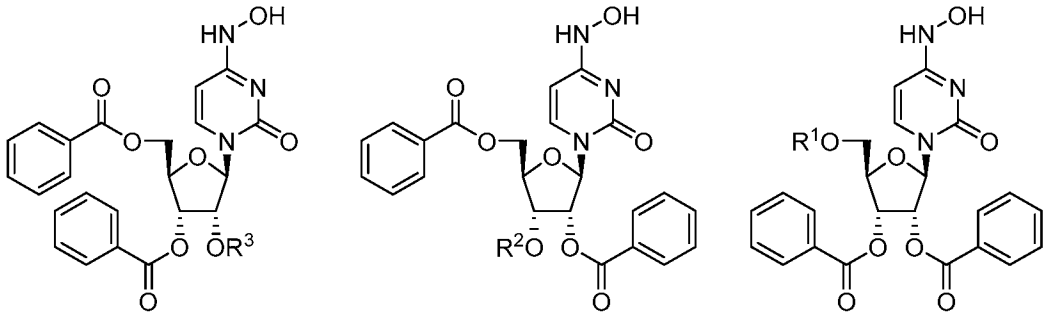
R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

7. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula VIa-f,



Formula VIa **Formula VIb** **Formula VIc**



Formula VId **Formula VIe** **Formula VIf**

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^3 are each independently selected from the following: optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^3 are optionally substituted with one or more, the same or different, R^{10};

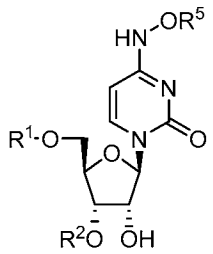
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio,

heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula VII,



Formula VII

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^2, and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally

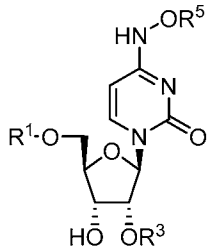
substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^2, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

9. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula VIII,



Formula VIII

or a pharmaceutical or physiological salt thereof, wherein

R^1, R^3, and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

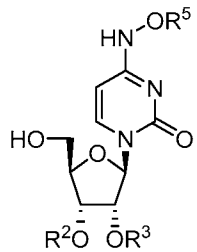
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

10. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula IX,



Formula IX

or a pharmaceutical or physiological salt thereof, wherein

R^2, R^3, and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally

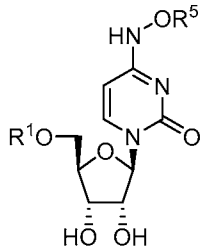
susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2, R^3, and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

11. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula X,



Formula X

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^5 are optionally substituted with one or more, the same or different, R^{10};

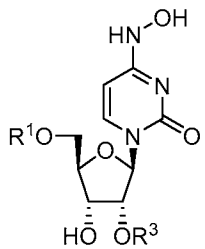
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

12. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XI,



Formula XI

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^3 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

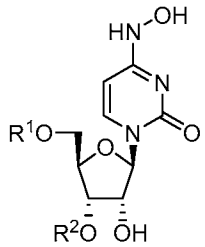
hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^3 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

13. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XII,



Formula XII

or a pharmaceutical or physiological salt thereof, wherein

R^1 and R^2 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 and R^2 are optionally substituted with one or more, the same or different, R^{10};

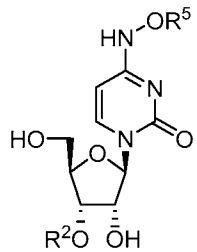
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

14. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XIII,



Formula XIII

or a pharmaceutical or physiological salt thereof, wherein

R^2 and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

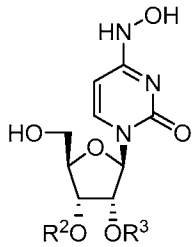
hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

15. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XIV,



Formula XIV

or a pharmaceutical or physiological salt thereof, wherein

R^2 and R^3 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 and R^3 are optionally substituted with one or more, the same or different, R^{10};

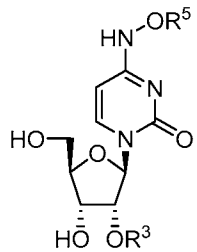
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

16. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XV,



Formula XV

or a pharmaceutical or physiological salt thereof, wherein

R^3 and R^5 are each independently selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted

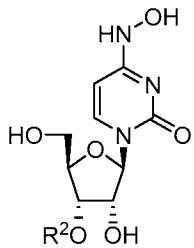
hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^3 and R^5 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

17. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XVI,



Formula XVI

or a pharmaceutical or physiological salt thereof, wherein

R^2 is selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^2 are optionally substituted with one or more, the same or different, R^{10};

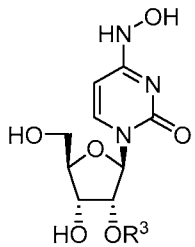
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino,

heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

18. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XVII,



Formula XVII

or a pharmaceutical or physiological salt thereof, wherein

R^3 is selected from the following: optionally substituted esters, optionally substituted branched esters, optionally substituted carbonates, optionally substituted carbamates, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and

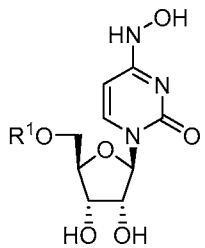
BAB-esters, wherein R^3 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

19. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XVIII,



Formula XVIII

or a pharmaceutical or physiological salt thereof, wherein

R^1 is selected from the following: optionally substituted branched esters, optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted

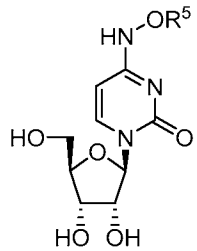
dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^1 are optionally substituted with one or more, the same or different, R^{10};

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

20. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula XIX,



Formula XIX

or a pharmaceutical or physiological salt thereof, wherein

R^5 is selected from the following: optionally substituted thioesters, optionally substituted branched thioesters, optionally substituted thiocarbonates, optionally substituted S-thiocarbonate, optionally substituted dithiocarbonates, optionally substituted thiocarbamates, optionally substituted oxymethoxycarbonyl, optionally substituted oxymethoxythiocarbonyl, optionally substituted oxymethylcarbonyl, optionally substituted oxymethylthiocarbonyl, L-amino acid esters, D-amino acid esters, N-substituted L-amino acid esters, N,N-disubstituted L-amino acid esters, N-substituted D-amino acid esters, N,N-disubstituted D-amino acid esters, optionally substituted sulfenyl, optionally substituted imidate, optionally substituted hydrazonate, optionally substituted oximyl, optionally substituted imidinyl, optionally substituted imidyl, optionally substituted aminal, optionally susbstituted hemiaminal, optionally substituted acetal, optionally susbstituted hemiacetal, optionally substituted carbonimidate, optionally substituted thiocarbonimidate, optionally substituted carbonimidyl, optionally substituted carbamimidate, optionally substituted carbamimidyl, optionally substituted thioacetal, optionally substituted S-acyl-2-thioethyl, optionally substituted bis-(acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, and BAB-esters, wherein R^5 are optionally substituted with one or more, the same or different, R^{10};

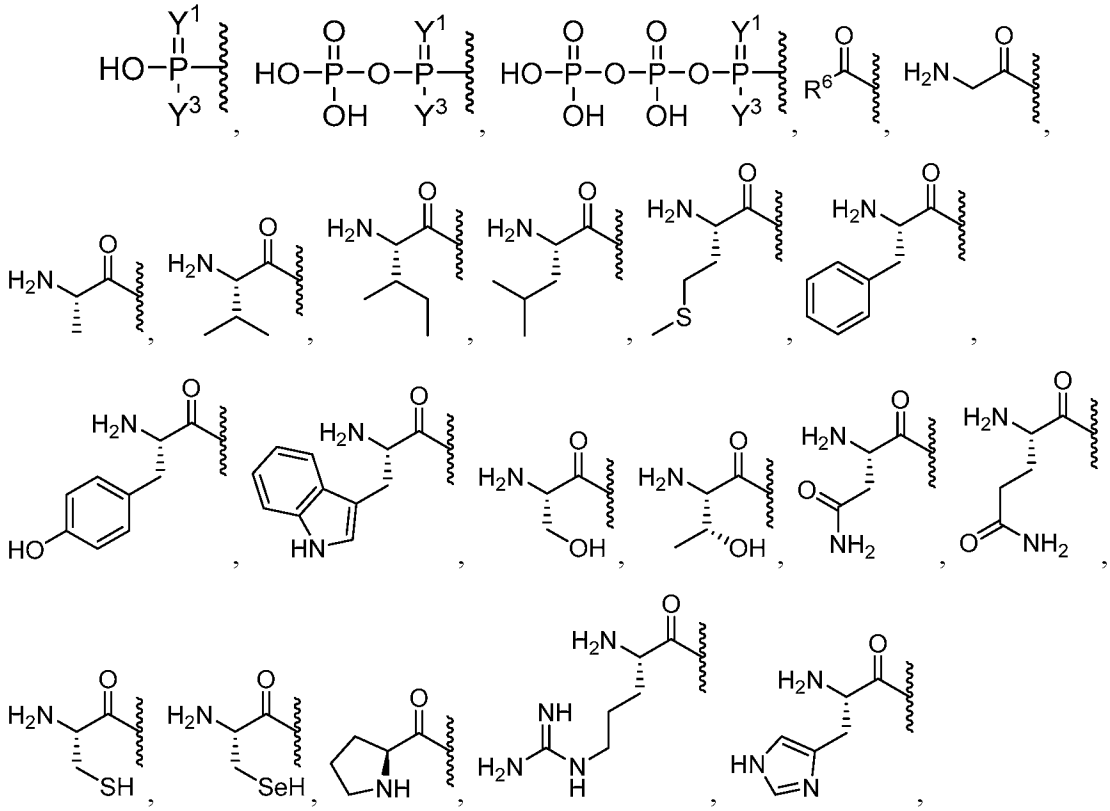
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

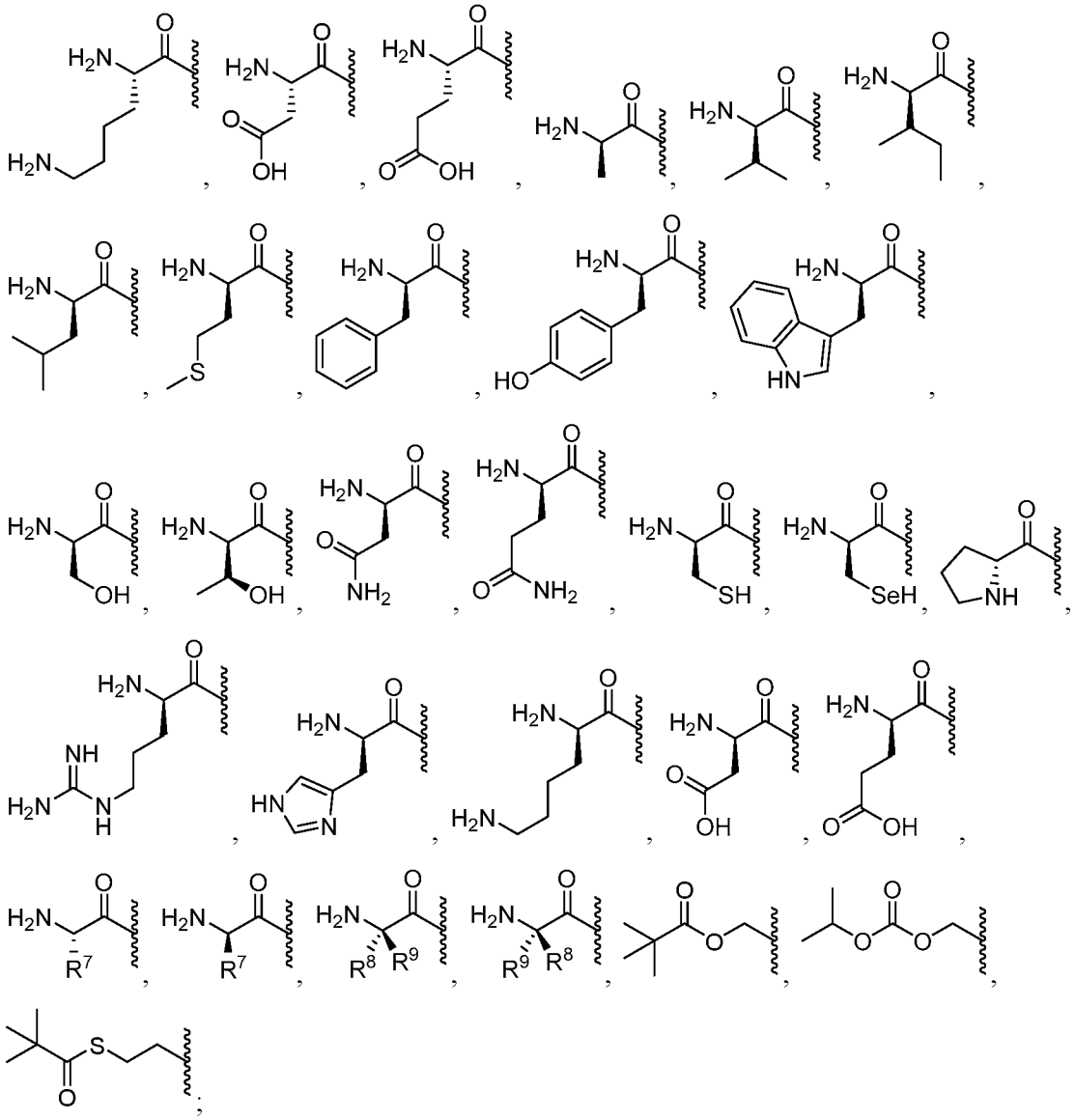
lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

21. A pharmaceutical composition of claim 1 wherein R^1, R^2, R^3, and R^5 are each independently selected from H,





Y^1 is O or S;

Y^3 is OH or $BH_3^-M^+$;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

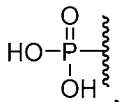
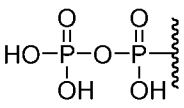
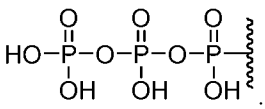
R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino,

heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

22. A pharmaceutical composition of claim 21 wherein R^1 is hydrogen, , , .

23. A pharmaceutical composition of claim 1 wherein R' is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

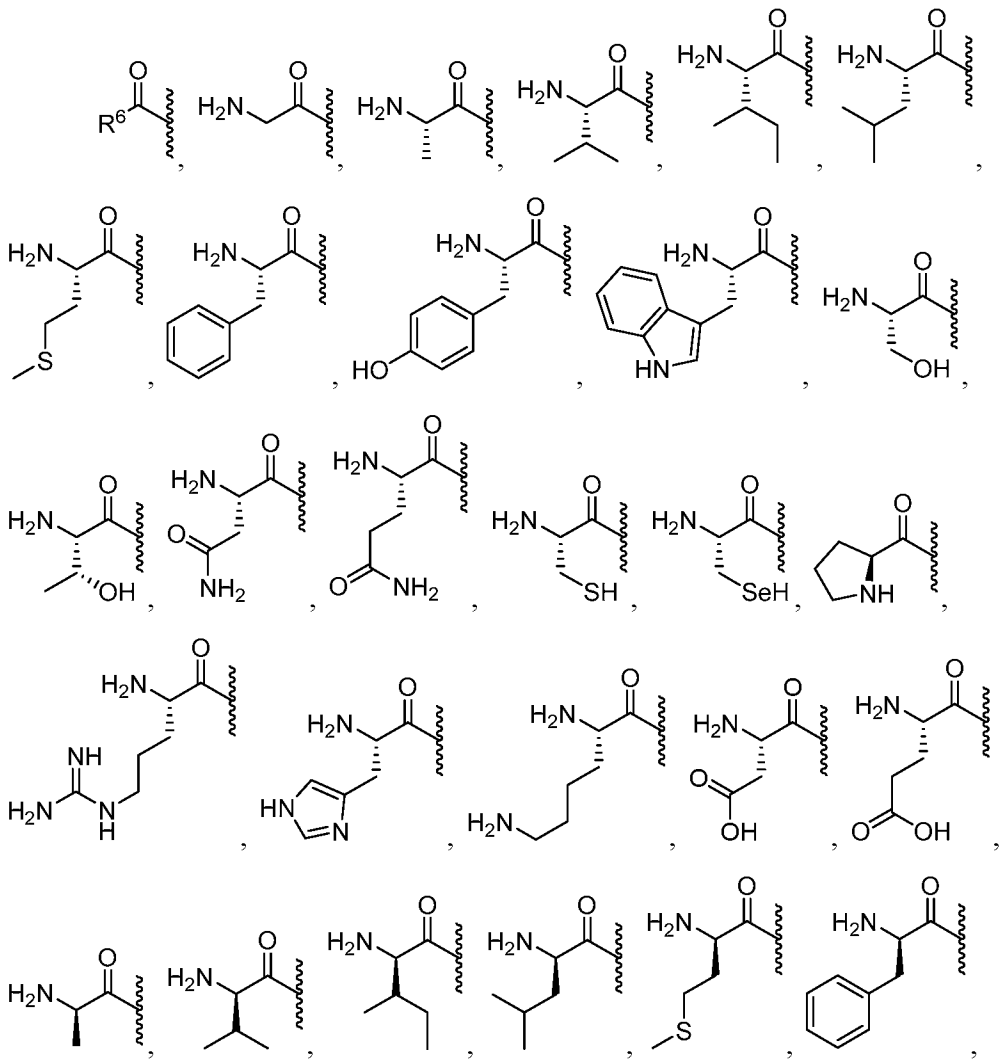
24. A pharmaceutical composition of claim 1 wherein R" is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

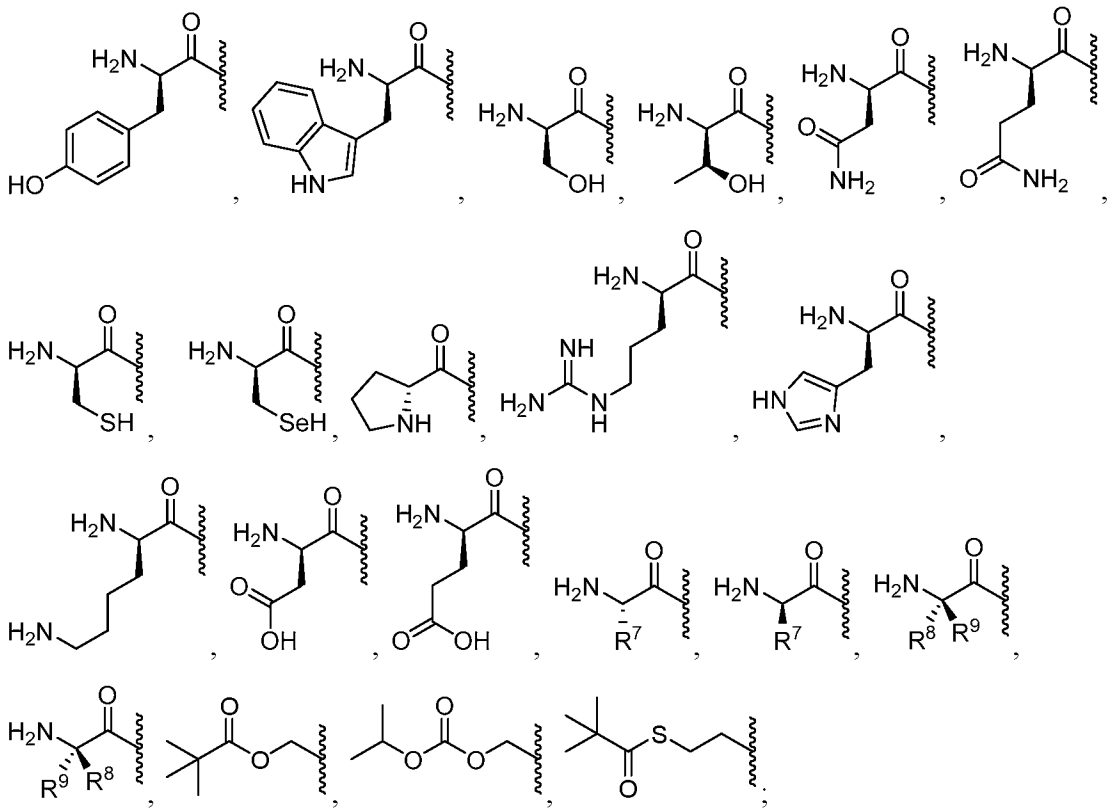
25. A pharmaceutical composition of claim 2, wherein R' is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

26. A pharmaceutical composition of claim 2, wherein R" is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

27. A pharmaceutical composition of claim 3, wherein R" is methyl, fluoro, hydroxymethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, thiomethyl, carboxylic acid, formyl, vinyl, or ethynyl.

28. A pharmaceutical composition of any one of claims 2-5, or 8-17, wherein R^1, R^2, R^3, and R^5 are each independently selected from H,





with the proviso that R^1, R^2, R^3, and R^5 are not all H;

R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

R^8 and R^9 can form a ring with the α-carbon which they are attached;

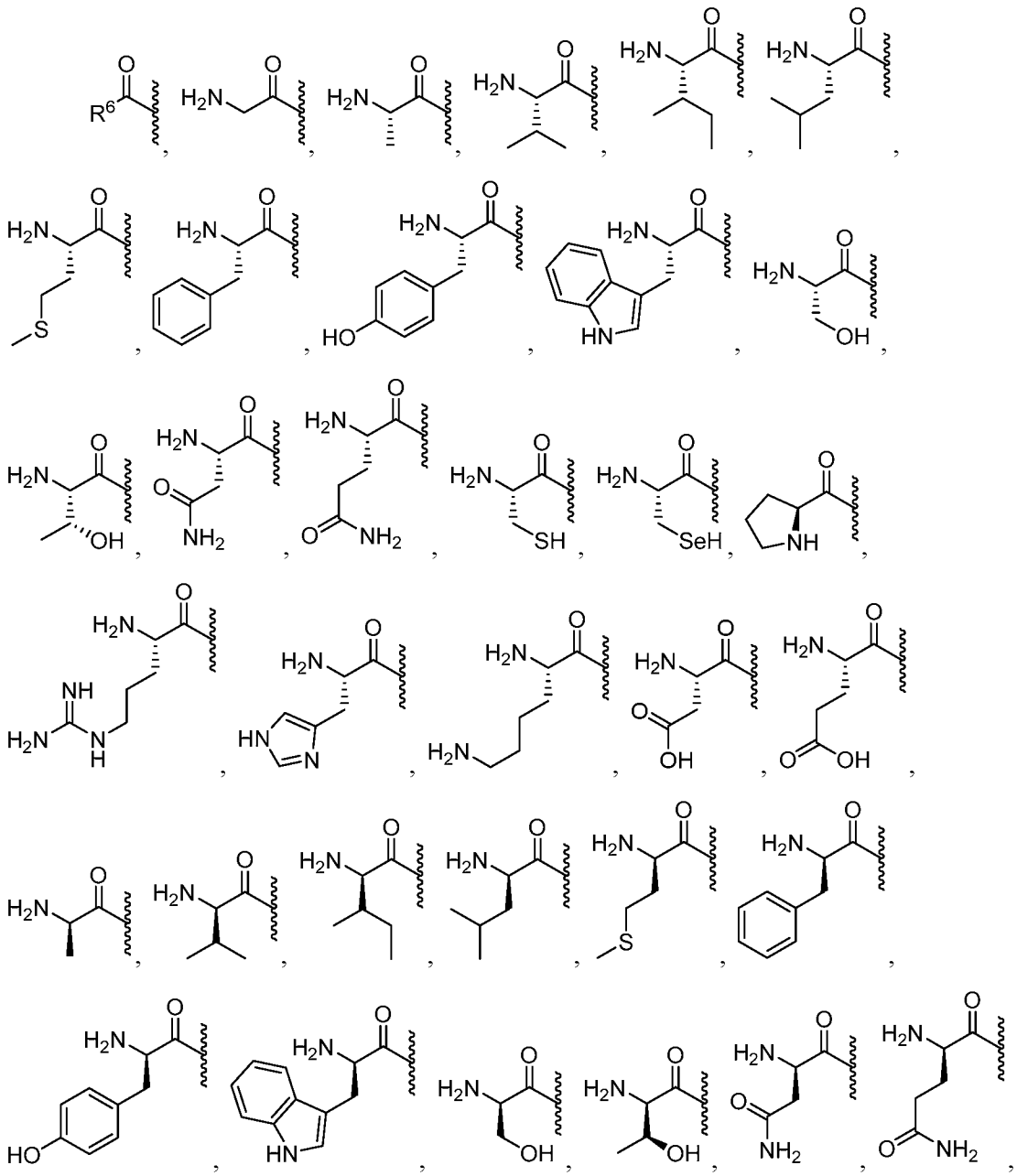
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

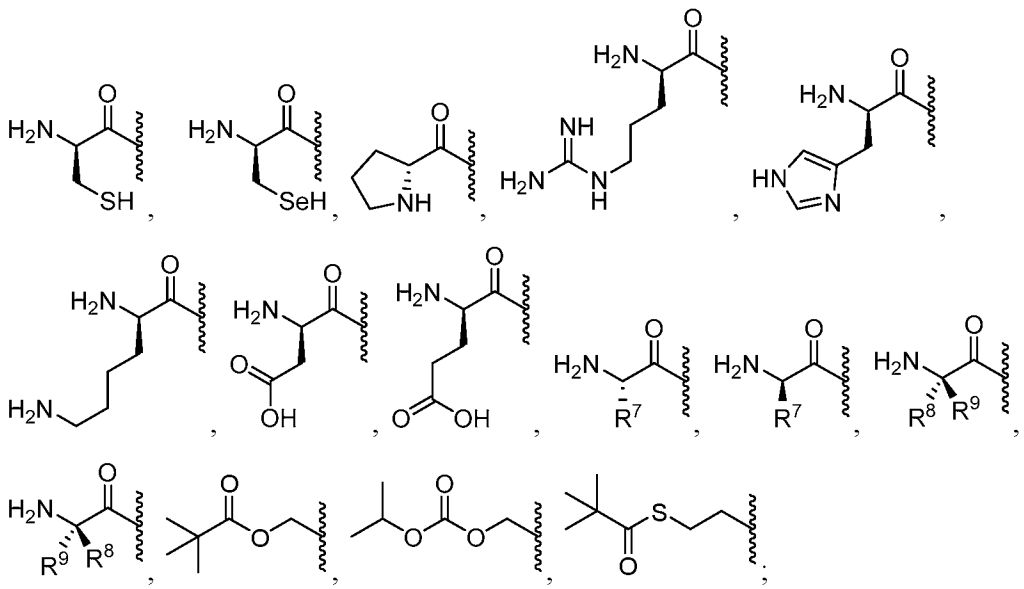
R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino,

heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

29. A pharmaceutical composition of claims 6 or 7 wherein R^1, R^2, and R^3 are each independently selected from the following:





R^6 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, optionally substituted phenyl, optionally substituted aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino,

cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

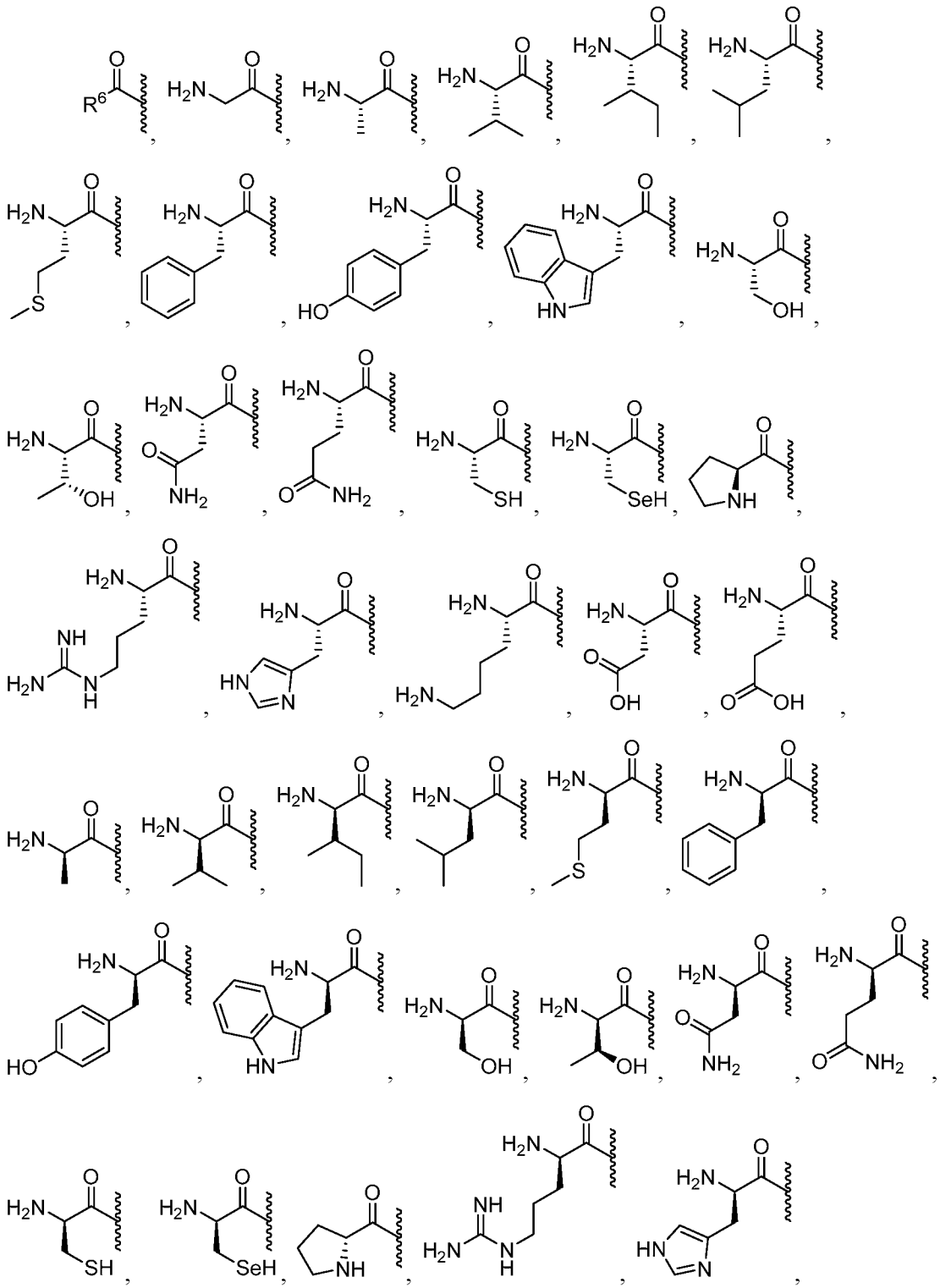
R^8 and R^9 can form a ring with the α-carbon which they are attached;

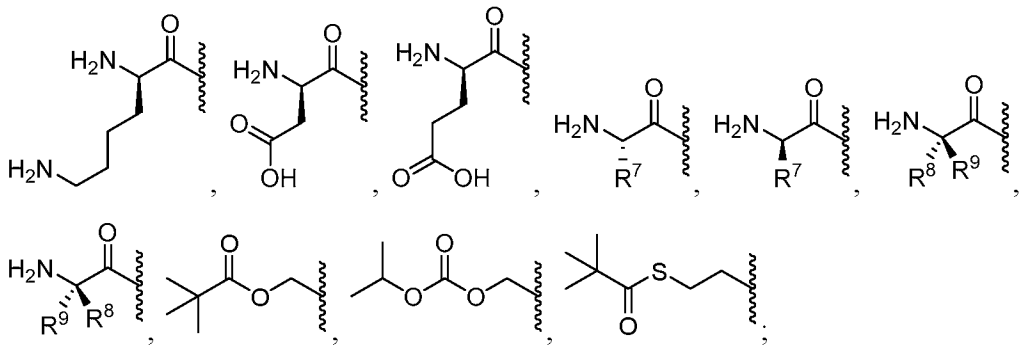
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

30. A pharmaceutical composition of claim 18 wherein R^1 is selected from the following:





R^6 is hydrogen, C_1-C_7 n-alkyl, C_9-C_{22} n-alkyl, optionally substituted C_8 n-alkyl, branched alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, -O(C_1-C_6 n-alkyl), -O(C_8-C_{21} n-alkyl), optionally substituted –O(C_7 n-alkyl), -O(branched alkyl) carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, -NH(C_1-C_6 n-alkyl), -NH(C_8-C_{21} n-alkyl), optionally substituted -NH(C7 n-alkyl), -NH(branched alkyl) (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl,

lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

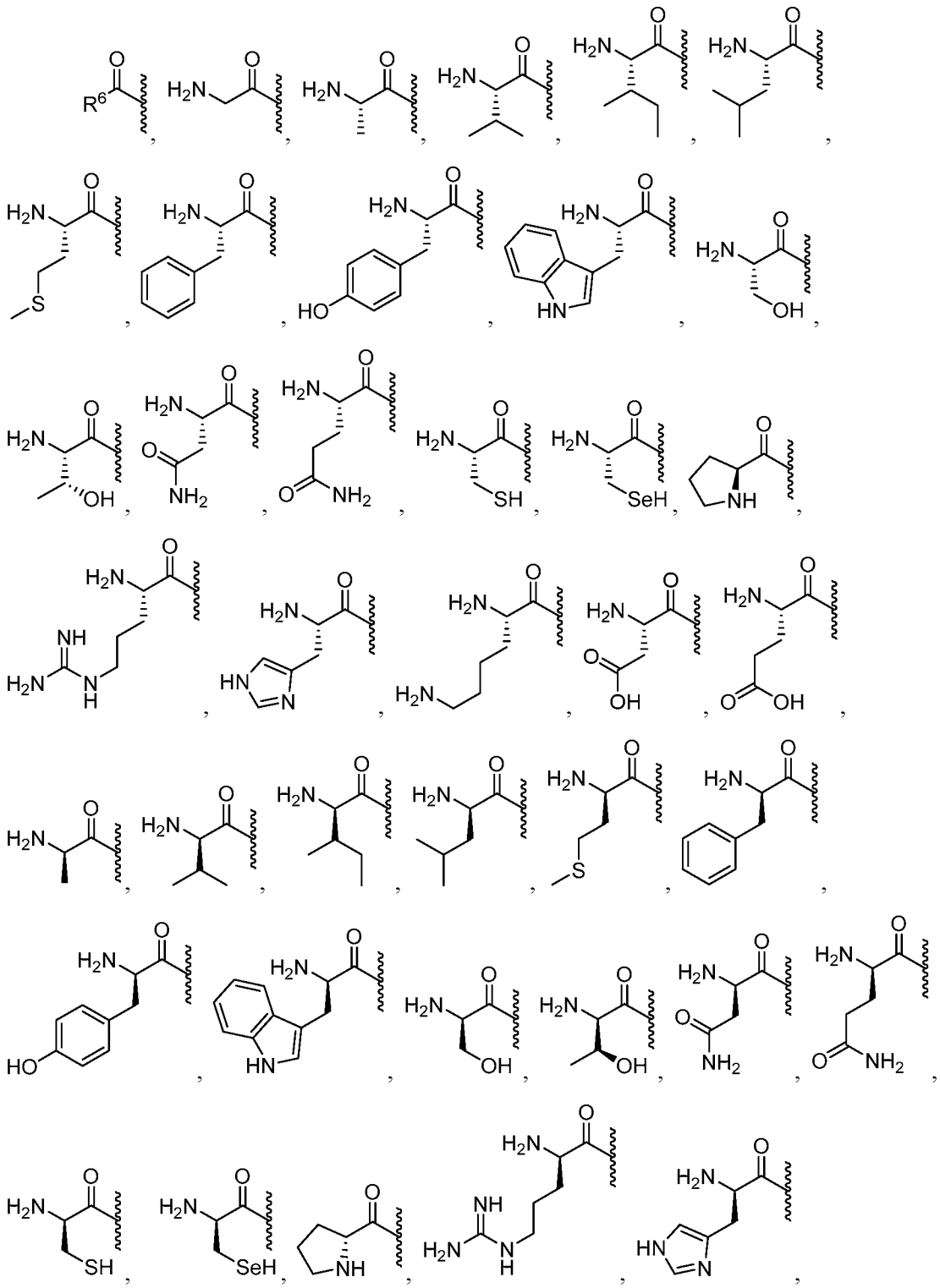
R^8 and R^9 can form a ring with the α-carbon which they are attached;

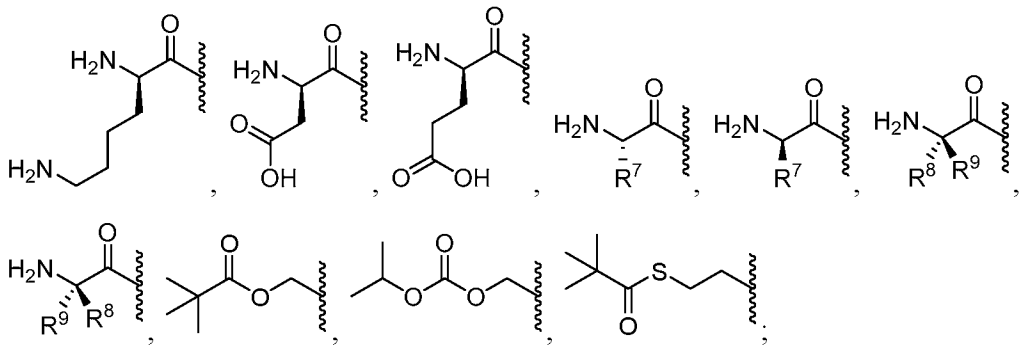
R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

31. A pharmaceutical composition of claim 19 wherein R^5 is selected from the following:





R^6 is hydrogen, C_2-C_7 n-alkyl, optionally substituted C_8 n-alkyl, C_9-C_{22} n-alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, C_3-C_9 cycloalkyl, C_{11}-C_{22} cycloalkyl, optionally substituted C_{10} cycloalkyl, cycloalkenyl, -O(C_1-C_6 n-alkyl), -O(optionally substituted C_7 n-alkyl), -O(C_8-C_{21} n-alkyl), -O(branched alkyl), carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, -N(C_2-C_{21} n-alkyl)$_2$, -N(optionally substituted C_1 alkyl)$_2$, -NH(optionally substituted C_1 alkyl), -NH(C_2-C_6 n-alkyl), -NH(optionally substituted C_7 n-alkyl), -NH(C_8-C_{15} n-alkyl), -NH(optionally substituted C_{16} n-alkyl), -NH(C_{17} n-alkyl), -NH(optionally substituted C_{18} n-alkyl), -NH(C_{19}-C_{21} n-alkyl), -NH(branched alkyl), -N(branched alkyl)$_2$, carbocyclamino, heterocarbocyclamino, optionally substituted arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, cyano, or lipid, wherein R^6 is optionally substituted with one or more, the same or different, R^{10};

R^7 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^7 is optionally substituted with one or more, the same or different, R^{10};

R^8 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, (alkyl)$_2$amino, carbocyclamino,

heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^8 is optionally substituted with one or more, the same or different, R^{10};

R^9 is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^9 is optionally substituted with one or more, the same or different, R^{10};

R^7, R^8, and R^9 can form a ring with the α-carbon they are attached to and the amino group attached to the α-carbon;

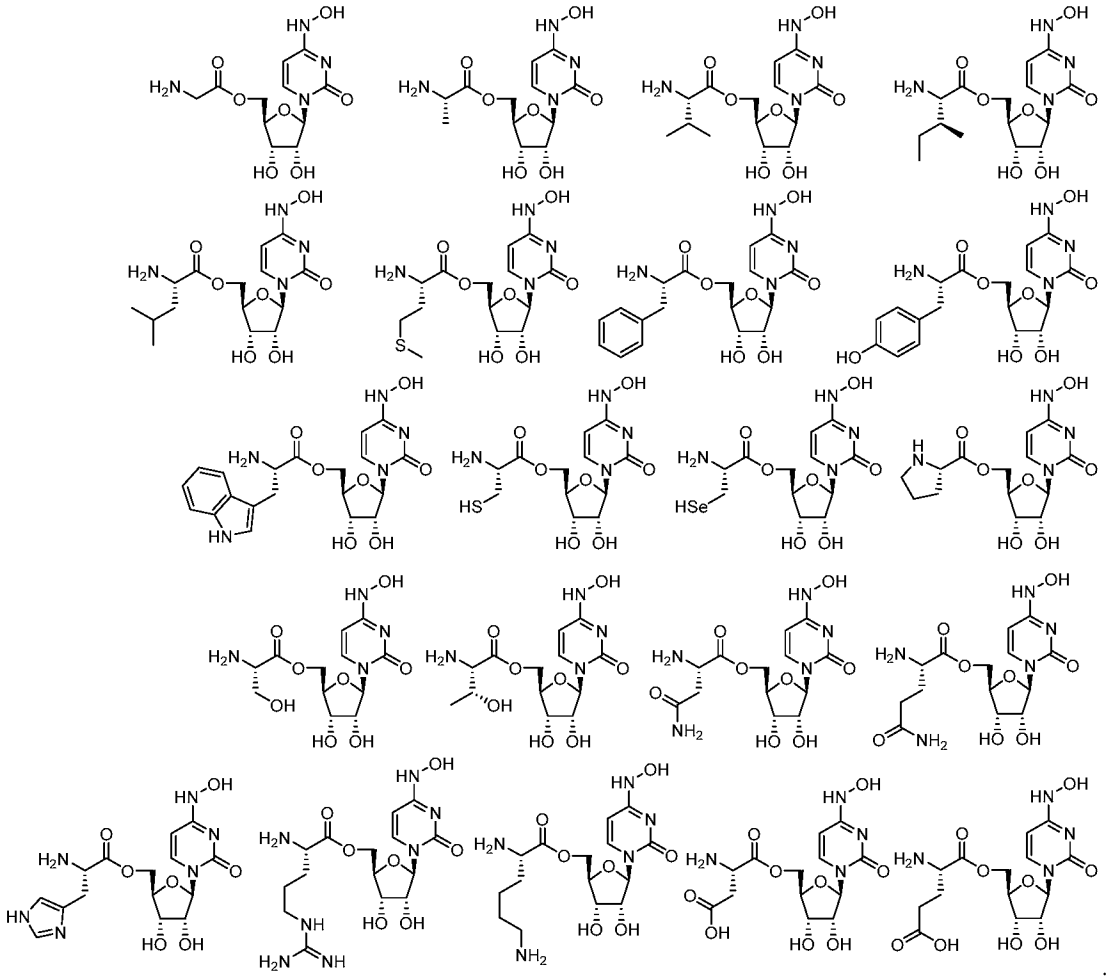
R^8 and R^9 can form a ring with the α-carbon which they are attached;

R^{10} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{11};

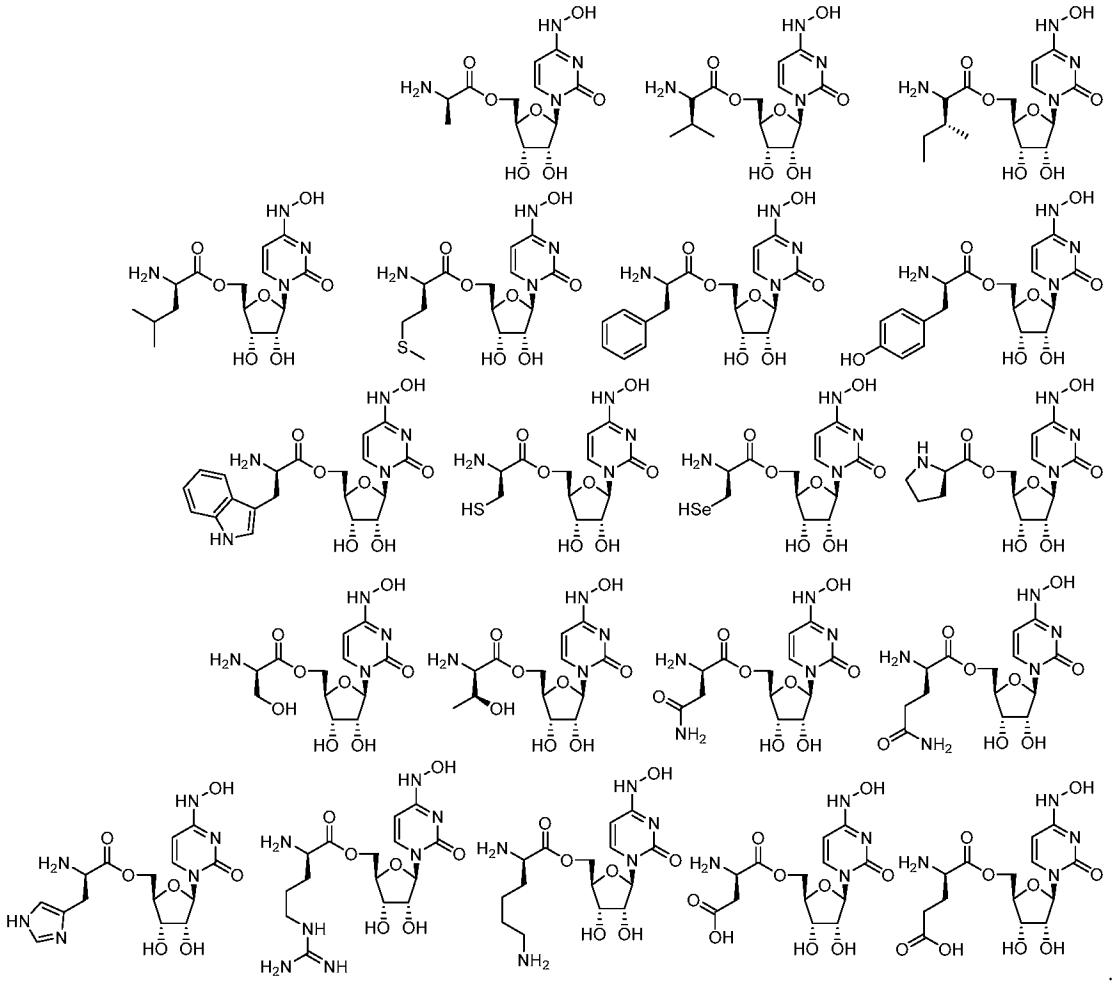
R^{11} is deuterium, hydroxy, azido, thiol, amino, cyano, halogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocarbocyclyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkoxy, carbocycloxy, heterocarbocycloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkoxy, cycloalkenoxy, alkylamino, $(alkyl)_2$amino, carbocyclamino, heterocarbocyclamino, arylamino, heteroarylamino, heterocyclamino, cycloalkamino, cycloalkenamino, alkylthio, carbocyclylthio, heterocarbocyclylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, allenyl, sulfinyl, sulfamoyl, sulfonyl, lipid, nitro, or carbonyl; and

Lipid is a C11-C22 higher alkyl, C11-C22 higher alkoxy, polyethylene glycol, or aryl substituted with an alkyl group, or a lipid as described herein.

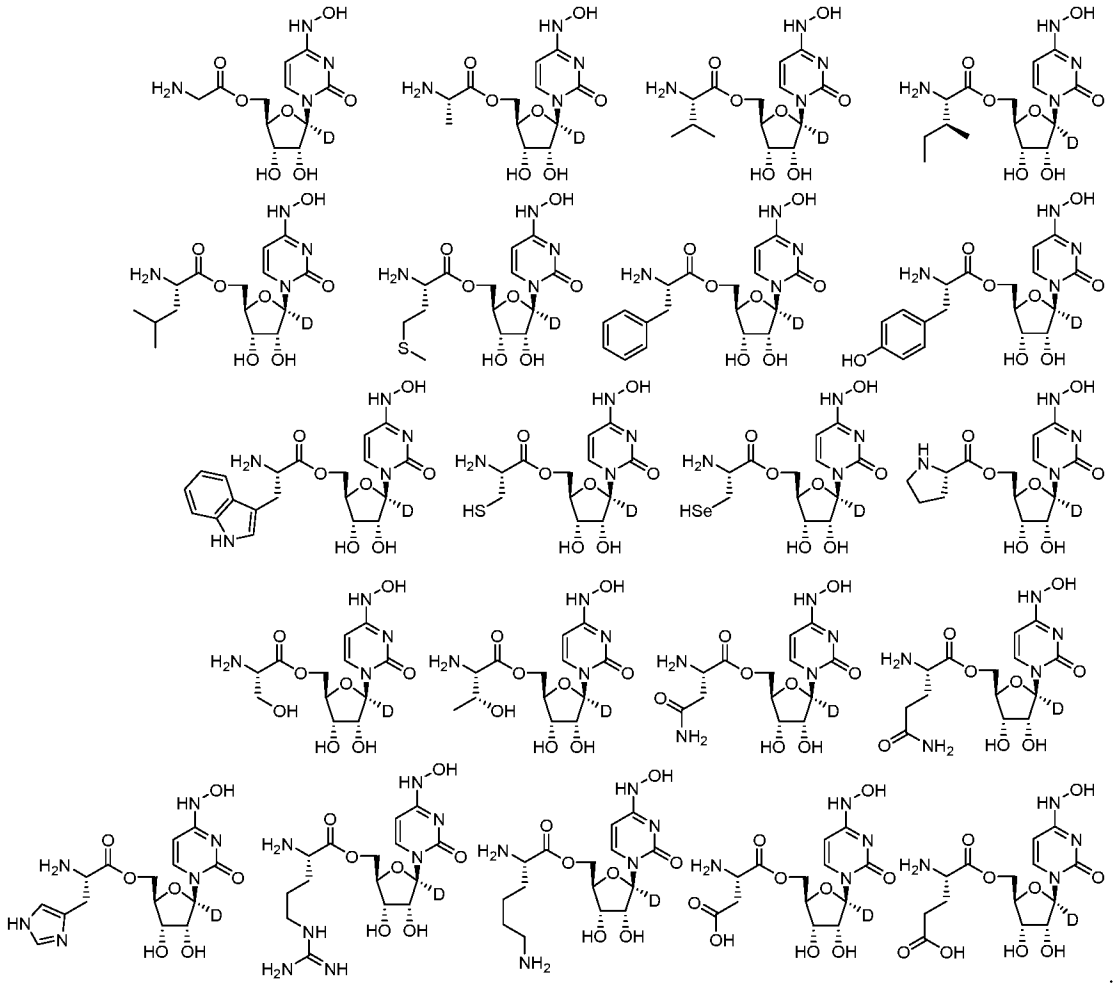
32. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:



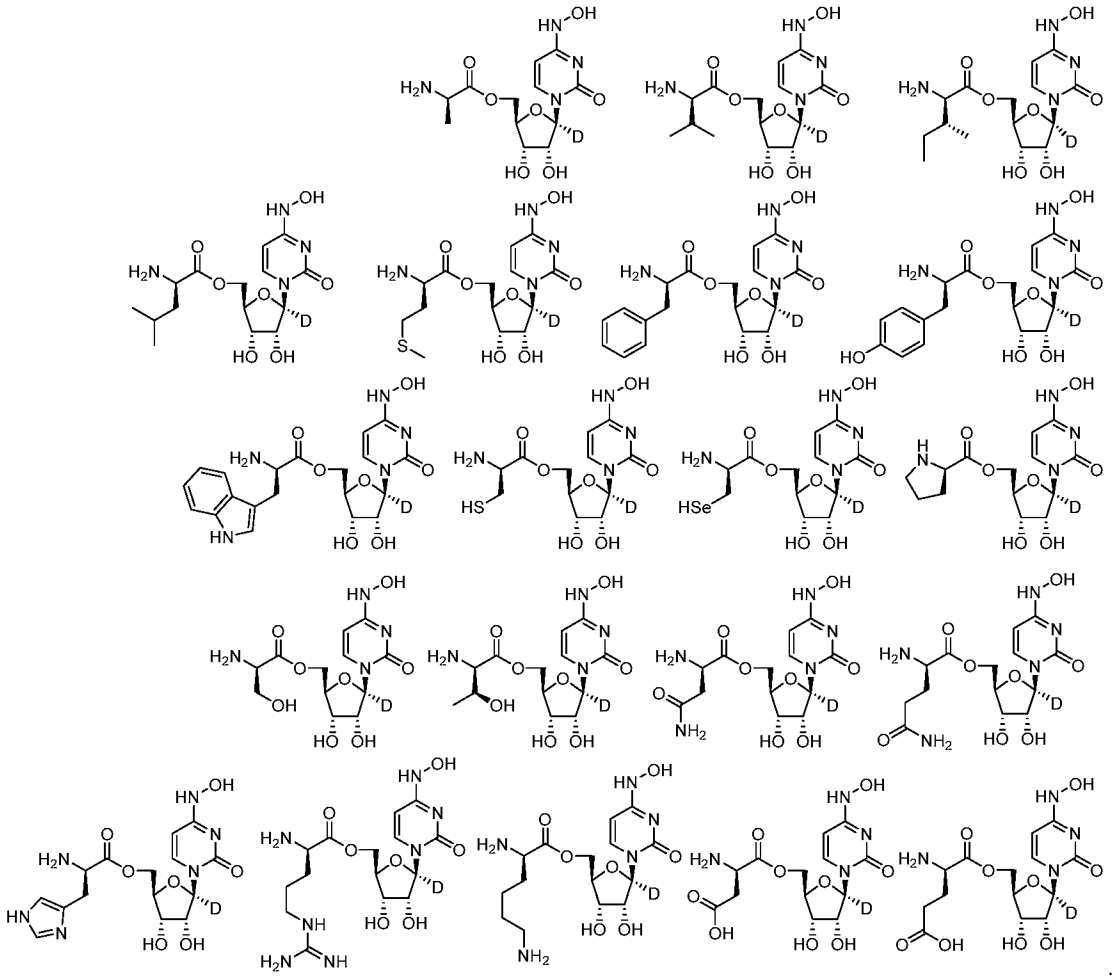
33. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:



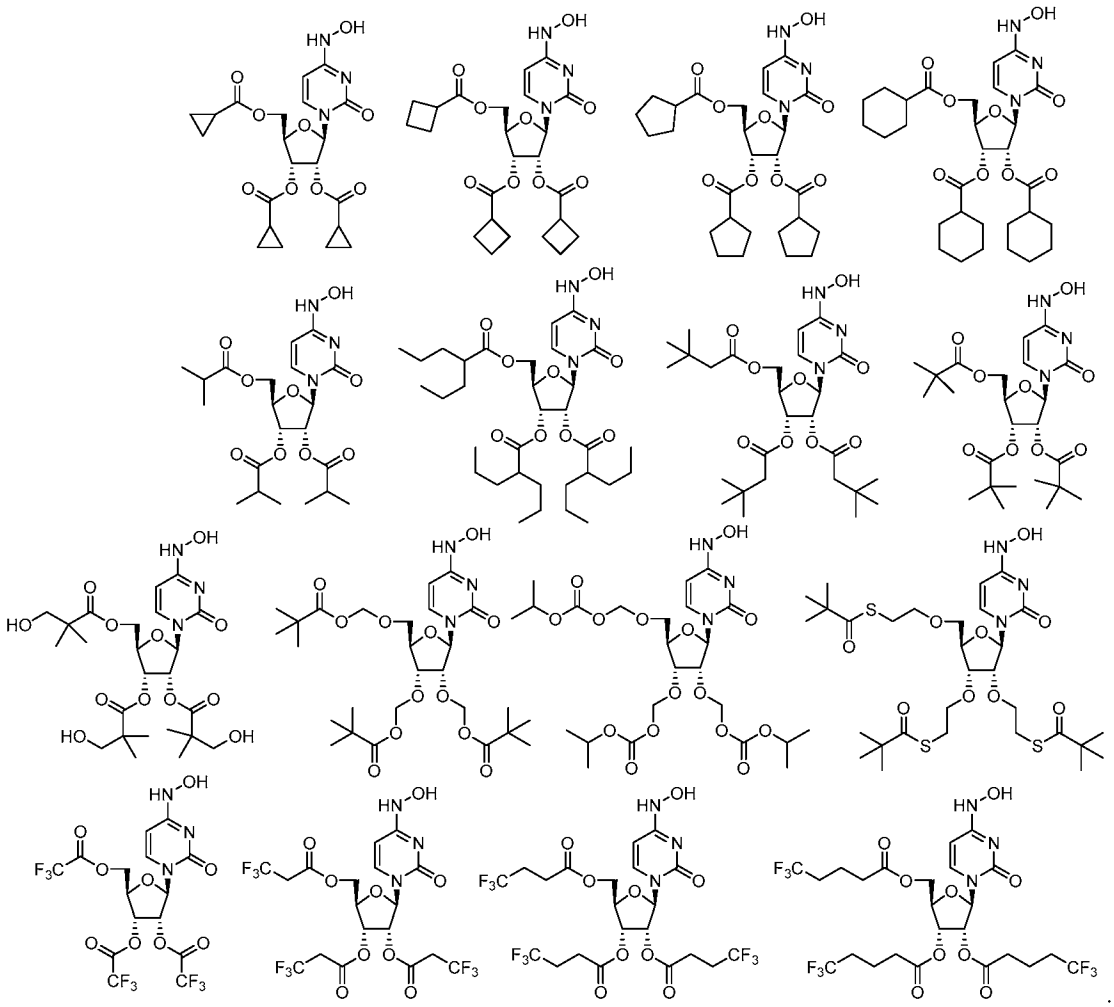
34. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:



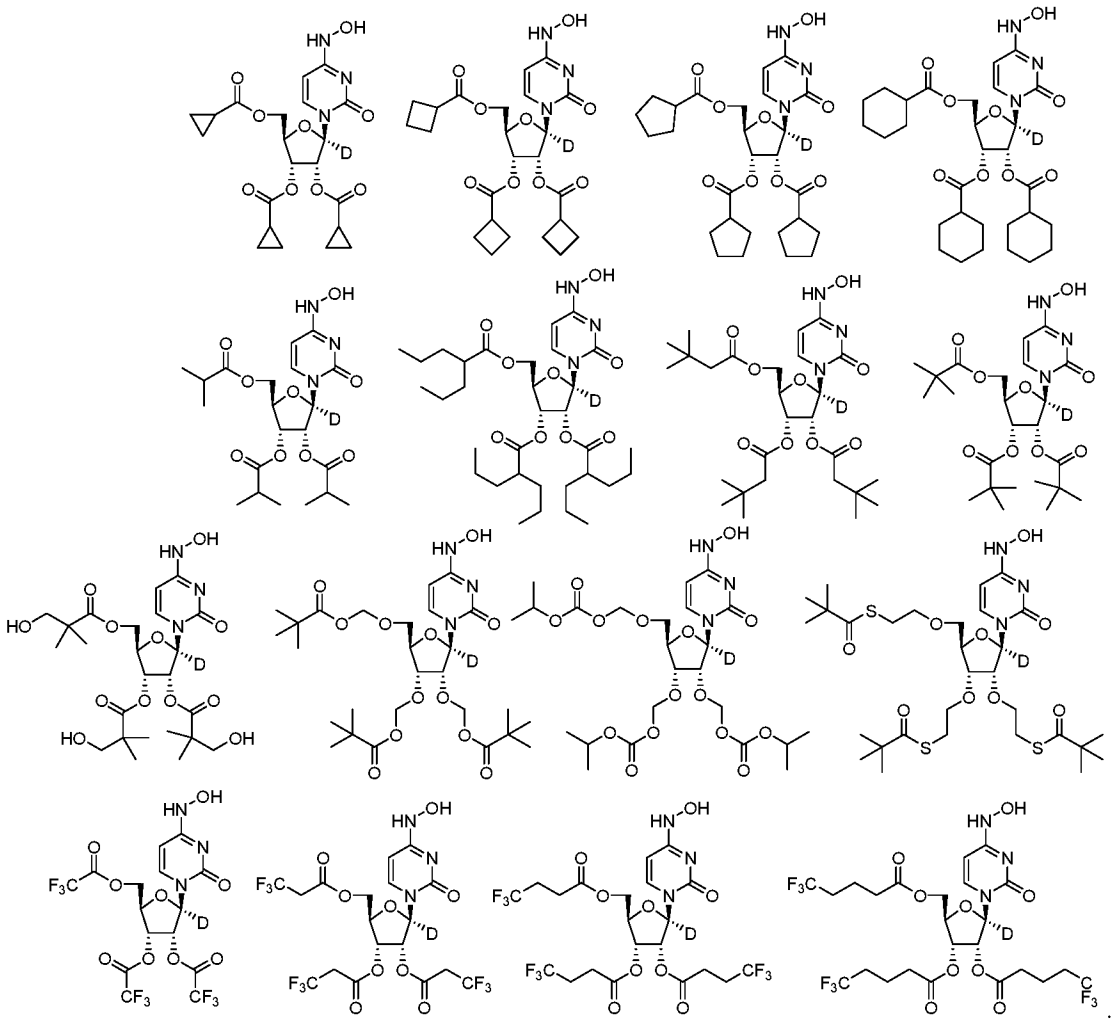
35. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:



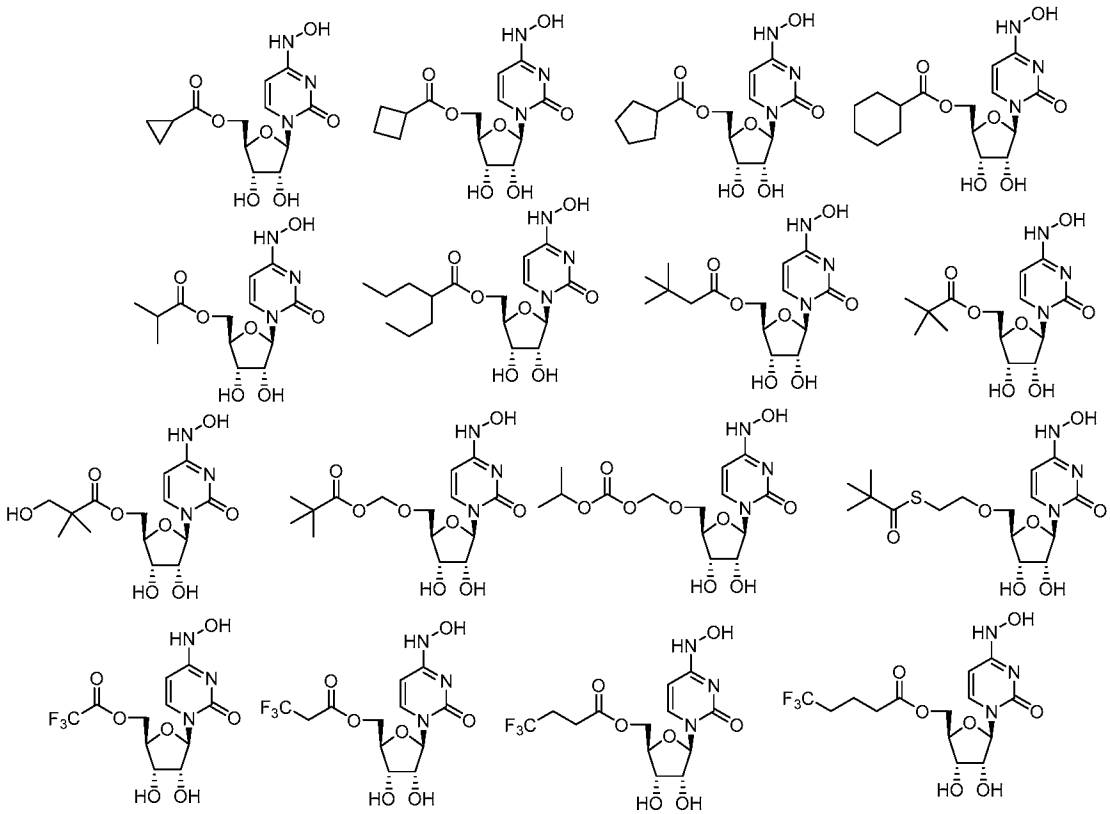
36. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:



37. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:

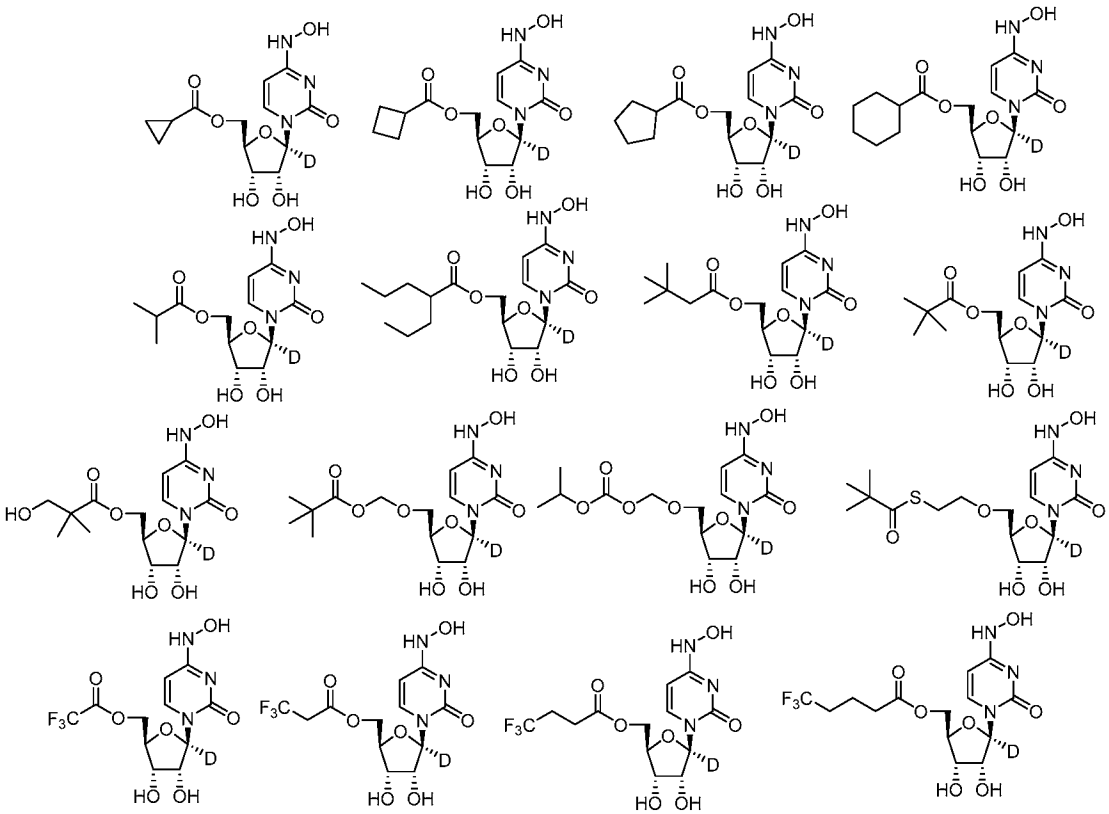


38. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:

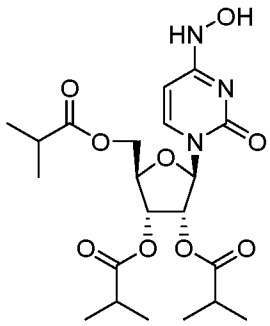


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39. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound selected from the following:

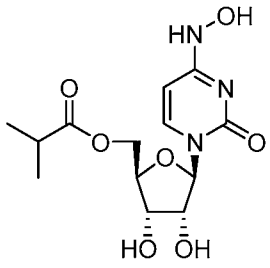


40. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound with the following structure:



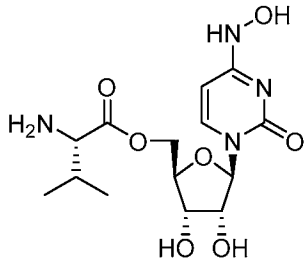
or pharmaceutically acceptable or physiological salts thereof.

41. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound with the following structure:



or pharmaceutically acceptable or physiological salts thereof.

42. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound with the following structure:



or pharmaceutically acceptable or physiological salts thereof.

43. The pharmaceutical composition of any one of claims 1-42, further comprising a propellant.

44. The pharmaceutical composition of claim 43, wherein the propellant is compressed air, ethanol, nitrogen, carbon dioxide, nitrous oxide, hydrofluoroalkanes (HFA), 1,1,1,2,-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or combinations thereof.

45. A pressurized container comprising a pharmaceutical composition of any one of claims 1-42.

46. The container of claim 45 which is a manual pump spray, inhaler, meter-dosed inhaler, dry powder inhaler, nebulizer, vibrating mesh nebulizer, jet nebulizer, or ultrasonic wave nebulizer.

47. A method of treating or preventing a viral infection comprising administering in effective amount of a compound of any one of claims 1-42 to a subject in need thereof.

48. The method of claim 47, wherein the viral infection is an alphavirus.

49. The method of claim 48, wherein the virus is selected from Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, and Ross River virus.

50. The method of claim 47, wherein the viral infection is a coronavirus.

51. The method of claim 50, wherein the viral infection is a human coronavirus, SARS coronavirus, and MERS coronavirus.

52. The method of claim 47, wherein the viral infection is a filoviridae virus.

53. The method of claim 52, wherein the viral infection is an ebola virus.

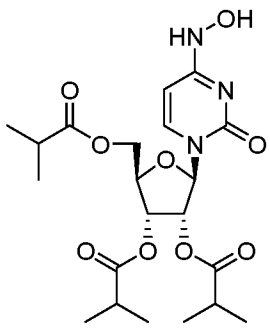
54. The method of claim 47, wherein the viral infection is an orthomyxoviridae virus.

55. The method of claim 54, wherein the viral infection is influenza A virus and influenza B virus.

56. The method of claim 47, wherein the viral infection is a paramyxoviridae virus.

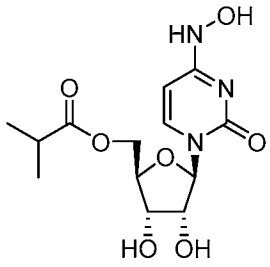
57. The method of claim 56, wherein the viral infection is RSV.

58. A method of treating or preventing a human coronavirus, SARS coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, and Ross River infection infection, orthomyxoviridae virus or paramyxoviridae virus or RSV virus, or influenza A virus and influenza B virus, or filoviridae virus or ebola virus infection in a patient comprising administering in effective amount of a compound to a patient in need thereof with the structure:



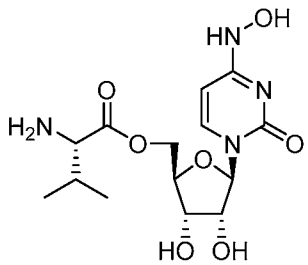
or pharmaceutically acceptable or physiological salts thereof.

59. A method of treating or preventing a human coronavirus, SARS coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, and Ross River infection infection, orthomyxoviridae virus or paramyxoviridae virus or RSV virus, or influenza A virus and influenza B virus, or filoviridae virus or ebola virus infection in a patient comprising administering in effective amount of a compound to a patient in need thereof with the structure:



or pharmaceutically acceptable or physiological salts thereof.

60. A method of treating or preventing a human coronavirus, SARS coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, and Ross River infection infection, orthomyxoviridae virus or paramyxoviridae virus or RSV virus, or influenza A virus and influenza B virus, or filoviridae virus or ebola virus infection in a patient comprising administering in effective amount of a compound to a patient in need thereof with the structure:



or pharmaceutically acceptable or physiological salts thereof.

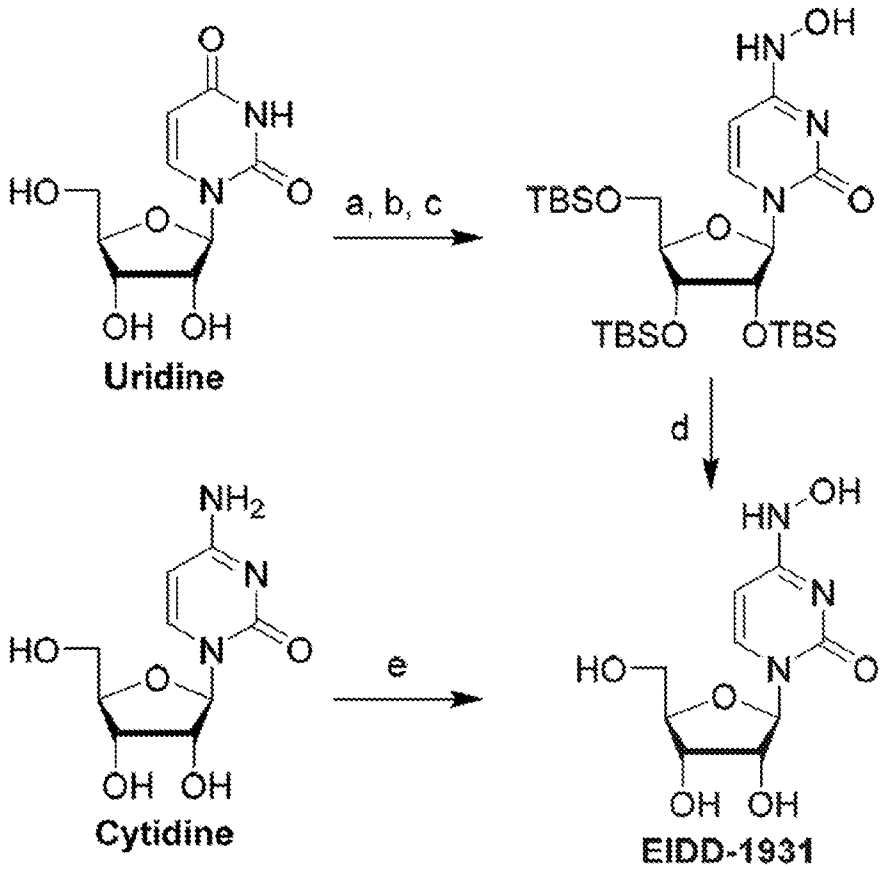

a, b, c
d
e
Uridine
Cytidine
EIDD-1931

FIG. 1

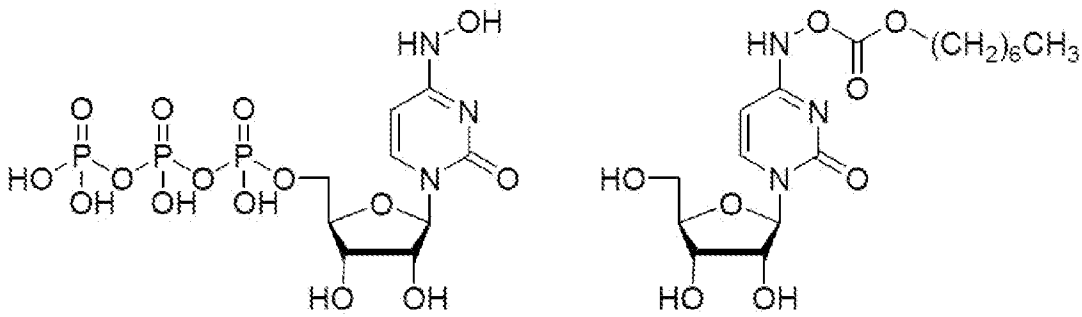

EIDD-2061
(Triphosphate of EIDD-1931)
EIDD-2051

FIG. 2

W = CH2, CF2, CD2
Q = O, NH
R1 = H, F, Cl, Br, I, CH3, CF3, SMe, D, alkyl, alkenyl, allenyl, alkynyl
R2 = H, OH, CH3, alkyl, alkenyl, allenyl, alkynyl
R3 = OH, H, F, Cl
R4, R5 = H,
where X = CH2, O, S, or NH, and
lipid = n-C6H13 through C16H33
phospholipid,
phosphoramidate,
cycloSal phosphotriester
dipil
where R6 = H or OBn, and
lipid = n-C6H13 through C16H33

FIG. 3

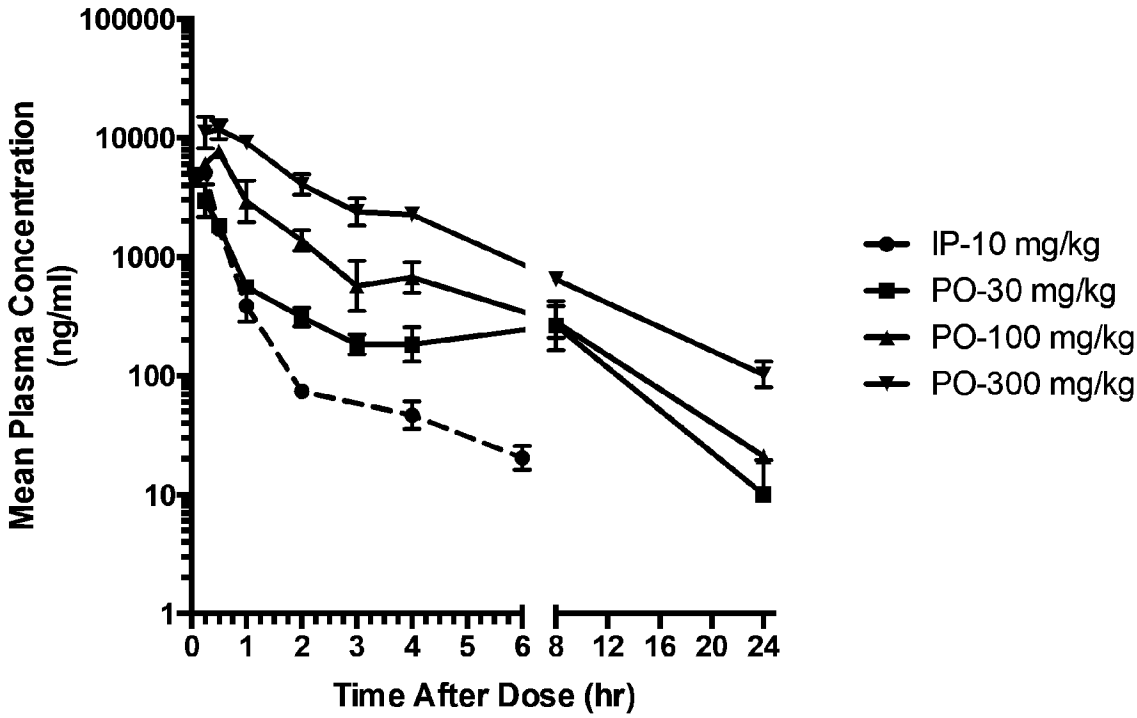

Mean Plasma Concentration (ng/ml)
100000
10000
1000
100
10
1
0 1 2 3 4 5 6 8 12 16 20 24
Time After Dose (hr)
IP-10 mg/kg
PO-30 mg/kg
PO-100 mg/kg
PO-300 mg/kg

FIG. 4

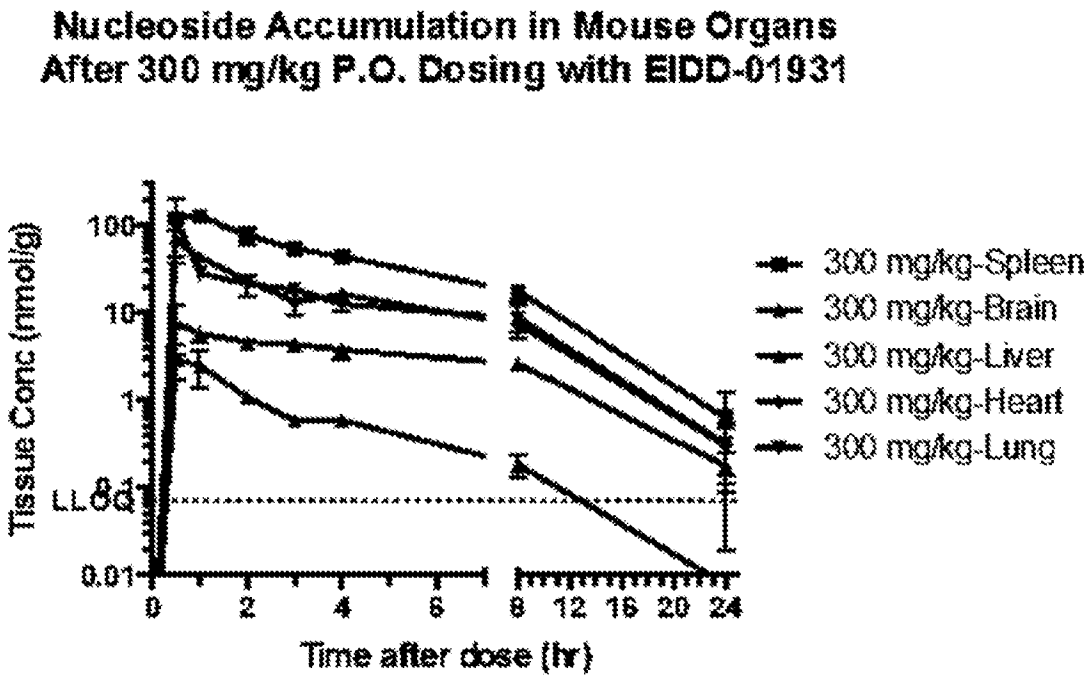

Nucleoside Accumulation in Mouse Organs
After 300 mg/kg P.O. Dosing with EIDD-01931
Tissue Conc (nmol/g)
100
10
1
LLOQ
0.01
0 2 4 6 8 12 16 20 24
Time after dose (hr)
300 mg/kg-Spleen
300 mg/kg-Brain
300 mg/kg-Liver
300 mg/kg-Heart
300 mg/kg-Lung

FIG. 5

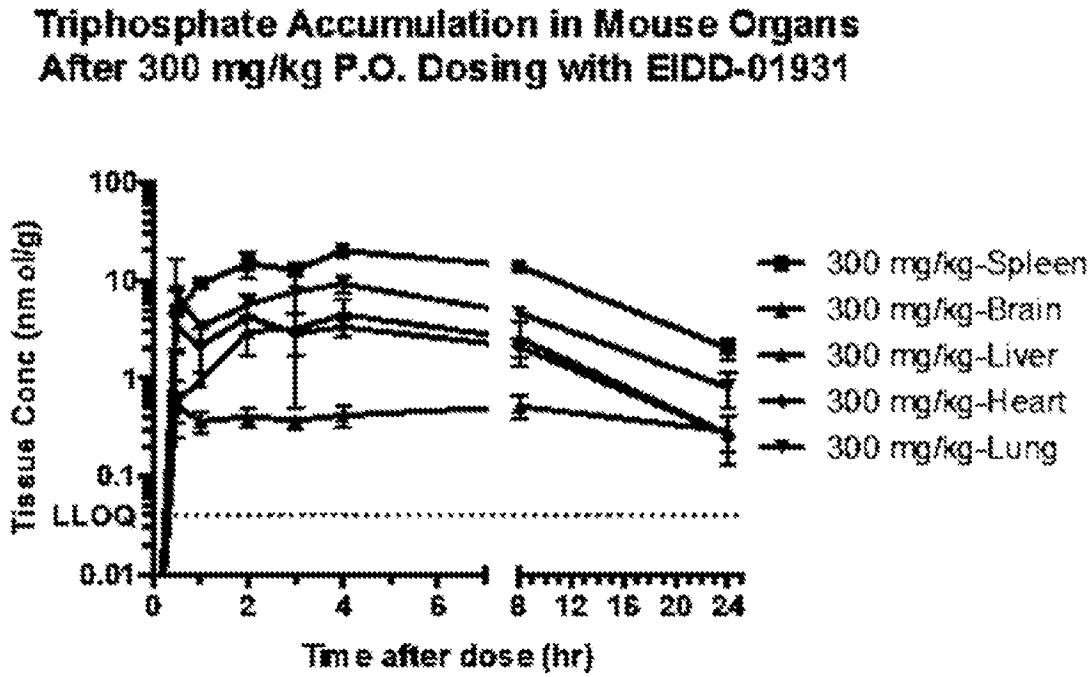

Triphosphate Accumulation in Mouse Organs
After 300 mg/kg P.O. Dosing with EIDD-01931
Tissue Conc (nmol/g)
100
10
1
0.1
LLOQ
0.01
0
2
4
6
8
12
16
20
24
Time after dose (hr)
300 mg/kg-Spleen
300 mg/kg-Brain
300 mg/kg-Liver
300 mg/kg-Heart
300 mg/kg-Lung

FIG. 6

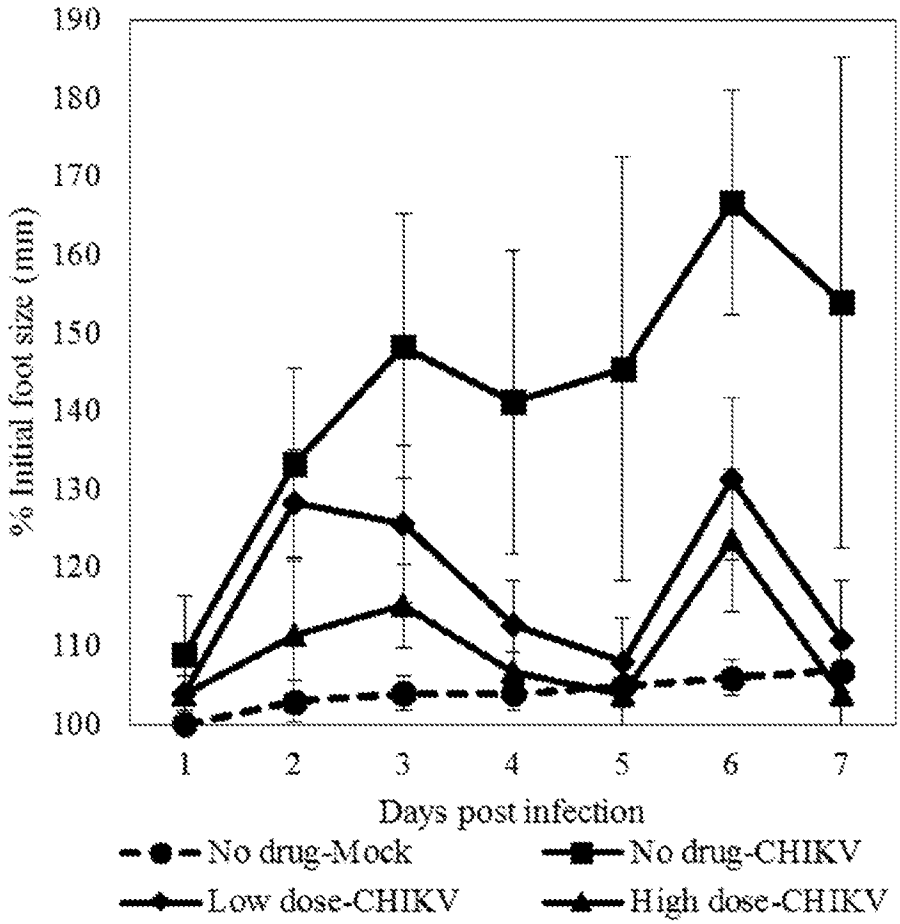

190
180
170
160
150
140
130
120
110
100
% Initial foot size (mm)
1
2
3
4
5
6
7
Days post infection
No drug-Mock
No drug-CHIKV
Low dose-CHIKV
High dose-CHIKV

FIG. 7

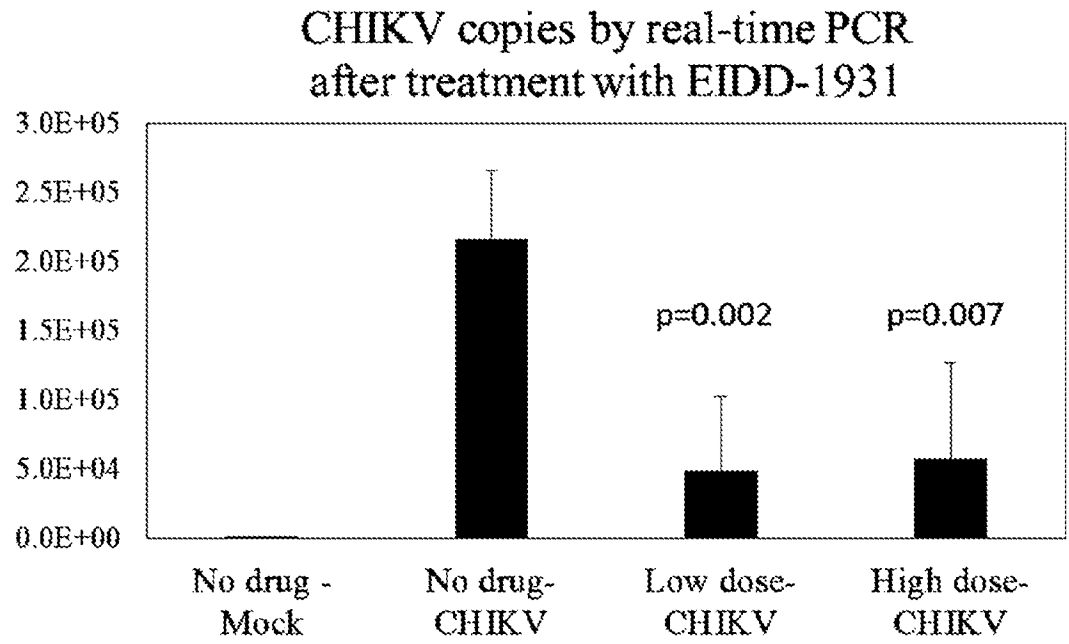

CHIKV copies by real-time PCR
after treatment with EIDD-1931
3.0E+05
2.5E+05
2.0E+05
1.5E+05
1.0E+05
5.0E+04
0.0E+00
p=0.002
p=0.007
No drug - Mock
No drug- CHIKV
Low dose- CHIKV
High dose- CHIKV

FIG. 8

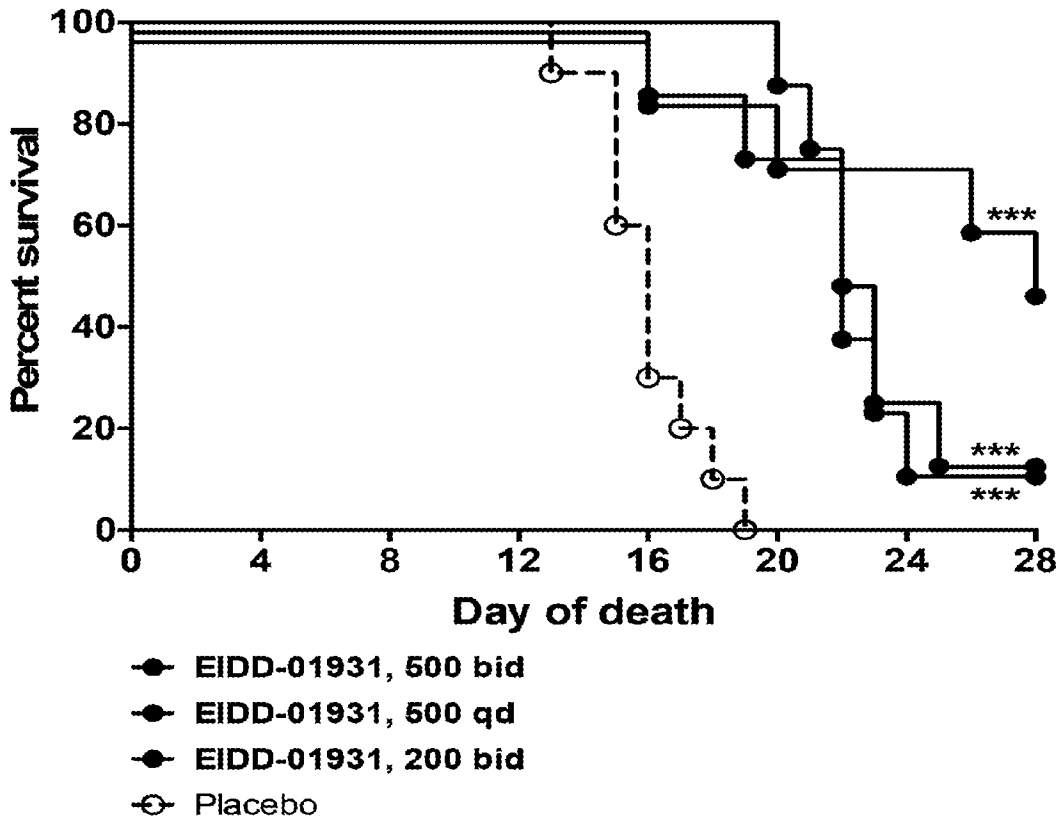

Percent survival
100
80
60
40
20
0
0
4
8
12
16
20
24
28
Day of death
***
***
***
EIDD-01931, 500 bid
EIDD-01931, 500 qd
EIDD-01931, 200 bid
Placebo

FIG. 9

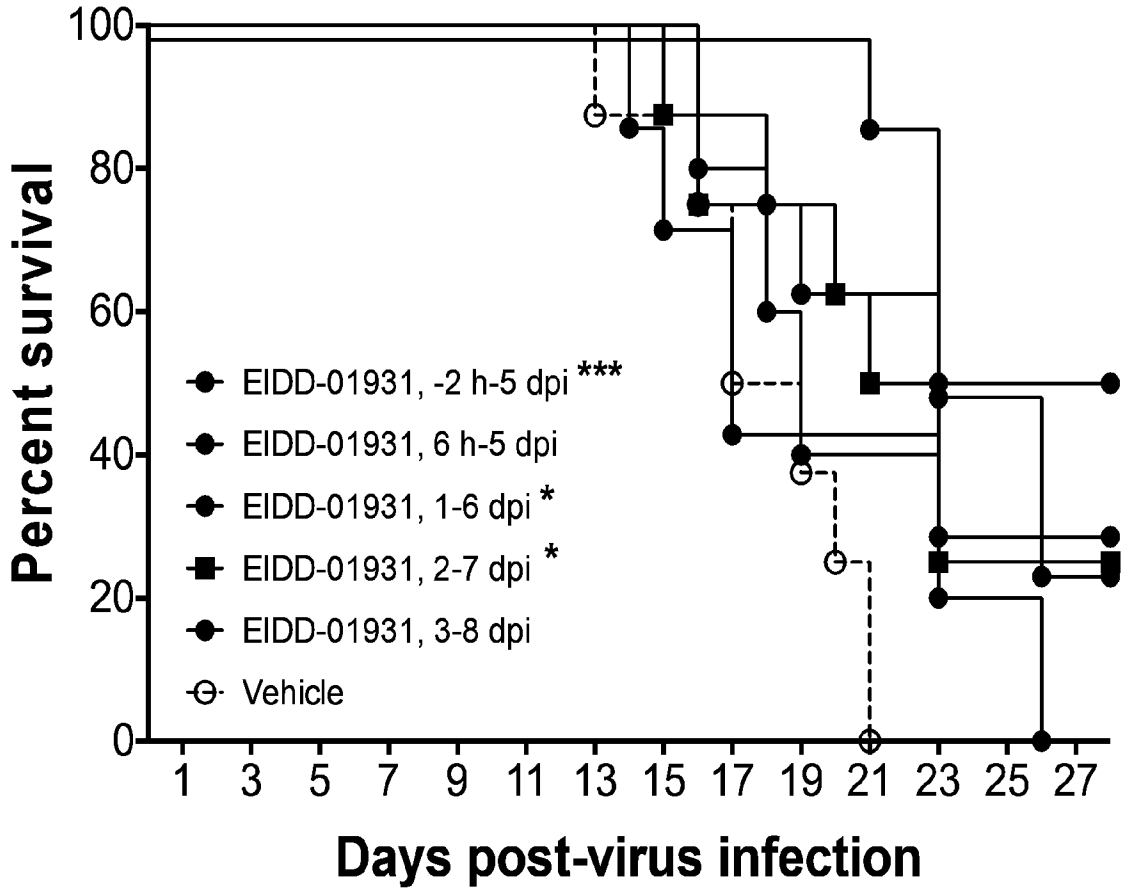

Percent survival
100
80
60
40
20
0
EIDD-01931, -2 h-5 dpi ***
EIDD-01931, 6 h-5 dpi
EIDD-01931, 1-6 dpi *
EIDD-01931, 2-7 dpi *
EIDD-01931, 3-8 dpi
Vehicle
1 3 5 7 9 11 13 15 17 19 21 23 25 27
Days post-virus infection

FIG. 10

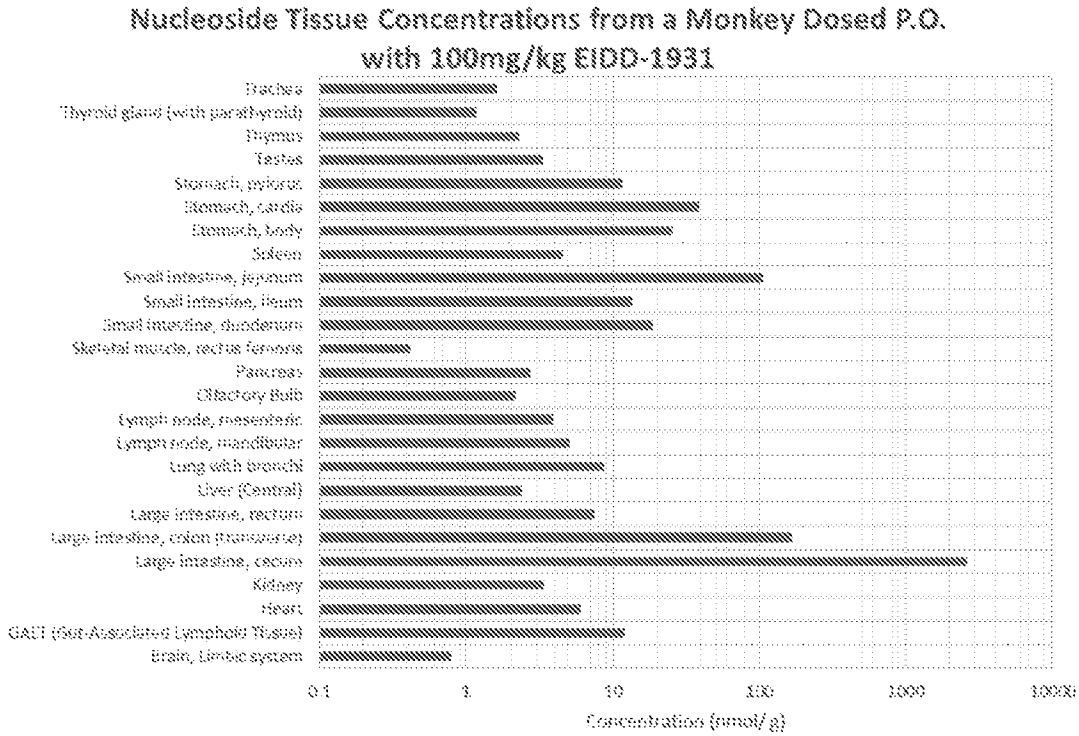

Nucleoside Tissue Concentrations from a Monkey Dosed P.O. with 100mg/kg EIDD-1931
Trachea
Thyroid gland (with parathyroid)
Thymus
Testes
Stomach, pylorus
Stomach, cardia
Stomach, body
Spleen
Small intestine, jejunum
Small intestine, ileum
Small intestine, duodenum
Skeletal muscle, rectus femoris
Pancreas
Olfactory Bulb
Lymph node, mesenteric
Lymph node, mandibular
Lung with bronchi
Liver (Central)
Large intestine, rectum
Large intestine, colon (transverse)
Large intestine, cecum
Kidney
Heart
GALT (Gut-Associated Lymphoid Tissue)
Brain, Limbic system
0.1
1
10
100
1000
10000
Concentration (nmol/ g)

FIG. 11

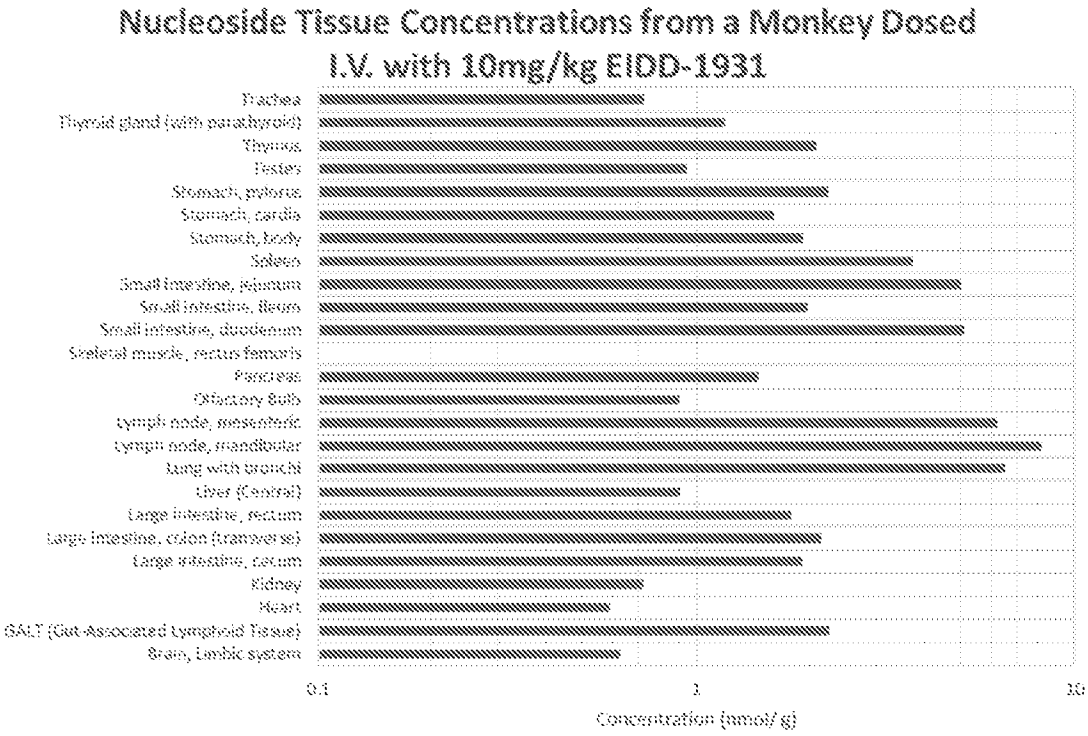

Nucleoside Tissue Concentrations from a Monkey Dosed I.V. with 10mg/kg EIDD-1931
Trachea
Thyroid gland (with parathyroid)
Thymus
Testes
Stomach, pylorus
Stomach, cardia
Stomach, body
Spleen
Small intestine, jejunum
Small intestine, ileum
Small intestine, duodenum
Skeletal muscle, rectus femoris
Pancreas
Olfactory Bulb
Lymph node, mesenteric
Lymph node, mandibular
Lung with bronchi
Liver (Central)
Large intestine, rectum
Large intestine, colon (transverse)
Large intestine, cecum
Kidney
Heart
GALT (Gut-Associated Lymphoid Tissue)
Brain, Limbic system
0.1
1
10
Concentration (nmol/ g)

FIG. 12

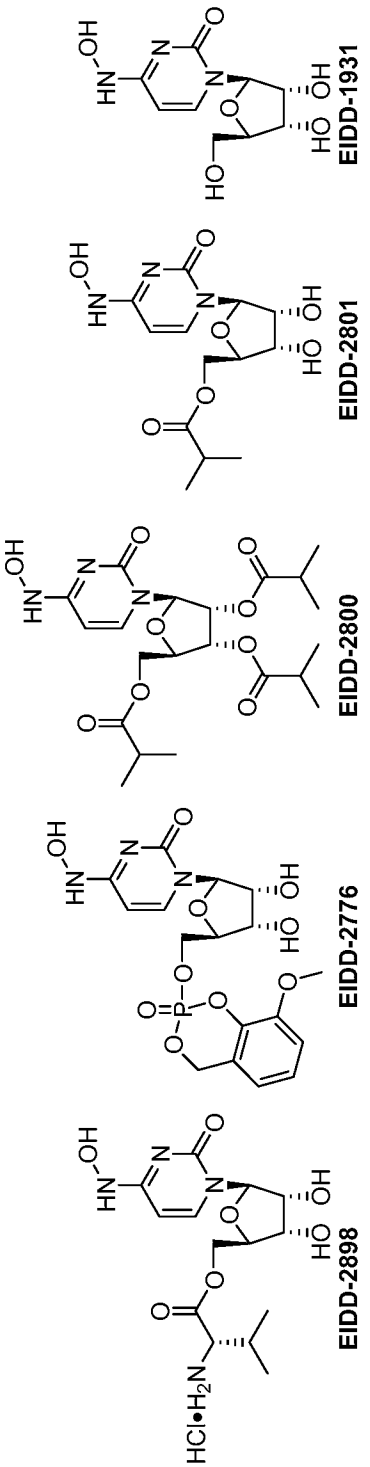


FIG. 13

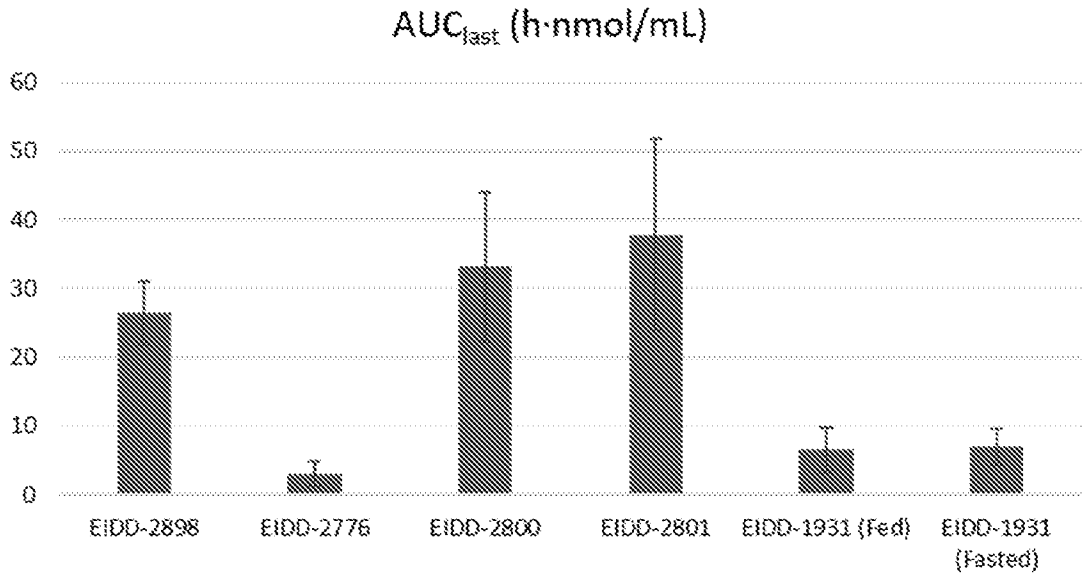

AUC$_{last}$ (h·nmol/mL)
60
50
40
30
20
10
0
EIDD-2898
EIDD-2776
EIDD-2800
EIDD-2801
EIDD-1931 (Fed)
EIDD-1931 (Fasted)

FIG. 14

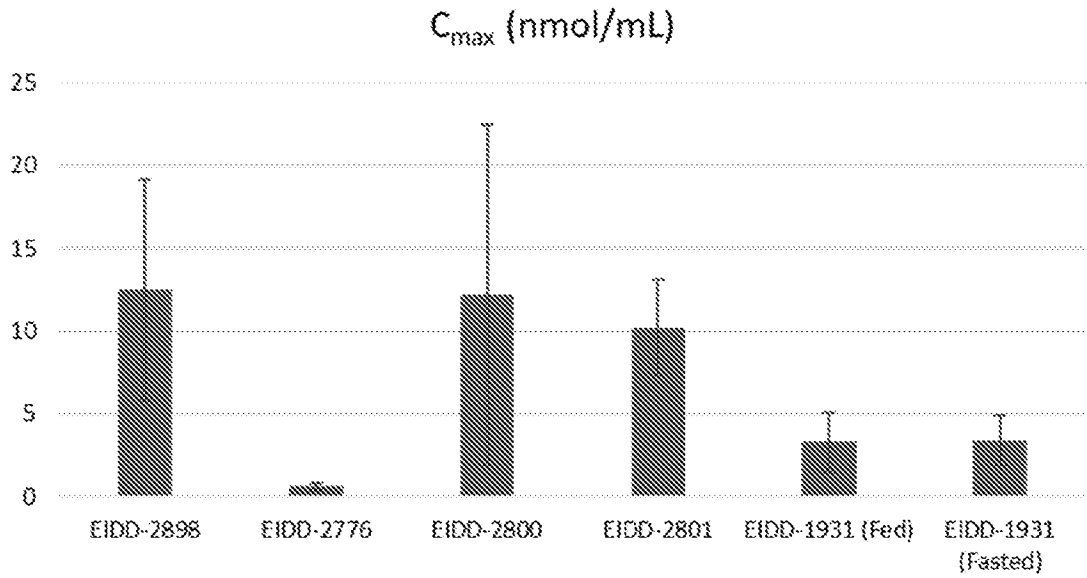

C$_{max}$ (nmol/mL)
25
20
15
10
5
0
EIDD-2898
EIDD-2776
EIDD-2800
EIDD-2801
EIDD-1931 (Fed)
EIDD-1931 (Fasted)

FIG. 15

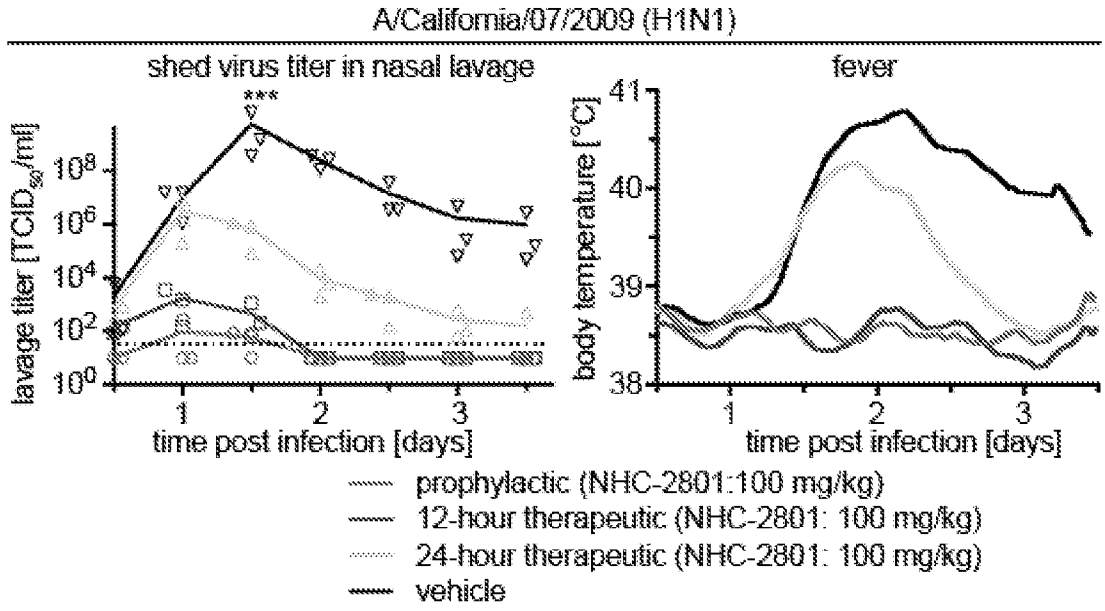

A/California/07/2009 (H1N1)
shed virus titer in nasal lavage
fever
lavage titer [TCID50/ml]
body temperature [°C]
time post infection [days]
time post infection [days]
prophylactic (NHC-2801:100 mg/kg)
12-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 100 mg/kg)
vehicle

FIG. 16

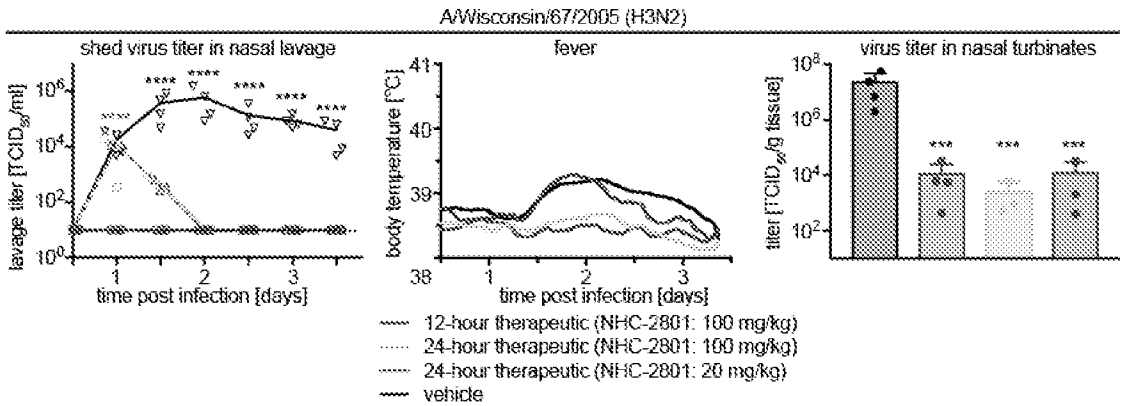

A/Wisconsin/67/2005 (H3N2)
shed virus titer in nasal lavage
fever
virus titer in nasal turbinates
lavage titer [TCID50/ml]
body temperature [°C]
titer [TCID50/g tissue]
time post infection [days]
time post infection [days]
12-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 20 mg/kg)
vehicle

FIG. 17

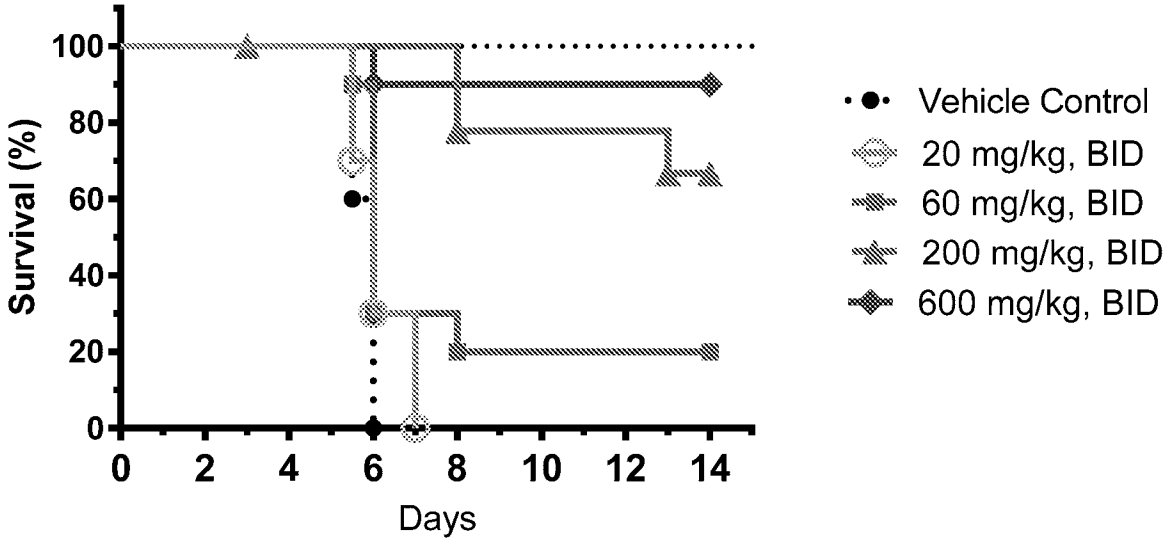

Survival (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14
Days
Vehicle Control
20 mg/kg, BID
60 mg/kg, BID
200 mg/kg, BID
600 mg/kg, BID

FIG. 18

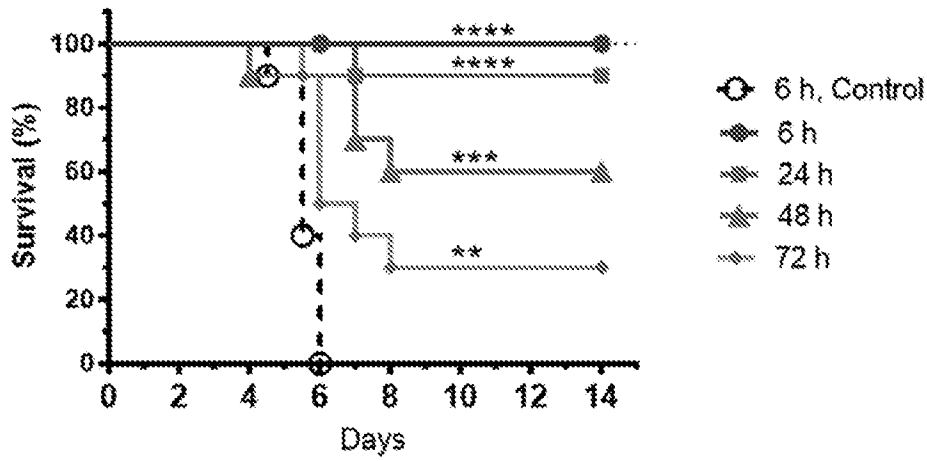

Survival (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14
Days
****
****
***
**
6 h, Control
6 h
24 h
48 h
72 h

FIG. 19

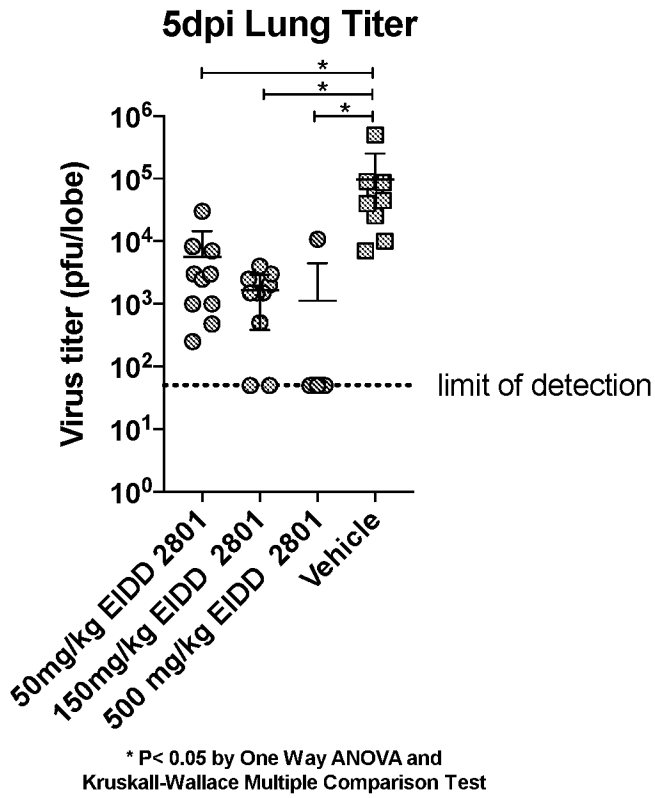

5dpi Lung Titer
Virus titer (pfu/lobe)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
limit of detection
50mg/kg EIDD 2801
150mg/kg EIDD 2801
500 mg/kg EIDD 2801
Vehicle
* P< 0.05 by One Way ANOVA and
Kruskall-Wallace Multiple Comparison Test

FIG. 20

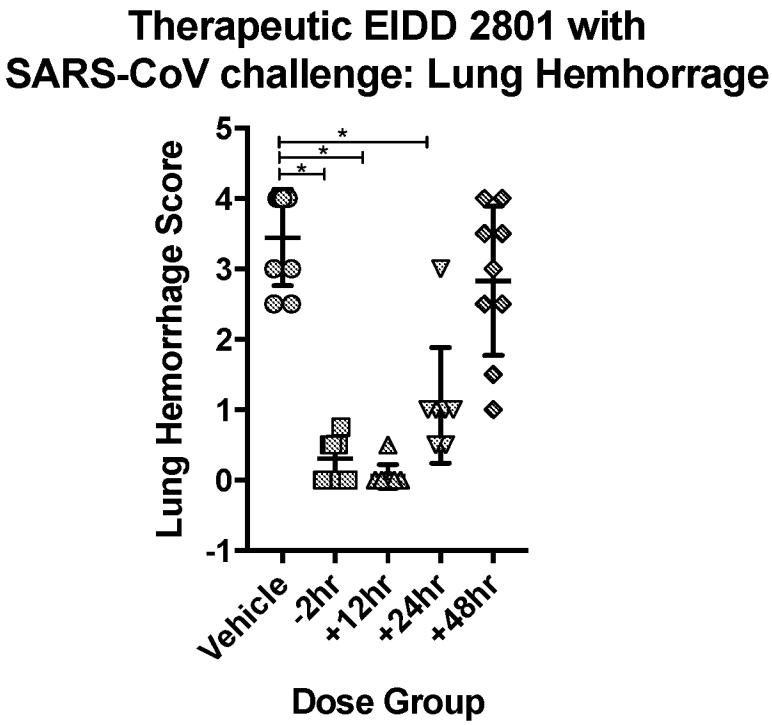

Therapeutic EIDD 2801 with
SARS-CoV challenge: Lung Hemhorrage
Lung Hemorrhage Score
5
4
3
2
1
0
-1
*
*
*
Vehicle
-2hr
+12hr
+24hr
+48hr
Dose Group

FIG. 21

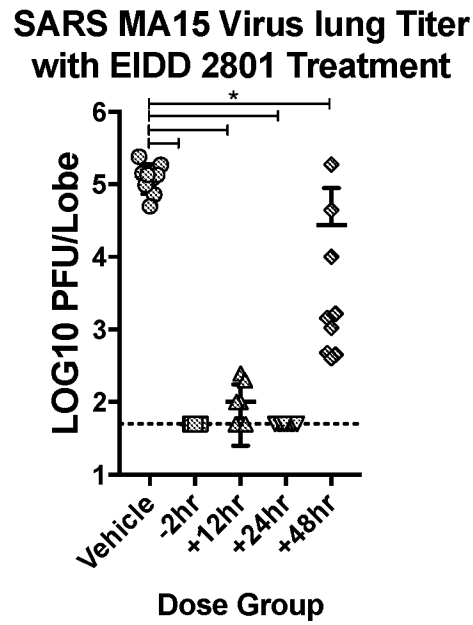

SARS MA15 Virus lung Titer
with EIDD 2801 Treatment
LOG10 PFU/Lobe
6
5
4
3
2
1
*
Vehicle
-2hr
+12hr
+24hr
+48hr
Dose Group

FIG. 22

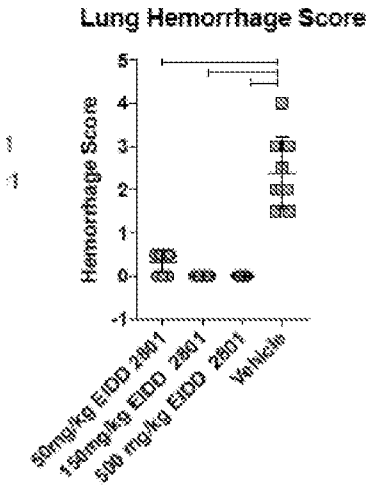

Lung Hemorrhage Score
Hemorrhage Score
5
4
3
2
1
0
-1
90mg/kg EOD 28d1
150mg/kg EOD 28d1
500 mg/kg EOD 28d1
Vehicle

FIG. 23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/064503

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/706; A61K 31/7064; A61K 31/7068; C07H 19/06; C07H 19/067; C07H 19/10 (2019.01)
CPC - A61K 31/706; A61K 31/7064; A61K 31/7068; C07H 19/06; C07H 19/067; C07H 19/10 (2019.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/49; 536/26.8; 536/28.51 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2016/106050 A1 (EMORY UNIVERSITY) 30 June 2016 (30.06.2016) entire document	1, 19, 21-23 --- 3, 17, 18
X	US 2009/0105186 A1 (MATTHES et al) 23 April 2009 (23.04.2009) entire document	15, 28
Y	MERTES et al. Nucleic Acid Components and Their Analogues. Cxv.* synthesis of n4 -hydroxy -6-azacytidine 5' -phosphate and 5' -diphosphate, Collection of Czechoslovak Chemical Communications, Vol. 33, Issue. 10, 1968 [retrieved on 23 January 2019]. Retrieved from the Internet: <URL: http://cccc.uochb.cas.cz/33/10/3304/> Pgs. 3304-3312	3
Y	BROWN et al. Mechanism of the Mutagenic Action of Hydroxylamine, Journal of Molecular Biology, Vol. 11, No. 4, 01 April 1965 [retrieved on 23 January 2019]. Retrieved from the Internet: <URL: https://www.sciencedirect.com/science/article/pii/S0022283665800249> Pgs. 663-671	17, 18
A	US 2003/0008841 A1 (DEVOS et al) 09 January 2003 (09.01.2003) entire document	1-42, 58-60
A	US 2014/0235566 A1 (EMORY UNIVERSITY et al) 21 August 2014 (21.08.2014) entire document	1-42, 58-60
A	WO 2017/165489 A1 (EMORY UNIVERSITY) 28 September 2017 (28.09.2017) entire document	1-42, 58-60

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2019	07 FEB 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/064503

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

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

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

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

3. ☒ Claims Nos.: 43-57
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.