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(54) **Titre : COMPOSITIONS THERAPEUTIQUES RENFERMANT DES NUCLEOTIDES ET DES NUCLEOSIDES, COMBINAISONS ET UTILISATIONS ASSOCIEES**
(54) **Title: NUCLEOTIDE AND NUCLEOSIDE THERAPEUTIC COMPOSITIONS, COMBINATIONS AND USES RELATED THERETO**



FIG. 3

(57) **Abrégé/Abstract:**
This disclosure relates to nucleotide and nucleoside therapeutic compositions and uses in treating infectious diseases, viral infections, and cancer, where the base of the nucleotide or nucleoside contains at least one thiol, thione or thioether. The nucleotide and nucleoside therapeutic compositions can include at least one second antiviral agent, such as an antiviral agent that treats or prevents enterovirus infections.

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Abstract:

This disclosure relates to nucleotide and nucleoside therapeutic compositions and uses in treating infectious diseases, viral infections, and cancer, where the base of the nucleotide or nucleoside contains at least one thiol, thione or thioether. The nucleotide and nucleoside therapeutic compositions can include at least one second antiviral agent, such as an antiviral agent that treats or prevents enterovirus infections.

NUCLEOTIDE AND NUCLEOSIDE THERAPEUTIC COMPOSITIONS, COMBINATIONS AND USES RELATED THERETO

CROSS REFERECE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application 63/184,609 filed May 5, 2021, which is incorporated by reference herein in its entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to nucleotide and nucleoside therapeutic compositions and uses related thereto. In certain embodiments, the disclosure relates to sulfur-containing nucleosides optionally conjugated to a phosphorus oxide or salts thereof. In certain embodiments, the disclosure relates to conjugate compounds or salts thereof comprising an amino acid ester, a lipid or a sphingolipid or derivative linked by a phosphorus oxide to a nucleotide or nucleoside. In certain embodiments, the disclosure contemplates pharmaceutical compositions comprising these compounds in combinations for uses in treating infectious diseases, viral infections, and cancer.

BACKGROUND

Nucleoside and nucleotide phosphates and phosphonates are clinically useful as antiviral agents. Two examples are tenofovir disoproxil fumarate for the treatment of human immunodeficiency virus and adefovir dipivoxil for the treatment of hepatitis B virus infections. Administration of three or more antiretroviral agents in combination, e.g., Highly Active Antiretroviral Therapy (HAART), has significantly reduced the morbidity and mortality associated with HIV infection. However, there is a growing need for new antiviral agents to address the critical issues of resistance and penetration into viral sanctuaries (commonly referred to as privileged compartments). Permeability into privileged compartments may be partially responsible for the current inability of chemotherapy to totally clear a patient of HIV infection and the emergence of resistance.

Anti-viral agents that are unphosphorylated nucleotides and nucleotide derivatives need to be phosphorylated to actively inhibit viral replication. Nucleoside analogues enter a cell via two types of broad-specificity transporters, concentrative nucleoside transporters (CNTs) and equilibrative nucleoside transporters (ENTs). Once inside, they utilize the host's nucleoside salvage pathway for sequential phosphorylation by deoxynucleoside kinases (dNKs), deoxynucleoside monophosphate kinases (dNMPKs) and nucleoside diphosphate

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kinase (NDPK). However, intracellular activation of these compounds is often compromised by the high substrate specificity of the host's endogenous kinases. In vitro and in vivo studies have demonstrated that the first and/or second phosphorylation, catalyzed by dNKs and dNMPKs, often represent the rate-limiting steps in nucleoside analogue activation. Thus, there is a need to identifying improved antiviral nucleoside analogues with structural features that are sufficiently activated by cellular kinases.

McGuigan et al., J Med Chem, 2005, 48(10), 3504-3515, report phenylmethoxyalaninyl phosphoramidate of abacavir as a prodrug leads to enhancement of antiviral potency. Painter et al., Antimicrob Agents Chemother, 2007, 51(10), 3505-3509, report promoting the oral availability of tenofovir with a hexadecyloxypropyl prodrug ester, designated CMX157. PCT Patent Application No. PCT/US2014/054930 and PCT publication No. WO 2015/038596 A1 report nucleotide analogs showing antiviral activity that were not developed into clinical testing.

The diverse viruses in the genus *enterovirus*, family *Picornaviridae*, are positive-sense single-stranded RNA viruses known to cause a range of diseases such as hand, foot and mouth disease (HFMD), encephalitis, aseptic meningitis, myocarditis and various respiratory diseases.*See Journal of Biomedical Science* 28, 10, (2021). Although most EV infections are mild, the symptoms can be severe in the very young and immunodeficient individuals. In recent years, viruses such as EV-A71 and CV-A16 have emerged as serious public health threats, as they have caused major outbreaks of HFMD in China and South East Asia. Additionally, EV-D68 has caused a large outbreak of severe lower respiratory infections in North America in 2014. Therefore, broad-spectrum antiviral drugs that could inhibit multiple EVs across the genus will be instrumental to overcome the public health burden caused by these EVs. *Id.* Five compounds that have been evaluated in phase I and II clinical trials associated with entrovirus infection include disoxaril, pleconaril, pirodavir, vapendavir and pocapavir. Despite their promising in-vitro potencies, the majority of these inhibitors demonstrated insufficient efficacy and unwanted side effects at doses tested in clinical trials. References cited herein are not an admission of prior art.

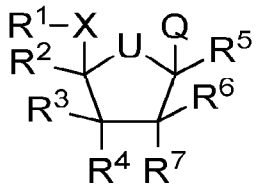
There is a need for compounds, compositions, and methods effective for treating and preventing viral infections, and particularly infections from viruses in the genus *enterovirus*. The compounds, compositions, and methods disclosed herein address these and other needs.

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SUMMARY OF THE DISCLOSURE

This disclosure relates to nucleotide and nucleoside therapeutic compositions and uses related thereto. Included are sulfur-containing nucleosides optionally conjugated to a phosphorus oxide or salts thereof, prodrugs or conjugate compounds or salts thereof comprising an amino acid ester, lipid or a sphingolipid or derivative linked by a phosphorus oxide to a nucleotide or nucleoside.

In some aspects of the present disclosure, the compositions comprise a compound (β-D or β-L) of the following formula:



Formula Ia

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

R^1 is OH, monophosphate, diphosphate, or triphosphate;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

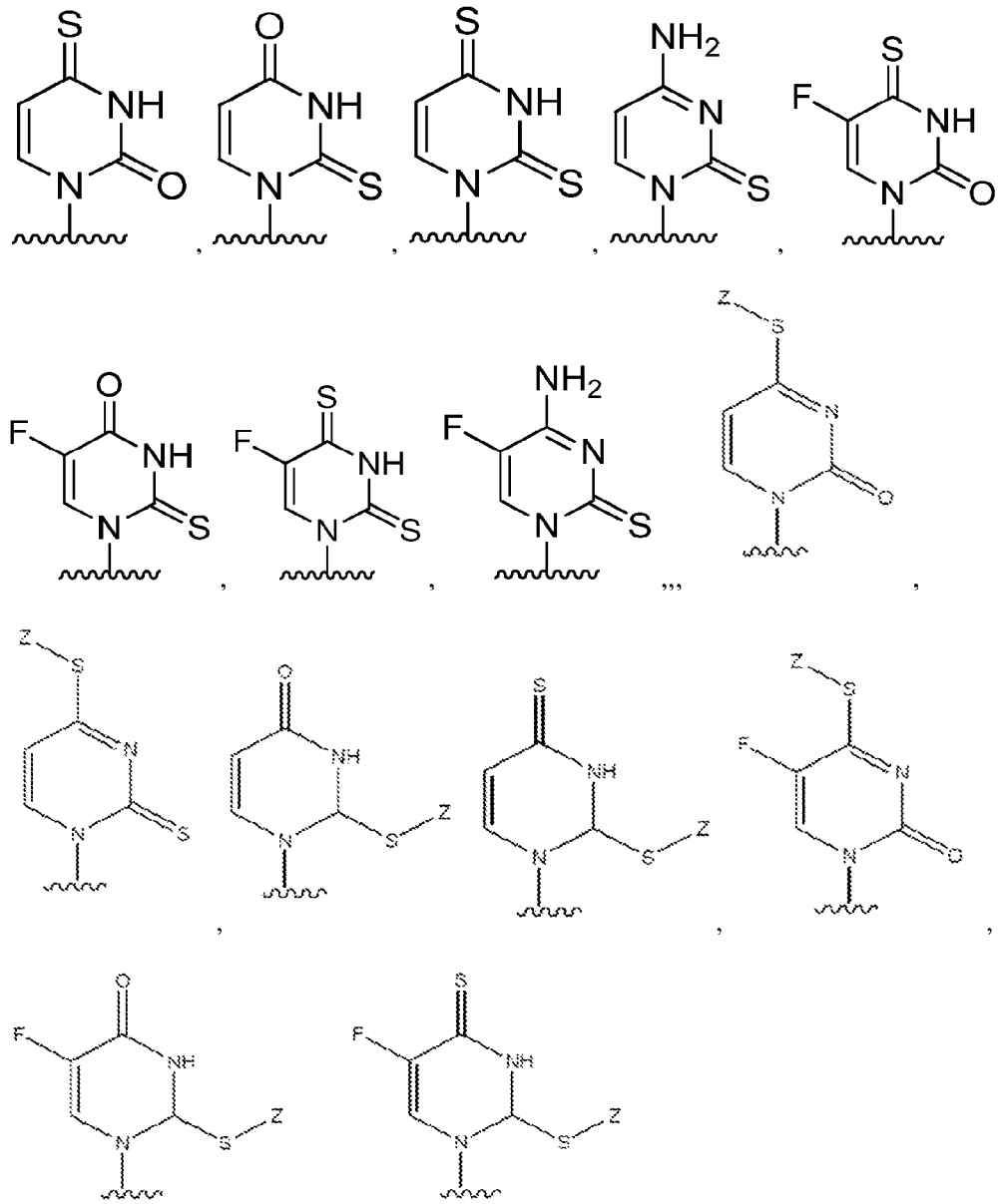
R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is H or D; and

Q is one of the following bases:

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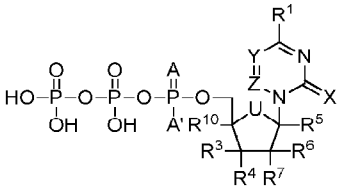
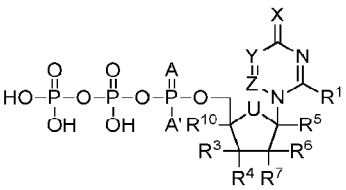
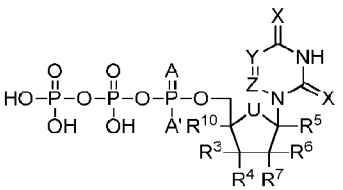


or

wherein Z is OH, alkoxide, methoxide, ethoxide, halogen, thiol, alkylthio, alkyl, lipid, or geranyl, and

a second antiviral agent.

In other aspects of the present disclosure, the compositions comprise a compound (β-D or β-L) of one of the following formulae:

Formula Ic **Formula Id** **Formula Ie**

or a pharmaceutically acceptable salt thereof, wherein

A is O or S;

A' is OH or $BH_3^-M^+$;

R^5 is H or D;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ic and Id, either X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Ie, at least one X is S;

Y is CH, N, or CR^2;

Z is CH, N, or CR^2;

R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

R^8 is methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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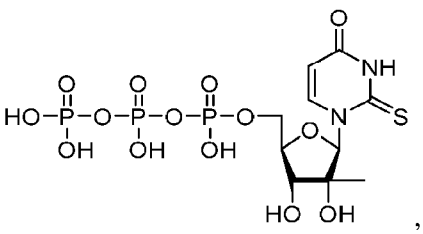
R^2 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9, and

a second antiviral agent.

In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, A is O; A' is OH; U is O; R^5 is H; Y and Z are CH; and R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, one X is S and the other X is O; R^3 is H; R^4 is OH; R^6 is CH_3; R^7 is OH; and R^{10} is H.

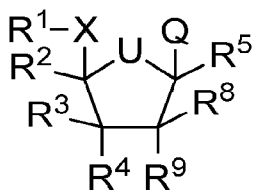
In further aspects of the present disclosure, the compositions comprise a compound having the following structure:



,

or a pharmaceutically acceptable salt thereof, and a second antiviral agent.

In other further aspects of the present disclosure, the compositions comprise a compound (β-D or β-L) of the following formula:



Formula If

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

R^5 is H or D;

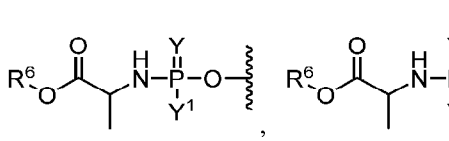
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R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

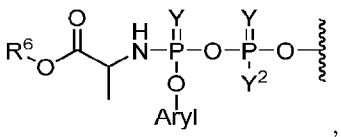
R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

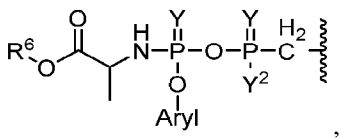
R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

R^1 is one of the formula:


,

,


, or


,

Y is O or S;

Y^1 is OAryl or $BH_3^-M^+$;

Y^2 is OH or $BH_3^-M^+$;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

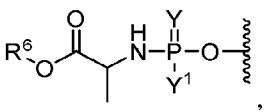
each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10} and

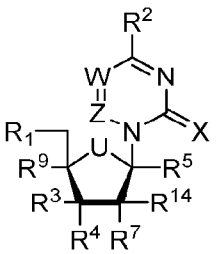
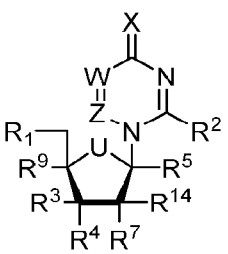
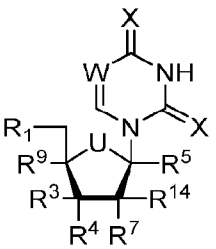
a second antiviral agent.

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In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, U is O; X is CH_2; Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine; R^5 is H; and R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In further embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, R^1 is , Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In still further aspects of the present disclosure, the compositions comprise a compound of one of the following formulae:

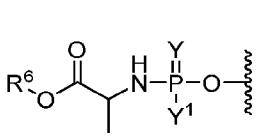
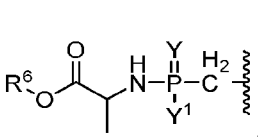
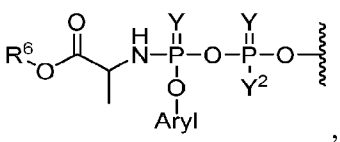
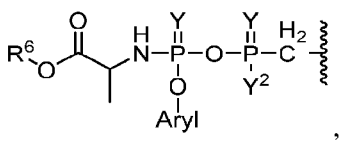
Formula Ig **Formula Ih** **Formula Ii**

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

R^5 is H or D;

R^1 is one of the formula:




, or

,

Y is O or S;

Y^1 is OAryl or $BH_3^-M^+$

Y^2 is OH or $BH_3^-M^+$

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ig and Ih, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

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wherein in Formula Ii, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

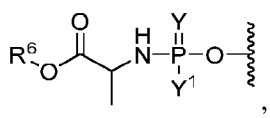
each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

R^8 is deutero, methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10}, and

a second antiviral agent.

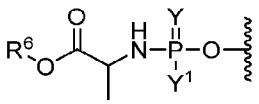
In other embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, U is O; W and Z are CH; R^5 is H; R^1 is , wherein Y is O and Y^1 is phenoxy; and R^6 is alkyl.

In further embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

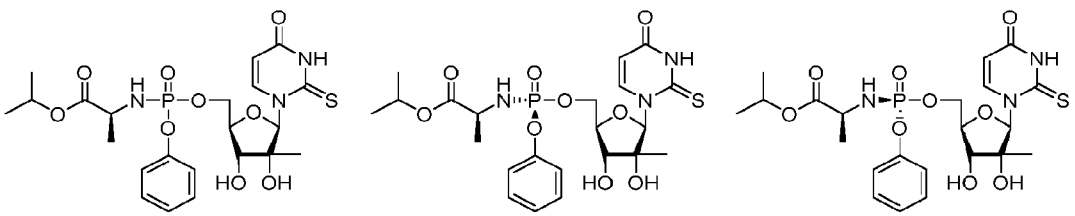
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In further embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, the compound can have a structure represented by formula Ia or a pharmaceutically acceptable salt thereof, wherein one X is O and the other X is S.

In other further embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, R^6 is *iso*-propyl.

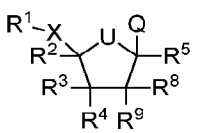
In still further embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, wherein R^5 is H, R^3 is H, R^4 is hydroxyl, R^7 is hyroxyl, R^{14} is methyl, R^1 is , Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In further aspects of the present disclosure, the compositions comprise a compound of one of the following structures:

, and

a second antiviral agent.

In some aspects of the present disclosure, the compositions comprise a compound (β-D or β-L) of the following formula:



Formula Io

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

R^5 is H or D;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

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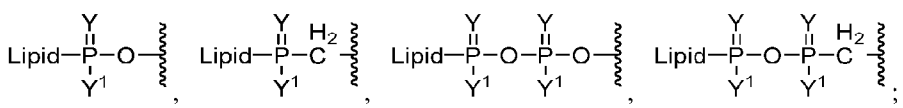
R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^8 and R^9 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^1 is one of the formula:



;

Y is O or S;

Y^1 is OH or $BH_3^-M^+$; and

lipid is as described herein and

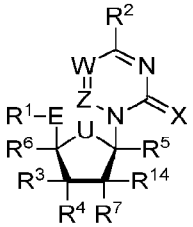
a second antiviral agent.

In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, U is O; Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine; and R^5 is H.

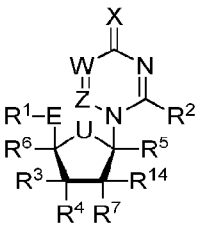
In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, lipid can be hexadecyloxypropyl, 2-aminohexadecyloxypropyl, 2-aminoarachidyl, lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, lignoceryl, or a sphingolipid as described herein.

In further aspects of the present disclosure, the compositions comprise a compound of one of the following structures:

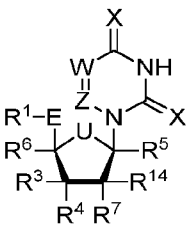
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Formala Ip



Formula Iq



Formula Ir

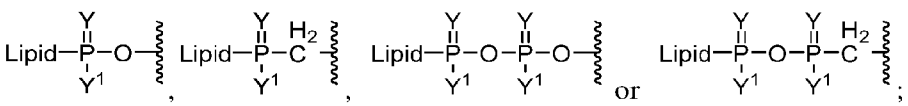
or a pharmaceutically acceptable salt thereof, wherein

R^5 is H or D;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

E is CH_2 or CD_2;

R^1 is one of the formula:



Y is O or S;

Y^1 is OH or $BH_3^-M^+$;

Lipid is as described herein;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ip and Iq, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Ir, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3, R^4, R^6, R^7 and R^{14} are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

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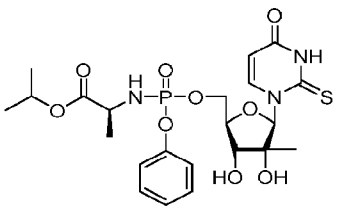
R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, and

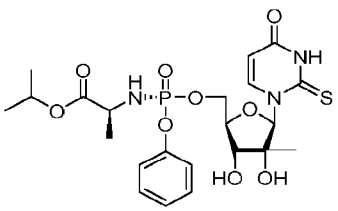
a second antiviral agent.

In some embodiments of the compounds or pharmaceutically acceptable salts disclosed herein, E is CH_2; U is O; and Y and Z are CH.

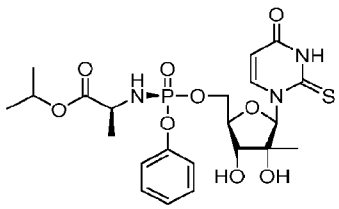
The second antiviral agent can be selected from disoxaril, pleconaril, pirodavir, vapendavir pocapavir, or combinations thereof. In some examples, the second antiviral agent is selected from disoxaril, pleconaril, pirodavir, vapendavir pocapavir, or combinations thereof, and the compound is selected from:



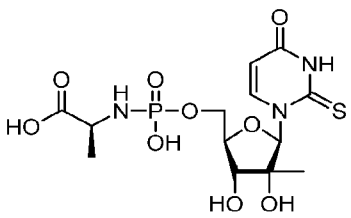
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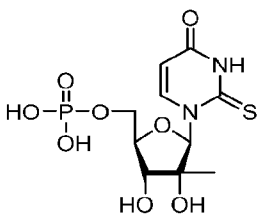


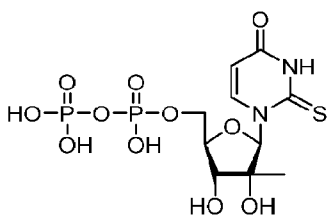
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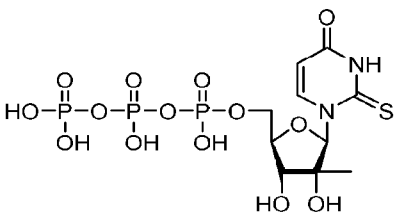


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Pharmaceutical compositions for the treatment or prevention of a viral infection comprising a composition as disclosed herein and a pharmaceutically acceptable carrier are also described. In some embodiments, the pharmaceutical formulation comprises EIDD-2023

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or a pharmaceutically acceptable salt thereof, vapendavir, and a pharmaceutically acceptable carrier.

Liposomal compositions comprising a composition as disclosed herein and a pharmaceutically acceptable carrier are also described.

Methods of treating infections caused by RNA and DNA viruses comprising administering to a host in need an effective amount of a composition as disclosed herein are described. The RNA or DNA virus can be picornaviruses, cardioviruses, enteroviruses, coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, echovirus, erboviruses, hepatovirus, kobuviruses, parechoviruses, teschoviruses, caliciviruses, which include noroviruses, sapoviruses, lagoviruses, vesiviruses, astroviruses, togaviruses, flaviviruses, hepacivirus, coronaviruses, arteriviruses, rhabdoviruses, filoviruses, paramyxoviruses, orthomyxoviruses, hantaviruses, reoviruses, rotaviruses, birnaviruses, chrysoviruses, cystoviruses, hypoviruses partitiviruses, totoviruses, lentiviruses, polyomaviruses, papillomaviruses, adenoviruses, circoviruses ,parvoviruses, erythroviruses, betaparvoviruses, amdoviruses, densoviruses, iteraviruses, brevidensoviruses, pefudensoviruses, herpes viruses 1, 2, 3, 4, 5, 6, 7 and 8, poxviruses, or hepadnaviruses.

In some embodiments, the RNA and DNA virus is an enterovirus. Accordingly, methods of treating or preventing an enterovirus infection comprising administering to a host in need an effective amount of the composition described herein, or a pharmaceutically acceptable salt thereof are provided. In specific embodiments, the composition comprises EIDD-2023 or a pharmaceutically acceptable salt thereof, vapendavir, and a pharmaceutically acceptable carrier. The enterovirus infection can be selected from the group consisting of coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, and echovirus. In specific examples, the enterovirus infection is a coxsackie virus such as Coxsackie A16. In some embodiments of the methods disclosed herein, the host being treated may be immune suppressed.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates certain embodiments of the disclosure.

Figure 2 illustrates exemplary thio-containing bases for certain embodiments provided herein.

Figure 3 illustrates the unraveling of McGuigan prodrugs in vivo. The metabolic unraveling of these prodrugs begins with an esterase-catalyzed cleavage of the carboxylic

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ester, followed by several chemical rearrangement steps resulting in an amino acid phosphoramidate. The final cleavage is carried out by one of several endogenous phosphoramidases, one of
which has been identified to be the histidine triad nucleotide binding protein 1 (hINT1)

Figure 4 illustrates embodiments of mono- and diphosphate structural types.

Figure 5 illustrates schemes for the synthesis of conjugates.

Figure 6 is the X-ray crystal structure for EIDD-02023 crystallized using method in Example 86.

DETAILED DESCRIPTION OF THE DISCLOSURE

This disclosure relates to nucleotide and nucleoside therapeutic compositions and uses related thereto. In certain embodiments, the disclosure relates to sulfur containing nucleosides optionally conjugated to a phosphorus oxide or salts thereof. In certain embodiments, the disclosure relates to conjugate compounds or salts thereof comprising an amino acid ester, a lipid or a sphingolipid or derivative linked by a phosphorus oxide to a nucleotide or nucleoside. In certain embodiments, the disclosure contemplates pharmaceutical compositions comprising these compounds for uses in treating infectious diseases, viral infections, and cancer.

In certain embodiments, the disclosure relates to phosphorus oxide prodrugs of 2'-fluoronucleosides containing sulfur-containing bases for the treatment of positive-sense and negative-sense RNA viral infections through targeting of the virally encoded RNA-dependent RNA polymerase (RdRp). This disclosure also provides the general use of lipids and sphingolipids to deliver nucleoside analogs for the treatment of infectious disease and cancer.

In certain embodiments, the disclosure relates to conjugate compounds or salts thereof comprising a sphingolipid or derivative linked by a phosphorus oxide to a nucleotide or nucleoside, wherein the nucleotide or nucleoside contains a sulfur-containing base. In certain embodiments, the phosphorus oxide is a phosphate, phosphonate, polyphosphate, or polyphosphonate, wherein the phosphate, phosphonate or a phosphate in the polyphosphate or polyphosphonate is optionally a phosphorothioate or phosphoroamidate. In certain embodiments, the lipid or sphingolipid is covalently bonded to the phosphorus oxide through an amino group or a hydroxyl group.

The nucleotide or nucleoside comprises a heterocycle comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein the

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substituted heterocycle is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl.

In certain embodiments, the heterocycle comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether or selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione or 4-amino-5-fluoropyrimidine-2-thione.

In certain embodiments, the sphingolipid is saturated or unsaturated 2-aminoalkyl or 2-aminooctadecane optionally substituted with one or more substituents. In certain embodiments, the sphingolipid derivative is saturated or unsaturated 2-aminooctadecane-3-ol optionally substituted with one or more substituents. In certain embodiments, the sphingolipid derivative is saturated or unsaturated 2-aminooctadecane-3,5-diol optionally substituted with one or more substituents.

In certain embodiments, the disclosure contemplates pharmaceutical compositions comprising any of the compounds disclosed herein and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is in the form of a pill, capsule, tablet, or saline buffer comprising a saccharide. In certain embodiments, the composition may contain a second active agent such as a pain reliever, anti-inflammatory agent, non-steroidal anti-inflammatory agent, anti-viral agent, anti-biotic, or anti-cancer agent.

In certain embodiments, the disclosure relates to methods of treating or preventing an infection comprising administering an effective amount of a compound disclosed herein to a subject in need thereof. Typically, the subject is diagnosed with or at risk of an infection from a virus, bacteria, fungi, protozoa, or parasite.

In certain embodiments, the disclosure relates the methods of treating a viral infection comprising administering an effective amount of a pharmaceutical composition disclosed herein to a subject in need thereof. In certain embodiments, the subject is a mammal, for example, a human. In certain embodiments, the subject is diagnosed with a chronic viral infection. In certain embodiments, administration is under conditions such that the viral infection is no longer detected. In certain embodiments, the subject is diagnosed with a RNA virus, DNA virus, or retroviruses. In certain embodiments, the subject is diagnosed with a virus that is a double stranded DNA virus, sense single stranded DNA virus, double stranded RNA virus, sense single stranded RNA virus, antisense single stranded RNA virus, sense single stranded RNA retrovirus or a double stranded DNA retrovirus.

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In certain embodiments, the subject is diagnosed with an infection caused by an enterovirus including the following fifteen species: *Enterovirus A* (formerly *Human enterovirus A*), *Enterovirus B* (formerly *Human enterovirus B*), *Enterovirus C* (formerly *Human enterovirus C*), *Enterovirus D* (formerly *Human enterovirus D*), *Enterovirus E* (formerly *Bovine enterovirus* group A), *Enterovirus F* (formerly *Bovine enterovirus* group B), *Enterovirus G* (formerly *Porcine enterovirus B*), *Enterovirus H* (formerly *Simian enterovirus A*), *Enterovirus I*, *Enterovirus J*, *Enterovirus K*, *Enterovirus L*, *Rhinovirus A* (formerly *Human rhinovirus A*), *Rhinovirus B* (formerly *Human rhinovirus B*), *Rhinovirus C* (formerly *Human rhinovirus C*). These fifteen species' serotype include:

Coxsackievirus including

- *Enterovirus A:* serotypes CVA-2, CVA-3, CVA-4, CVA-5, CVA-6, CVA-7, CVA-8, CVA-10, CVA-12, CVA-14, and CVA-16.
- *Enterovirus B:* serotypes CVB-1, CVB-2, CVB-3, CVB-4, CVB-5, CVB-6, and CVA-9.
- *Enterovirus C:* serotypes CVA-1, CVA-11, CVA-13, CVA-17, CVA-19, CVA-20, CVA-21, CVA-22, and CVA-24.

Echovirus including

- *Enterovirus B:* serotypes E-1, E-2, E-3, E-4, E-5, E-6, E-7, E-9, E-11 through E-21, E-24, E-25, E-26, E-27, E-29, E-30, E-31, E32, and E-33.

Enterovirus including

- *Enterovirus A:* serotypes EV-A71, EV-A76, EV-A89 through EV-A92, EV-A114, EV-A119, EV-A120, EV-A121, SV19, SV43, SV46, and BabEV-A13.
- *Enterovirus B:* serotypes EV-B69, EV-B73 through EV-B75, EV-B77 through EV-B88, EV-B93, EV-B97, EV-B98, EV-B100, EV-B101, EV-B106, EV-B107, EV-B110 through EV-B113, and SA5.
- *Enterovirus C:* serotypes EV-C95, EV-C96, EV-C99, EV-C102, EV-C104, EV-C105, EV-C109, EV-C113, EV-C116, EV-C117, and EV-C118.
- *Enterovirus D:* serotypes EV-D68, EV-D70, EV-D94, EV-D111, and EV-D120.
- *Enterovirus E:* serotypes EV-E1, EV-E2, EV-E3, EV-E4, and EV-E5.
- *Enterovirus F:* serotypes EV-F1, EV-F2, EV-F3, EV-F4, EV-F5, EV-F6, and EV-F7.
- *Enterovirus G:* serotypes EV-G1 through EV-G20.
- *Enterovirus H:* serotype EV-H.
- *Enterovirus I:* serotype EV-I1 and EV-I2.
- *Enterovirus J:* serotypes: EV-J1, EV-J103, and EV-J108.

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- *Enterovirus K:* serotype EV-K1 and EV-K2.
- *Enterovirus L:* serotype EV-L1.

Rhinovirus including

- *Rhinovirus A:* serotypes RV-A1, RV-A1B, RV-A2, RV-A7 through RV-A13, RV-A15, RV-A16, RV-A18 through RV-A25, RV-A28 through RV-A34, RV-A36, RV-A38 through RV-A41, RV-A43, RV-A45 through RV-A47, RV-A49 through RV-A51, RV-A53 through RV-A68, RV-A71, RV-A73 through RV-A78, RV-A80 through RV-A82, RV-A85, RV-A88 through RV-A90, RV-A94, RV-A96, and RV-A100 through RV-A108
- *Rhinovirus B:* serotypes RV-B3 through RV-B6, RV-B14, RV-B17, RV-B26, RV-B27, RV-B35, RV-B37, RV-B42, RV-B48, RV-B52, RV-B69, RV-B70, RV-B72, RV-B79, RV-B83, RV-B84, RV-B86, RV-B91 through RV-B93, RV-B97, and RV-B99 through RV-B104
- *Rhinovirus C:* serotypes RV-C1 through RV-C51, RV-C54, RV-C55, and RV-C56.

Poliovirus including

- *Enterovirus C:* serotypes PV-1, PV-2, and PV-3.

In certain embodiments, the subject is 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, chikungunya, Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV), 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).

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

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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, 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:

poliomyelitis such as via the fecal-oral route;

polio-like syndrome such as those found in children who tested positive for enterovirus 68;

nonspecific febrile illness, which is the most common presentation of enterovirus infection. Other than fever, symptoms include muscle pain, sore throat, gastrointestinal distress/abdominal discomfort, and headache. In newborns the picture may be that of sepsis, however, and can be severe and life-threatening;

aseptic meningitis. In the United States, enteroviruses are responsible for 30,000 to 50,000 meningitis hospitalizations per year as a result of 10–15 million infections;

Bornholm disease or epidemic pleurodynia, which is characterized by severe paroxysmal pain in the chest and abdomen, along with fever, and sometimes nausea, headache, and emesis;

pericarditis and/or myocarditis, which are typically caused by enteroviruses. The symptoms may include fever with dyspnea and chest pain. Arrhythmias, heart failure, and myocardial infarction have also been reported as symptoms;

acute hemorrhagic conjunctivitis, which can be caused by enteroviruses;

herpangina, which can be caused by Coxsackie A virus. Herpangina causes a vesicular rash in the oral cavity and on the pharynx, along with high fever, sore throat, malaise, and often dysphagia, loss of appetite, back pain, and headache.;

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hand, foot and mouth disease, which is generally a childhood illness most commonly caused by infection by Coxsackie A virus or EV71;

encephalitis, which is rare manifestation of enterovirus infection. In general, when Encephalitis occurs, the most frequent enterovirus found to be causing it is echovirus 9;

myocarditis, which is characterized by inflammation of the myocardium (cardiac muscle cells). Over the last couple of decades, enterovirus has been identified as playing a role in myocarditis pathogenesis. One of the most common enteroviruses found to be responsible for causing Myocarditis is the Coxsackie B3 virus;

acute respiratory or gastrointestinal infections associated with enterovirus, which may be a factor in chronic fatigue syndrome; or

a combination thereof.

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.

In certain embodiments, pharmaceutical compositions disclosed herein are administered in combination with a second antiviral agent, such as 25-hydroxycholesterol, AN-12-H5, disoxaril, , pirodavir, vapendavir and pocapavir, abacavir, acyclovir, acyclovir, adefovir, amantadine, amiloride, amprenavir, ampligen, arbidol, atazanavir, atripla, aurintricarboxilic acid, BF738735, boceprevir, BPR-3P0128, buthionine sulfoxime, cidofovir, cyclosporin A, combivir, darunavir, DAS181, DC07090, delavirdine, dibucaine, didanosine, docosanol, DTrip-22, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, enviroxime, famciclovir, fluoxetine, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, geldanamycin, gemcitabine, gliotoxin, GPC-N114, guanidine hydrochloride, GW5074, HBB, HL05100P2, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, intrazonazole, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, MRL-1237, nelfinavir, nevirapine, nexavir, NIM-811, oseltamivir, OSW-1, peginterferon alfa-2a, penciclovir, peramivir, PIK93, pirlindole, pleconaril (Picovir), podophyllotoxin , raltegravir, ribavirin, rimantadine, ritonavir, rupintrivir, pyramidine, saquinavir, sofosbovir, stavudine, T-00127-HEV1, T-00127-HEV2, TBZE-029, telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, TP-219, TTP-8307, V-7404, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine zalcitabine, zanamivir, zidovudine, or zuclopenthixol and combinations thereof.

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In certain embodiment, the disclosure relates to uses of compounds disclosed herein in the production or manufacture of a medicament for the treatment or prevention of an infectious disease and/or viral infection.

In certain embodiments, the disclosure relates to derivatives of compounds disclosed herein or any of the formula.

Additional advantages of the disclosure will be set forth in part in the description which follows. 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 of the disclosure, as claimed.

It is to be understood that this disclosure is not limited to the particular embodiments described. 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,

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and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

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. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

Prior to describing the various embodiments, the following definitions are provided and should be used unless otherwise indicated.

As used herein, the term "phosphorus oxide" refers to any variety of chemical moieties that contain a phosphorus-oxygen (P-O or P=O) bond. When used as linking groups herein, the joined molecules may bond to oxygen or directly to the phosphorus atoms. The term is intended to include, but are not limited to phosphates, in which the phosphorus is typically bonded to four oxygens and phosphonates, in which the phosphorus is typically bonded to one carbon and three oxygens. A "polyphosphate" generally refers to phosphates linked together by at least one phosphorus-oxygen-phosphorus (P-O-P) bond. A "polyphosphonate" refers to a polyphosphate that contains at least one phosphorus-carbon (C-P-O-P) bond. In addition to containing phosphorus-oxygen bond, phosphorus oxides may contain a phosphorus-thiol (P-S or P=S) bond and/or a phosphorus-amine (P-N) bond, respectively referred to as phosphorothioate or phosphoroamidate. In phosphorus oxides, the oxygen atom may form a double or single bond to the phosphorus or combinations, and the oxygen may further bond with other atoms such as carbon or may exist as an anion which is counter balanced with a cation, e.g., metal or quaternary amine.

As used herein, "alkyl" means a noncyclic, cyclic, linear or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 22 carbon atoms, and specifically includes methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Alkyl groups can be optionally substituted with one or more moieties selected from, for example, hydroxyl, amino, halo, deutero, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, or any other viable functional group that does not inhibit the pharmacological activity of this compound, either unprotected, or protected, as necessary, as known to those skilled in the art, for example, as taught in T. W. Greene and P. G. M. Wuts, "Protective

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Groups in Organic Synthesis," 3ed., John Wiley & Sons, 1999, hereby incorporated by reference.

The term "lower alkyl," as used herein, and unless otherwise specified, refers to a C1 to C4 saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred.

The term "halo" or "halogen," as used herein, includes chloro, bromo, iodo and fluoro.

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups that contain 3 to 30 carbon atoms. 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 may be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may 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.

"Aryl" means an aromatic carbocyclic monocyclic or polycyclic ring that contains 6 to 32 carbon atoms, such as phenyl or naphthyl. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic.

As used herein, "heteroaryl" 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 may, 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.

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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 may 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 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 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, and t-butoxy.

"Alkylamino" refers an alkyl group as defined above 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 attached through a carbonyl bride (i.e., -(C=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above 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).

"Alkylsulfinyl" refers to an alkyl as defined above attached through a sulfinyl bridge (i.e. -S(=O)alkyl).

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 may be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context may 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 may 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 is optional and therefore it is possible for the designated atom to be unsubstituted.

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As used herein, "salts" refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In typical embodiments, the salts are conventional nontoxic pharmaceutically acceptable salts including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2- acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

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

The term “prodrug” refers to an agent that is converted into a biologically active form in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis.

As used herein, the term “derivative” refers to a structurally similar compound that retains sufficient functional attributes of the identified analogue. The derivative may be structurally similar because it is lacking one or more atoms, substituted with one or more substituents, a salt, in different hydration/oxidation states, e.g., substituting a single or double bond, substituting a hydroxy group for a ketone, or because one or more atoms within the molecule are switched, such as, but not limited to, replacing an oxygen atom with a sulfur or nitrogen atom or replacing an amino group with a hydroxyl group or vice versa. Replacing a carbon with nitrogen in an aromatic ring is a contemplated derivative. The derivative may be a prodrug. Derivatives may be prepared by any variety of synthetic methods or appropriate adaptations presented in the chemical literature or as in synthetic or organic chemistry text books, such as those provide in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th Edition (2007) Michael B. Smith or Domino

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Reactions in Organic Synthesis, Wiley (2006) Lutz F. Tietze hereby incorporated by reference.

As used herein, the terms "prevent" and "preventing" include the full or partial inhibition of the recurrence, spread or onset of a referenced pathological condition or disease. 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 may be administered prior to, together with, or after the additional treatment, or a combination thereof. The combination can for example be formulated as a single pharmaceutical formulation such as a single pill, as separate formulations such as two pills to be co-administered at the same time, or as separate formulations such as two pills to be sequentially administered but such that the agents/compounds overlap in the body. The agents in the combination can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Nucleoside Analogues as Antiviral Agents

Nucleoside analogs utilize the host's nucleoside salvage pathway for sequential phosphorylation by deoxynucleoside kinases (dNKs), deoxynucleoside monophosphate kinases (dNMPKs) and nucleoside diphosphate kinase (NDPK). However, intracellular activation of these compounds is often compromised by the high substrate specificity of the host's endogenous kinases. In vitro and in vivo studies have demonstrated that the first and/or second phosphorylation, catalyzed by dNKs and dNMPKs, often represent the rate-limiting steps in nucleoside analog activation. These significant blockades in the phosphorylation cascade of a given nucleoside analog will result in the lack of any observable activity in cellular assays. To circumvent these blockades, several kinase bypass strategies have been developed. For example, McGuigan phosphoramidates are chemical conjugates used for kinase bypass. See Serpi et al., J Med Chem, 2012, 55(10):4629-4639. The

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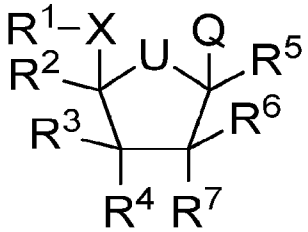
metabolism of these prodrugs begins with an esterase-catalyzed cleavage of the carboxylic ester, followed by several chemical rearrangement steps resulting in an amino acid phosphoramidate. The final cleavage is carried out by one of several endogenous phosphoramidases, one of which has been identified to be the histidine triad nucleotide binding protein 1 (hINT1).

An alternative prodrug strategy to circumvent these blockades is to utilize sphingoid bases to mask nucleotide analog phosphates. Sphingoid bases have the potential for delivering nucleotide analog phosphates to critical tissues such as the brain. The design concept driving the use of sphingoid bases to form nucleoside-lipid conjugates is based on observations that the sphingoid base analogs are: (a) well absorbed after oral administration, (b) resistant to oxidative catabolism in enterocytes, and (c) achieve high concentrations in the brain. Based on data for intestinal uptake of traditional phospholipid drug conjugates in mice and our data for sphingoid base oral absorption in rats, our sphingoid base conjugates should be well absorbed and resist first pass metabolism. After absorption, sphingoid bases, including sphingosine-1-phosphate, are transported in blood via both lipoproteins and free plasma proteins like albumin. Active epithelial cell uptake of sphingoid base phosphates has been demonstrated to occur via the ABC transporter, CFTR, but passive protein transport and endocytotic uptake are also possible; it is believed that extracellularly delivered drug conjugates would be processed similarly by target cells in the central nervous system (CNS) and the gut–associated lymphoid tissue (GALT). The rat sphingolipid PK studies mentioned above resulted in 24 hour tissue concentrations exceeding plasma Cmax concentrations by 10 to 300+ fold, with lung and brain levels being particularly high and without evidence of toxicity. This approach has significant potential for conjugate delivery of high drug concentrations to critical tissues.

Compounds

In certain embodiments, the disclosure relates to nucleosides having sulfur containing bases conjugated to a phosphorus moiety or pharmaceutically acceptable salts thereof.

In certain embodiments, the present disclosure relates to compounds of the following formula:



Formula I

or pharmaceutically acceptable salts thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is O, CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^1 is a phosphonate, phosphonophosphate, phosphonodiphosphate or phosphate, including monophosphate, diphosphate, triphosphate, and polyphosphate, or polyphosphonate;

wherein the phosphonate or a phosphate in the polyphosphate is optionally a phosphoroborate, phosphorothioate, or phosphoroamidate;

wherein the phosphonate or a phosphate in the polyphosphate, phosphoroborate, phosphorothiolate, or phosphoroamidate is optionally substituted with one or more, the same or different R^8;

wherein the phosphonate or a phosphate in the polyphosphate, phosphoroborate, phosphorothiolate, or phosphoroamidate optionally forms a phosphorus containing heterocyclic ring;

wherein the phosphonate, phosphonophosphate, phosphonodiphosphate, phosphate, polyphosphate, polyphosphonate, phosphorothiolate, or phosphoroamidate optionally forms a phosphorus containing heterocyclic ring with the R^3 or R^4 carbon;

R^2, R^3, R^4, R^6, R^7, and R^8 are independently H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, NO_2, $C(O)O(C_{1\text{-}22}$ alkyl), $C(O)O(C_{1\text{-}22}$ alkyl), $C(O)O(C_{1\text{-}22}$ alkynyl), $C(O)O(C_{1\text{-}22}$ alkenyl), $O(C_{1\text{-}22}$ acyl), $O(C_{1\text{-}22}$ alkyl), $O(C_{1\text{-}22}$ alkenyl), $S(C_{1\text{-}22}$ acyl), $S(C_{1\text{-}22}$ alkyl), $S(C_{1\text{-}22}$ alkynyl), $S(C_{1\text{-}22}$ alkenyl), $SO(C_{1\text{-}22}$ acyl), $SO(C_{1\text{-}22}$ alkyl), $SO(C_{1\text{-}22}$ alkynyl), $SO(C_{1\text{-}22}$ alkenyl), $SO_2(C_{1\text{-}22}$ acyl), $SO_2(C_{1\text{-}22}$ alkyl), $SO_2(C_{1\text{-}22}$ alkynyl), $SO_2(C_{1\text{-}22}$ alkenyl), $O_3S(C_{1\text{-}22}$ acyl), $O_3S(C_{1\text{-}22}$ alkyl), $O_3S(C_{1\text{-}22}$ alkenyl), NH_2, $NH(C_{1\text{-}22}$ alkyl), $NH(C_{1\text{-}22}$ alkenyl), $NH(C_{1\text{-}22}$ alkynyl), $NH(C_{1\text{-}22}$ acyl), $N(C_{1\text{-}22}$ alkyl)$_2$, $N(C_{1\text{-}22}$ acyl)$_2$, sulfamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl,

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methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, or carbocyclyl;

wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3, CN, one to three halogen (Cl, Br, F, I), deuterium, NO_2, $C(O)O(C_{1-22}$ alkyl), $C(O)O(C_{1-22}$ alkyl), $C(O)O(C_{1-22}$ alkynyl), $C(O)O(C_{1-22}$ alkenyl), $O(C_{1-22}$ acyl), $O(C_{1-22}$ alkyl), $O(C_{1-22}$ alkenyl), $S(C_{1-22}$ acyl), $S(C_{1-22}$ alkyl), $S(C_{1-22}$ alkynyl), $S(C_{1-22}$ alkenyl), $SO(C_{1-22}$ acyl), $SO(C_{1-22}$ alkyl), $SO(C_{1-22}$ alkynyl), $SO(C_{1-22}$ alkenyl), $SO_2(C_{1-22}$ acyl), $SO_2(C_{1-22}$ alkyl), $SO_2(C_{1-22}$ alkynyl), $SO_2(C_{1-22}$ alkenyl), $O_3S(C_{1-22}$ acyl), $O_3S(C_{1-22}$ alkyl), $O_3S(C_{1-22}$ alkenyl), NH_2, $NH(C_{1-22}$ alkyl), $NH(C_{1-22}$ alkenyl), $NH(C_{1-22}$ alkynyl), $NH(C_{1-22}$ acyl), $N(C_{1-22}$ alkyl)$_2$, $N(C_{1-22}$ acyl)$_2$, sulfamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, or carbocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^9;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl; and

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl.

In certain exemplary embodiments of any of the formulae described herein, U is selected from the group consisting of: NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, and $C{=}CF_2$.

In certain exemplary embodiments of any of the formulae described herein, X is selected from the group consisting of: CHMe, CMe_2, CHF, and CF_2.

In certain exemplary embodiments of any of the formulae described herein, R^3 and R^4, with the carbon atom they are attached to form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^9.

In certain exemplary embodiments of any of the formulae described herein,R^6 and R^7, with the carbon atom they are attached to, form a spirocycle containing carbon, oxygen,

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sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^9;

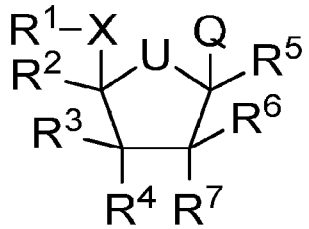
In certain exemplary embodiments of any of the formulae described herein, R^5 is selected from the group consisting of: Me, CN, alkyl, alkenyl, and alkynyl.

In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In preferred embodiments, X is CH_2.

In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



Formula Ia

or pharmaceutically acceptable salts thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is O, CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^1 is OH, monophosphate, diphosphate, or triphosphate;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

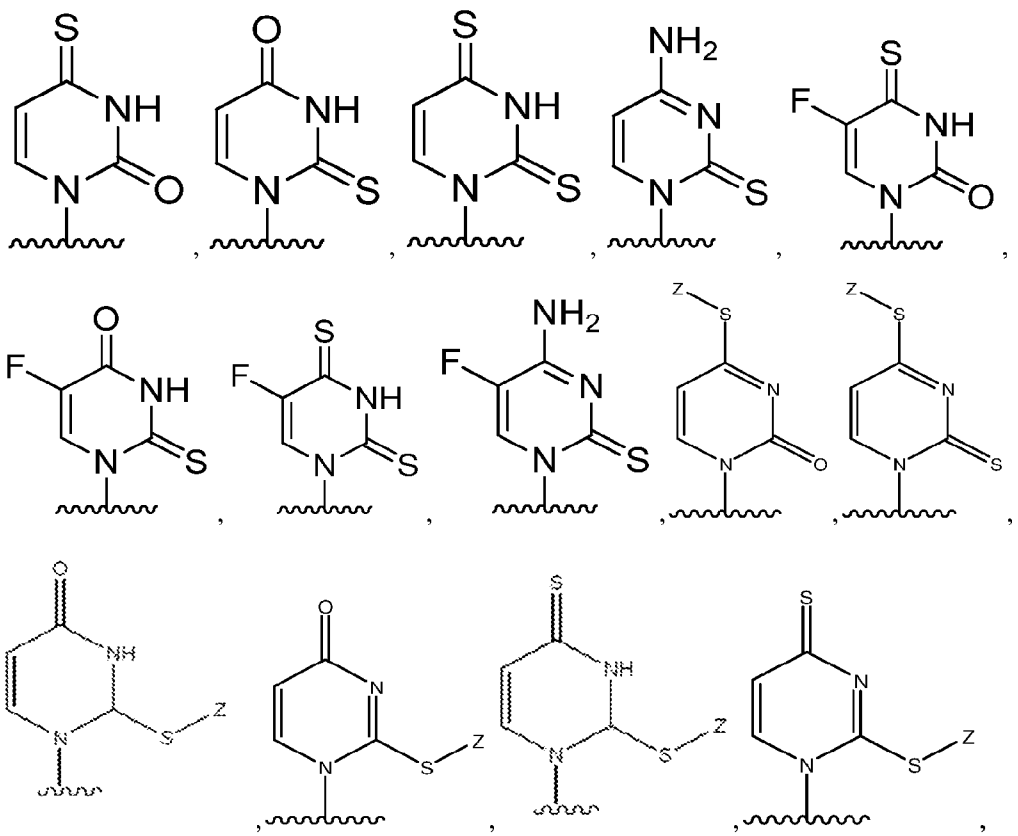
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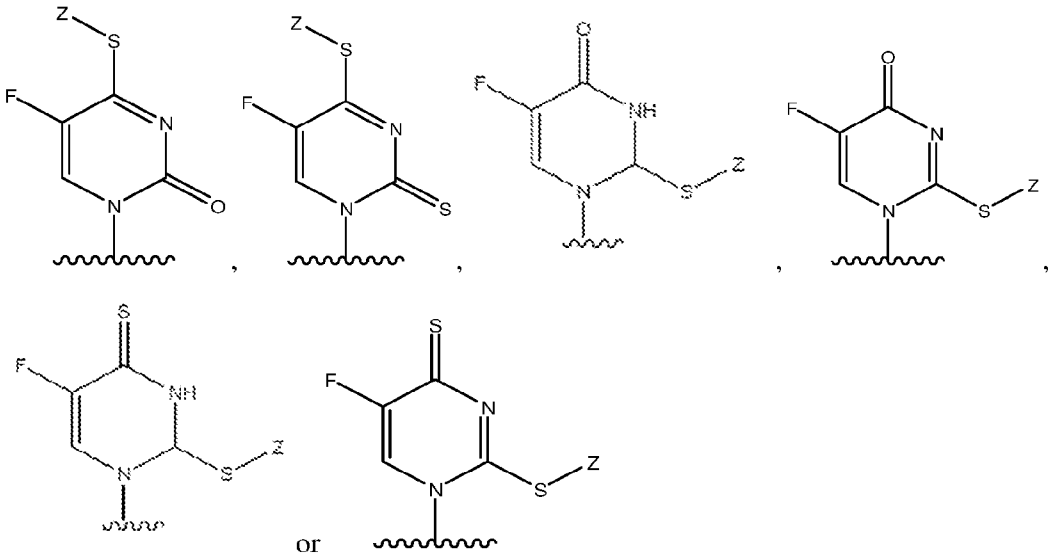
R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl; and

Q is one of the following bases:





wherein Z is alkyl, alkyenyl, acyl, lipid, or geranyl.

In a particular embodiment, R^2 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I. In one embodiment, R^2 is H.

In another particular embodiment, R^3 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In still another particular embodiment, R^4 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In a further particular embodiment, R^5 is selected from the group consisting of H and D.

In a further particular embodiment, R^6 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In yet another particular embodiment, R^7 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

Lipid, as used herein, is a C_{6-22} alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

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

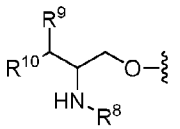
In certain embodiments, the lipid is 2-aminohexadecyloxypropyl.

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 having the formula:

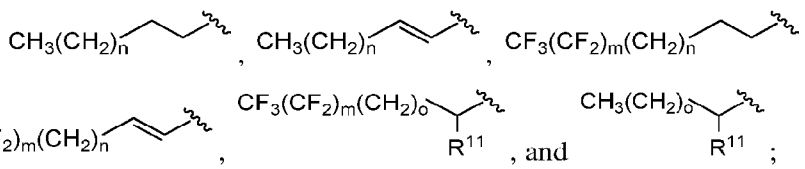


wherein,

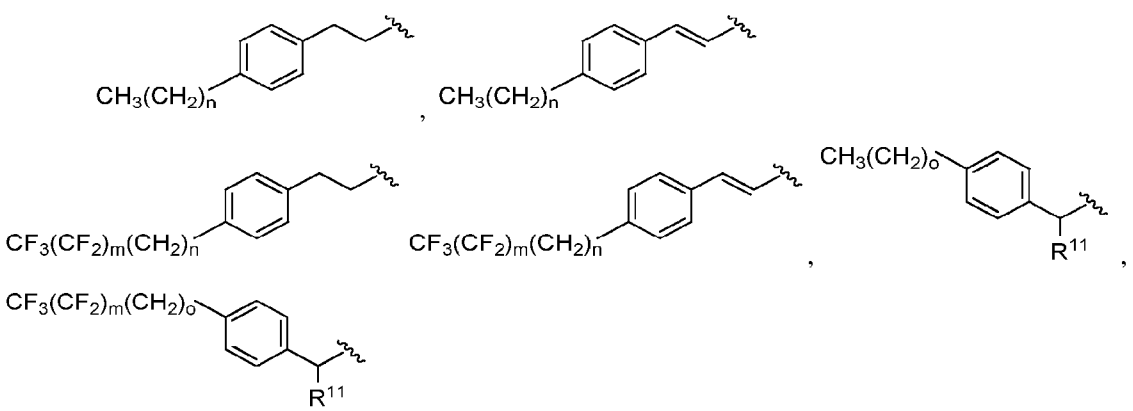
R^8 of the sphingolipid is hydrogen, alkyl, $C(=O)R^{12}$, $C(=O)OR^{12}$, or $C(=O)NHR^{12}$;

R^9 of the sphingolipid is hydrogen, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{10} 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:



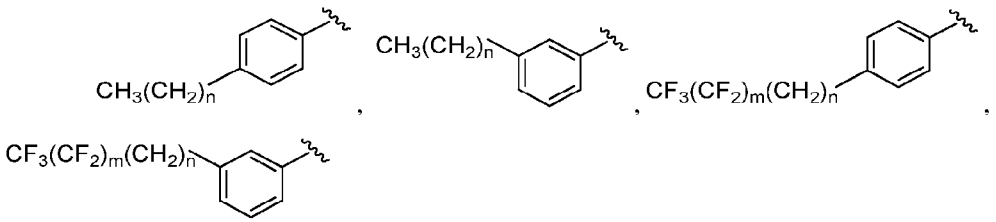
n is 8 to 14 or less than or equal to 8 to less than or equal to 14, o is 9 to 15 or less than or equal to 9 to less than or equal to 15, the total or m and n is 8 to 14 or less than or equal to 8 to less than or equal to 14, the total of m and o is 9 to 15 or less than or equal to 9 to less than or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



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

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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



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;

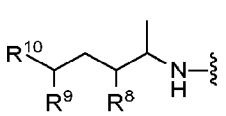
R^{11} of the sphingolipid is OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{12} of the sphingolipid is hydrogen, a branched or strait chain C_{1-12}alkyl, C_{13-22}alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{13}; and

R^{13} of the sphingolipid is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R^{12} of the sphingolipid is H, alkyl, methyl, ethyl, propyl, n-butyl, branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, phenyl, monosubstituted phenyl, disubstituted phenyl, trisubstituted phenyl, or saturated or unsaturated C12-C19 long chain alkyl.

In certain embodiments, the sphingolipid has the formula:



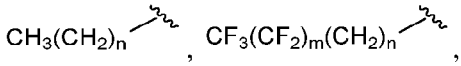
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wherein,

R^8 of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^9 of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{10} 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:



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^{12} of the sphingolipid is hydrogen, a branched or strait chain $C_{1\text{-}12}$alkyl, $C_{13\text{-}22}$alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{13}; and

R^{13} of the sphingolipid is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R^{12} of the sphingolipid is H, alkyl, methyl, ethyl, propyl, n-butyl, branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, phenyl, monosubstituted phenyl, disubstituted phenyl, trisubstituted phenyl, or saturated or unsaturated C_{12}-C_{19} long chain alkyl.

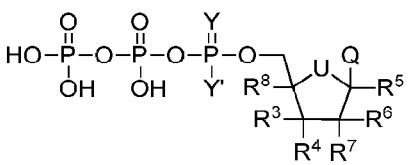
Suitable sphingolipids include, but are not limited to, sphingosine, ceramide, or sphingomyelin, or 2-aminoalkyl optionally substituted with one or more substituents.

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-

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(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 may be optionally substituted with one or more substituents.

In certain embodiments, the disclosure relates to compounds of the following formula:



Formula Ib

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y is O or S;

Y' is OH, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

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R^3, R^4, R^6, R^7 and R^8 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl.

In certain exemplary embodiments of any of the formulae described herein, Y' is selected from the group consisting of: OR", SR", NHR", and $NR"_2$.

In particular embodiments, Q is a heterocycle selected from the group consisting of pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In one embodiment, R^3 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In another embodiment, R^4 is selected from the group consisting of H, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

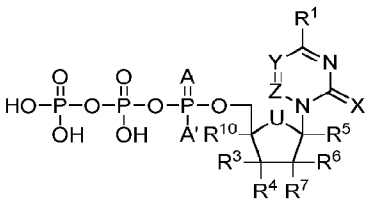
In still another embodiment, R^6 is selected from the group consisting of H, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In yet another embodiment, R^7 is selected from the group consisting of H, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

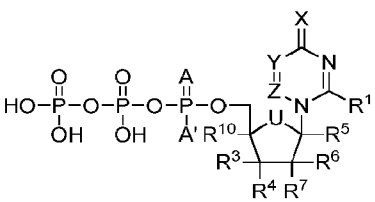
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In yet a further embodiment, R^8 is selected from the group consisting of H, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I. In one embodiment, R^8 is H.

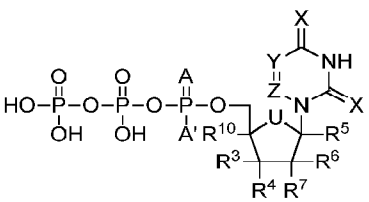
In certain embodiments, the disclosure relates to compounds of one of the following formulae:



Formula Ic



Formula Id



Formula Ic

or a pharmaceutically acceptable salt thereof, wherein

A is O or S;

A' is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ic and Id, either X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Ie, at least one X is S;

Y is CH, N, or CR^2;

Z is CH, N, or CR^2;

R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^8 is methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^2 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9.

In certain exemplary embodiments of any of the formulae described herein, A' is selected from the group consisting of: OR", SR", NHR", and $NR"_2$.

In certain exemplary embodiments of any of the formulae described herein, R^2 is deutero.

In one embodiment, R^3 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In another embodiment, R^4 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In still another embodiment, R^6 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In yet another embodiment, R^7 is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In yet a further embodiment, R^{10} is selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I. In one embodiment, R^8 is H.

In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is fluoro. In an still further embodiment, R^{10} is H.

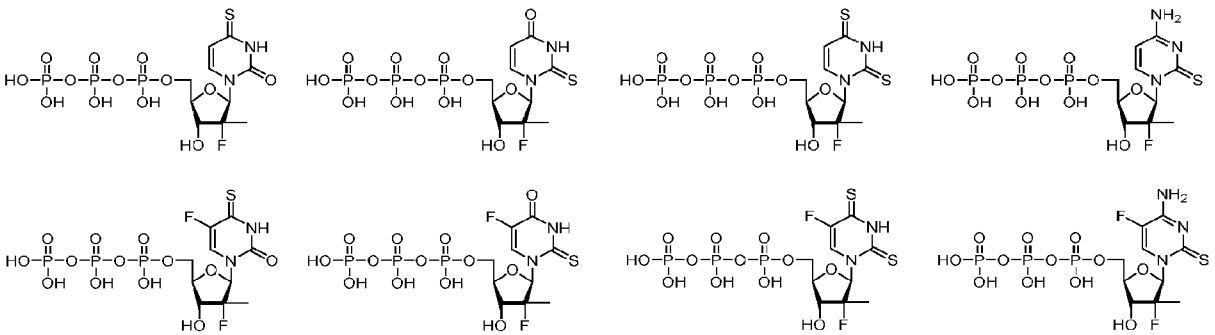
In other embodiments, the compound or a pharmaceutically acceptable salt thereof is defined wherein A is O; A' is OH; U is O; R^5 is H; Y and Z are CH; and R^3, R^4, R^6, R^7 and

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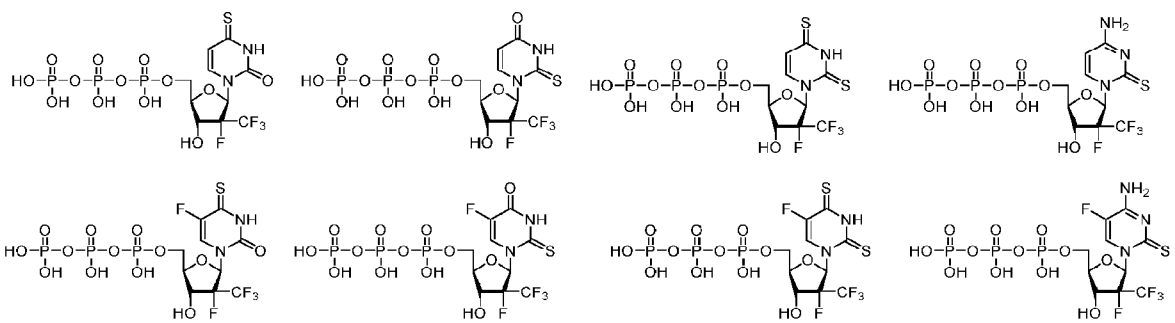
R^{10} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In other embodiments, the compound is represented by Formula Ie, or a pharmaceutically acceptable salt thereof, wherein one X is S and the other X is O; R^3 is H; R^4 is OH; R^6 is CH_3; R^7 is OH; and R^{10} is H.

In exemplary embodiments, the compound is selected from the group consisting of:

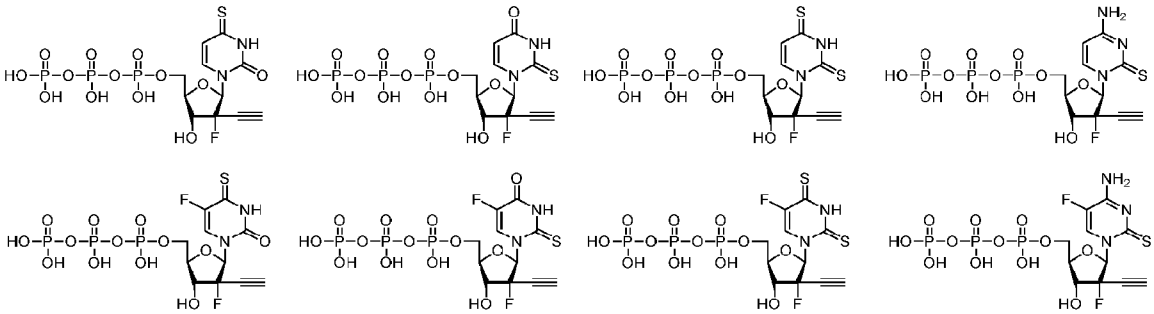


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is trifluoromethyl. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

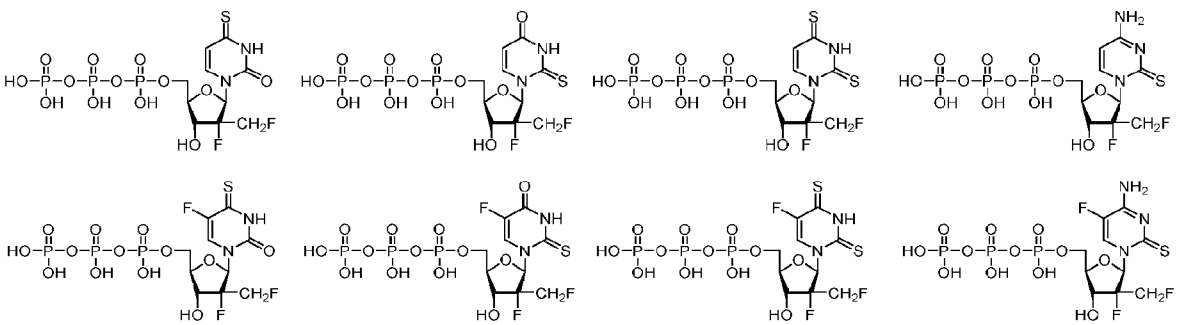


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is C≡CH. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

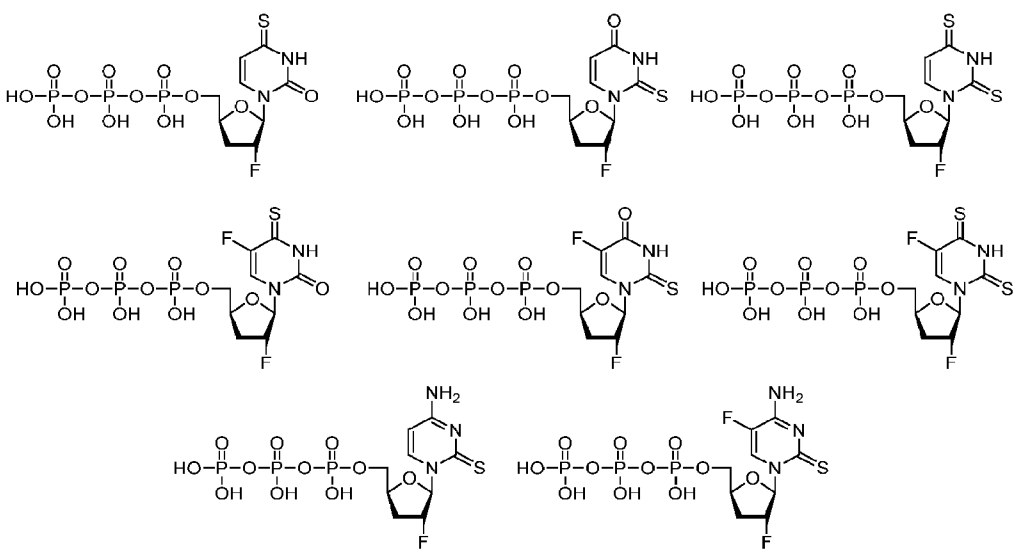
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In one embodiment, R^3 is II. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is CH_2F. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

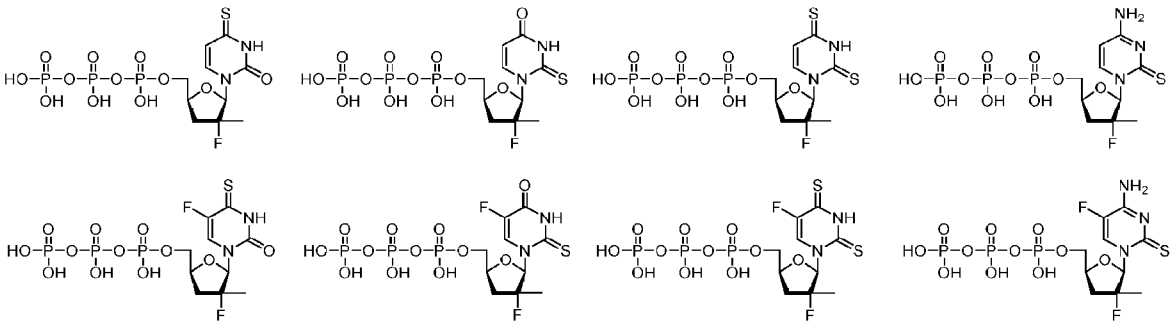


In one embodiment, R^3 is H. In another embodiment, R^4 is H. In a further embodiment, R^5 is H. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

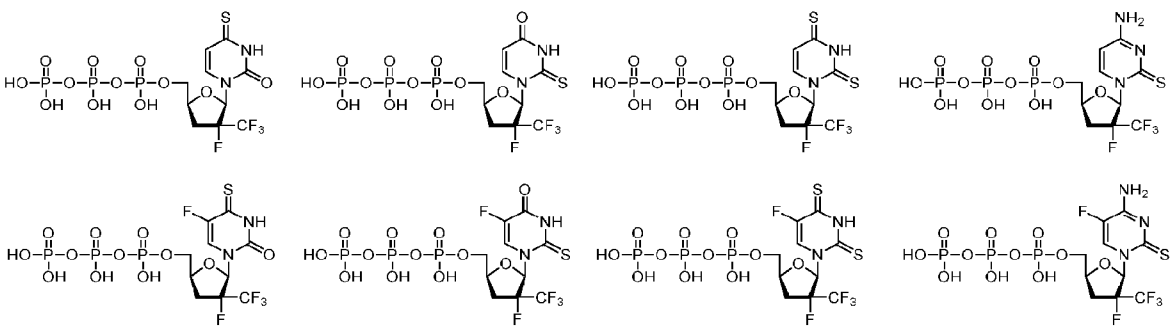


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In one embodiment, R^3 is H. In another embodiment, R^4 is H. In a further embodiment, R^5 is H. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

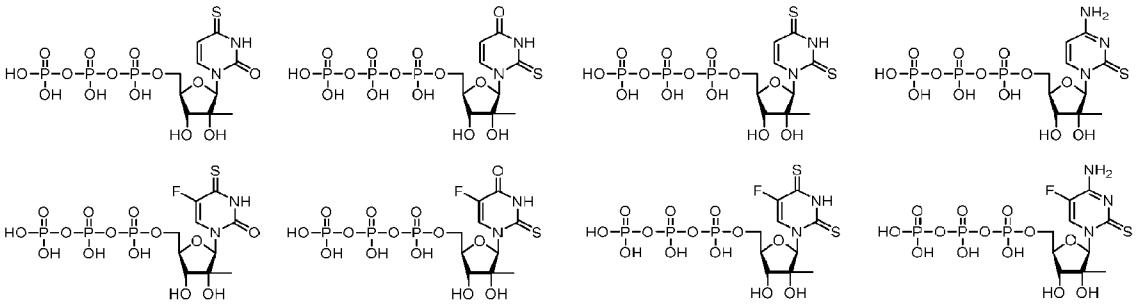


In one embodiment, R^3 is H. In another embodiment, R^4 is H. In a further embodiment, R^5 is H. In still another embodiment, R^6 is trifluoromethyl. In yet another embodiment, R^7 is fluoro. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:



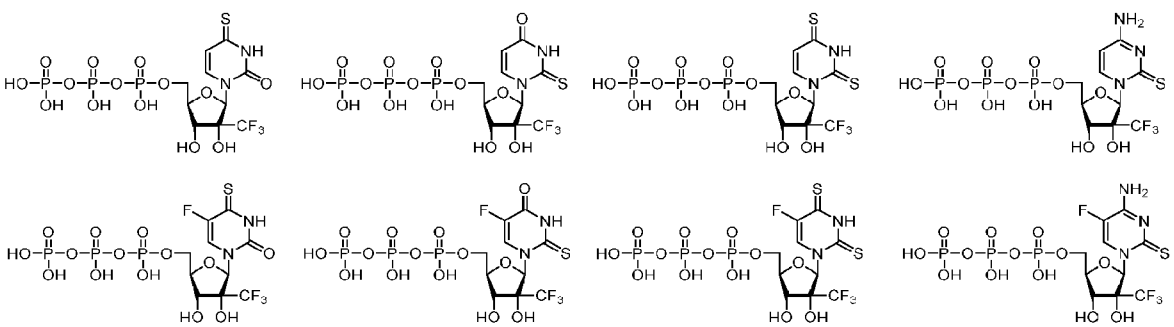
In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is hydroxyl. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

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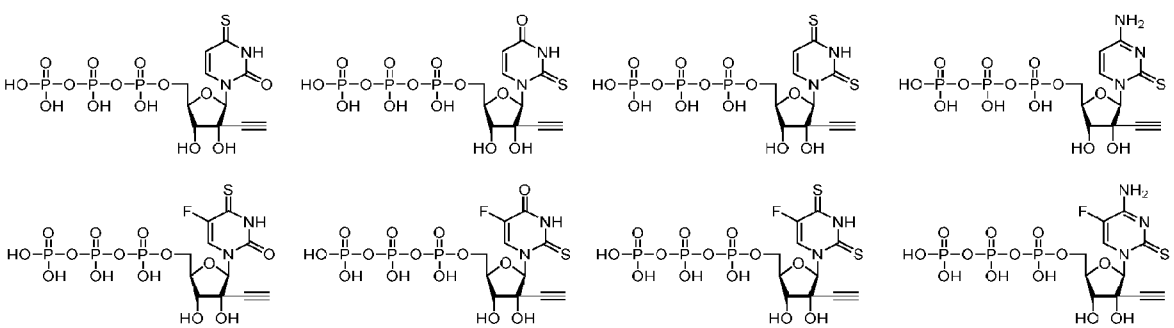


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In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is trifluoromethyl. In yet another embodiment, R^7 is hydroxyl. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:



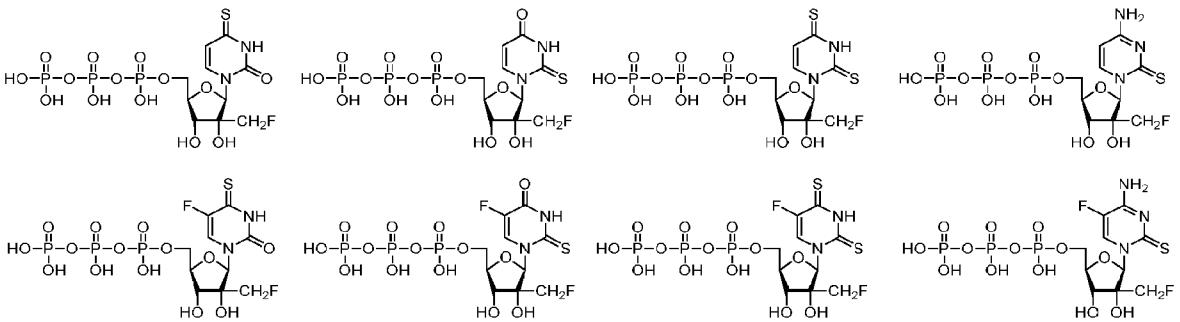
In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is C≡CH. In yet another embodiment, R^7 is hydroxyl. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:



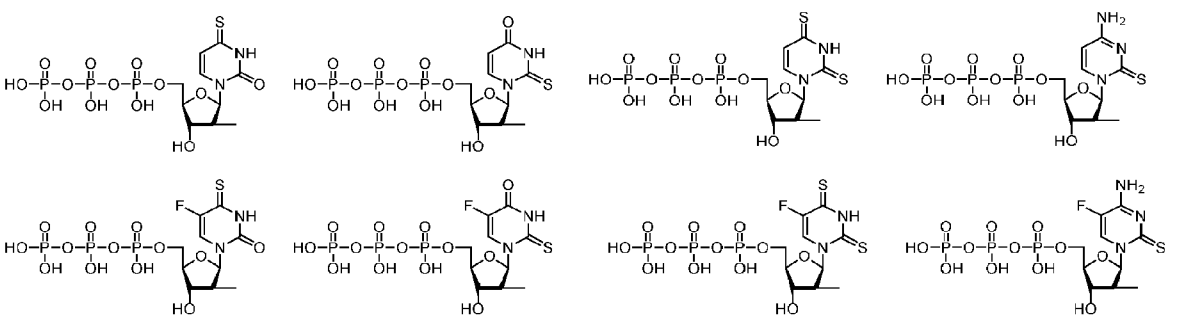
In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is CH_2F. In yet another embodiment,

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R^7 is hydroxyl. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:

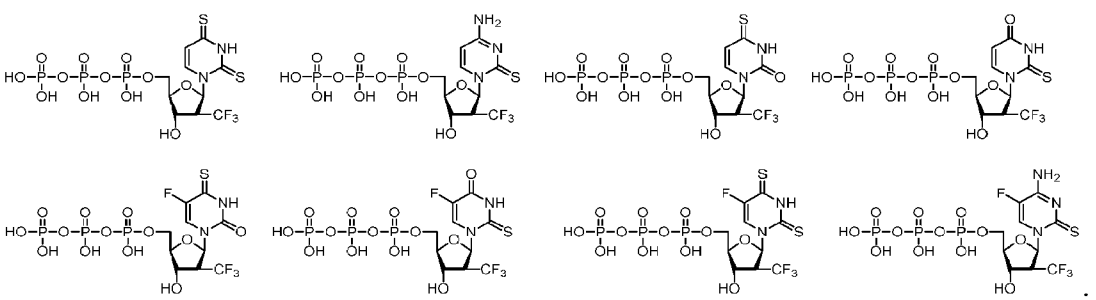


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is H. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:



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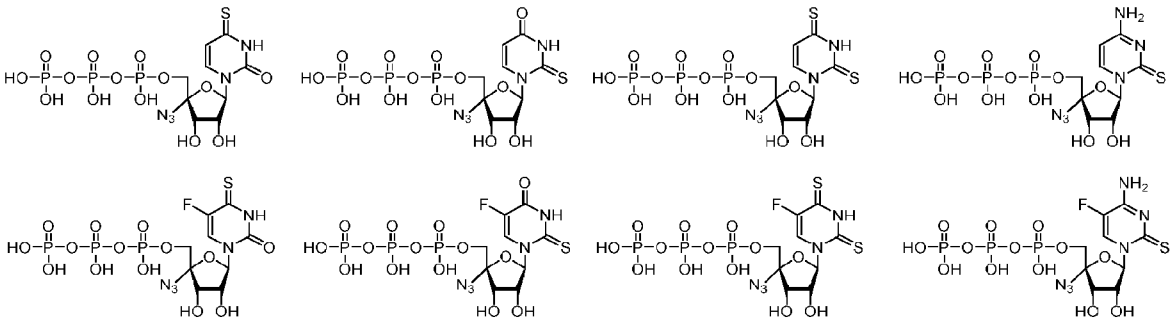
In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is trifluoromethyl. In yet another embodiment, R^7 is H. In a still further embodiment, R^{10} is H. In exemplary embodiments, the compound is selected from the group consisting of:



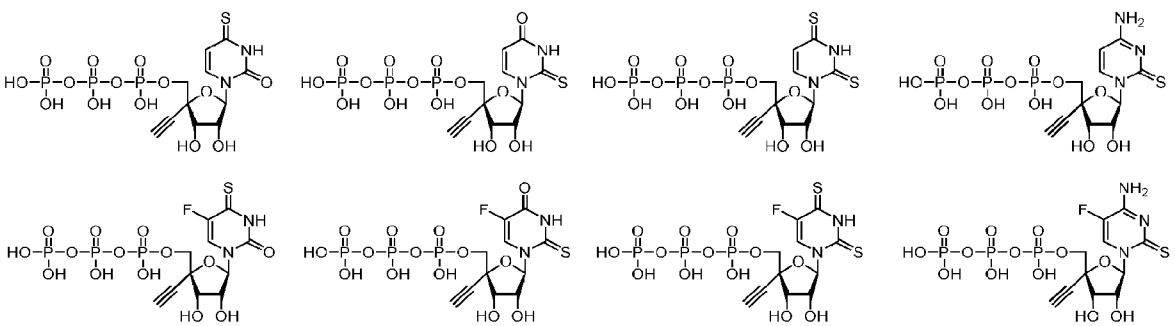
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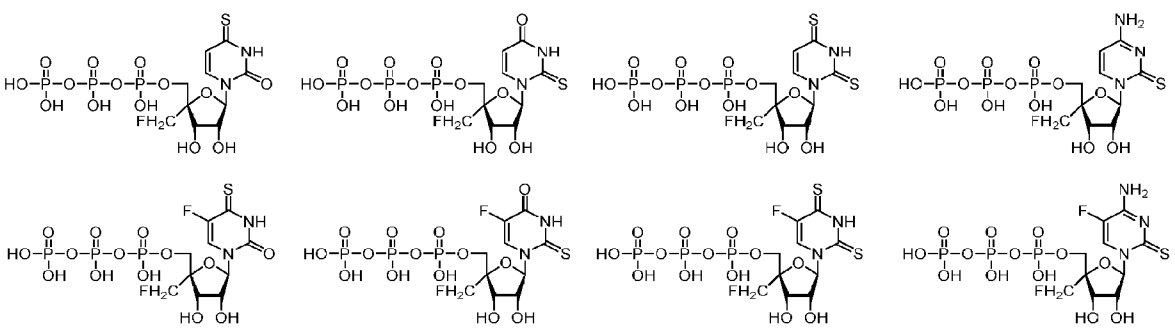
In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is N_3. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is C≡CH. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

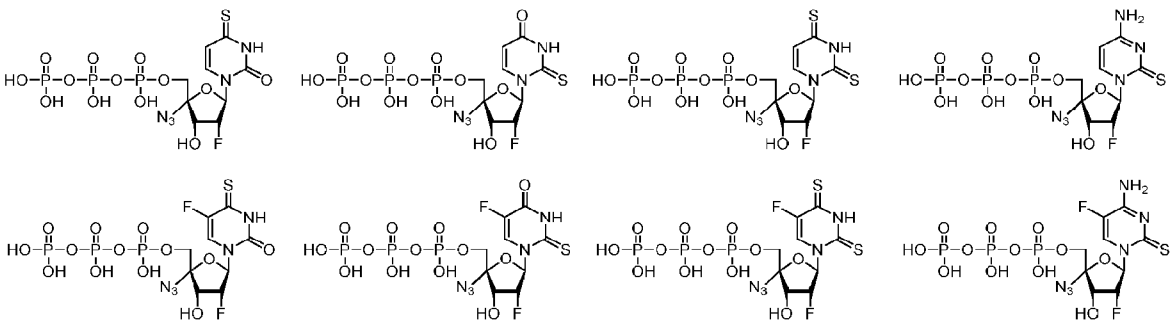


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is CH_2F. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

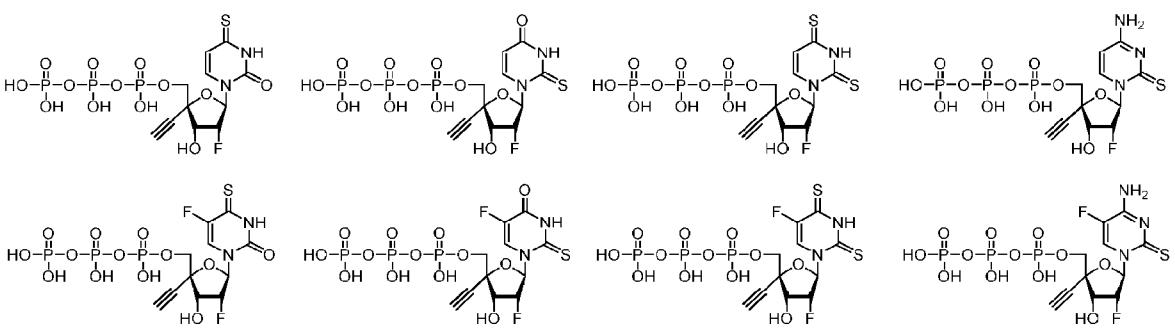


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In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is N_3. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

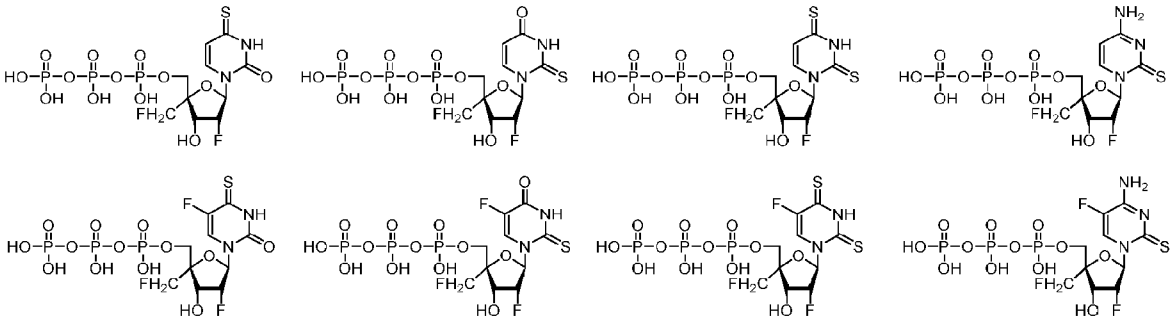


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is C≡CH. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

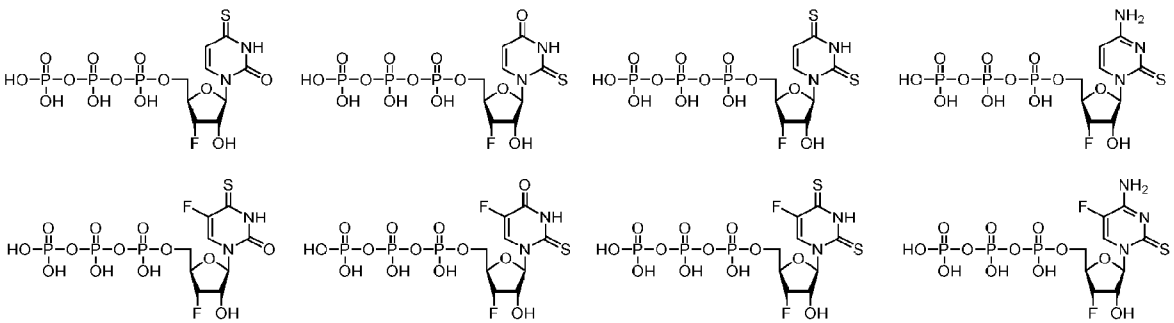


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is CH_2F. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

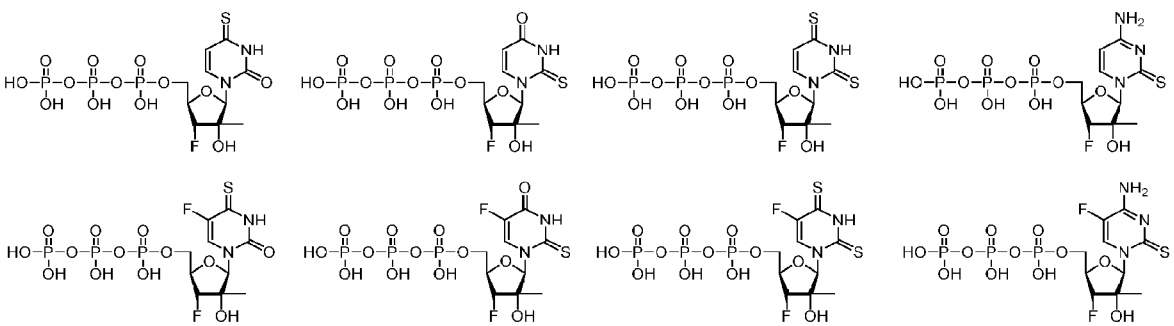
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In one embodiment, R^3 is H. In another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In another embodiment, R^{10} is H. In still another embodiment, R^6 is H. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

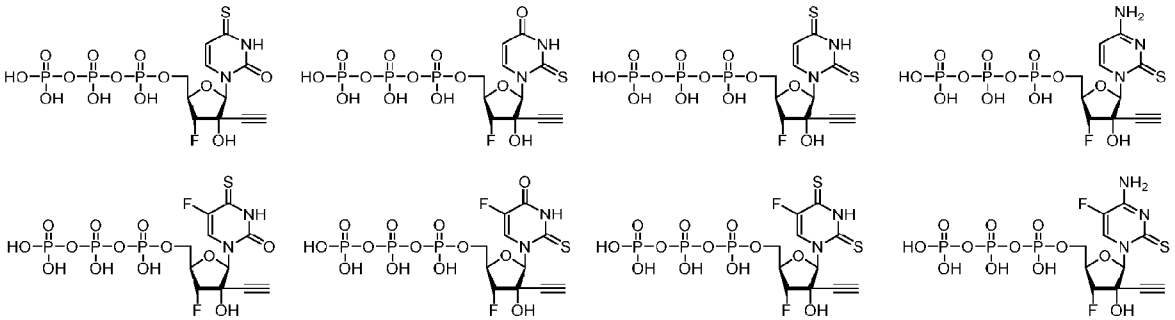


In one embodiment, R^3 is H. In another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In another embodiment, R^{10} is H. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

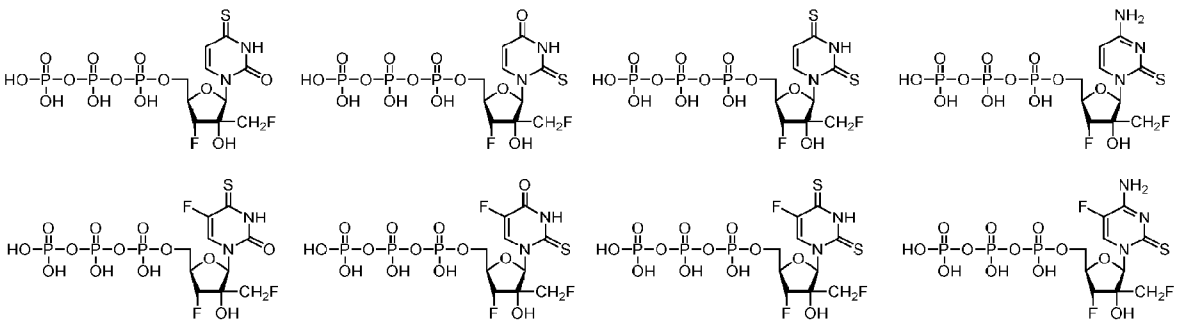


In one embodiment, R^3 is H. In another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In another embodiment, R^{10} is H. In still another embodiment, R^6 is C≡CH. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

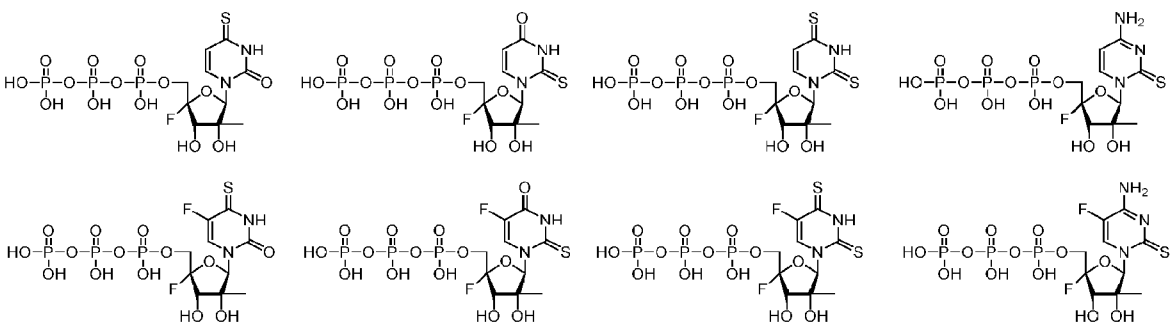
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In one embodiment, R^3 is H. In another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In another embodiment, R^{10} is H. In still another embodiment, R^6 is CH_2F. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

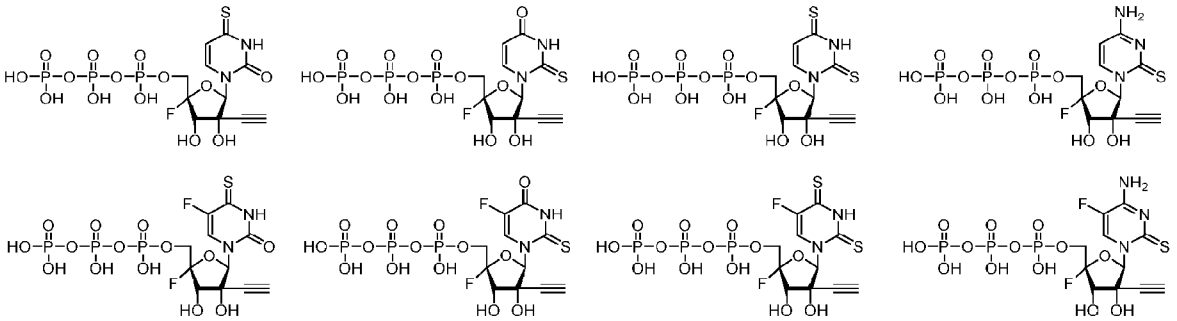


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

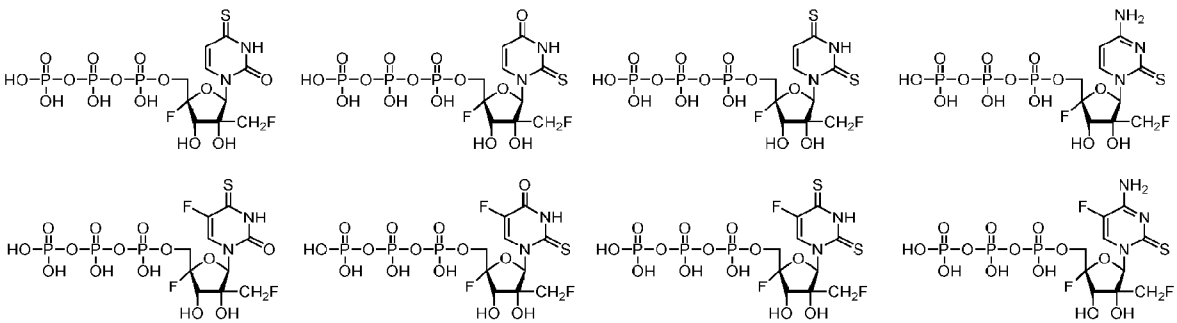


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is C≡CH. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

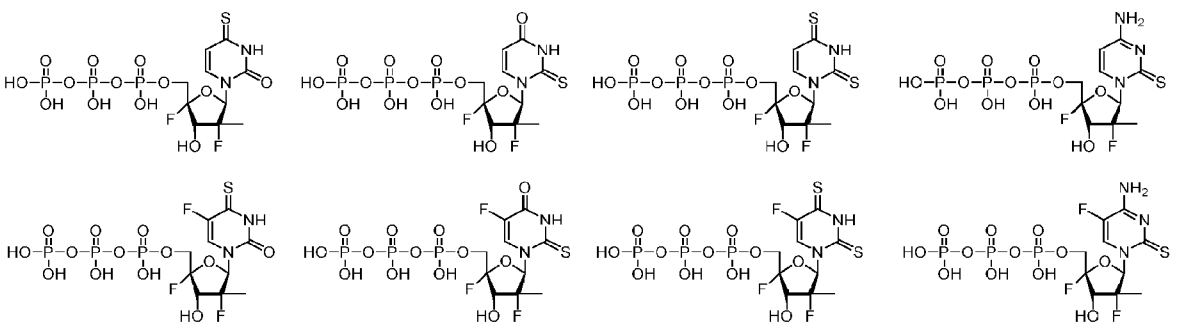
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In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is CH_2F. In yet another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

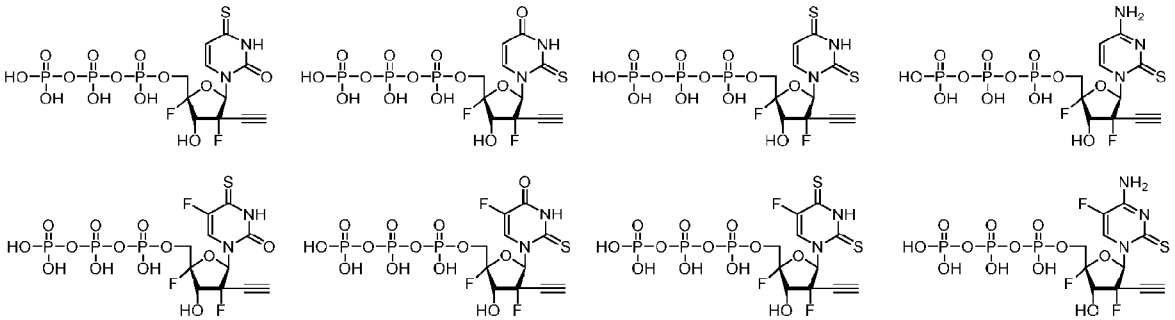


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is methyl. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

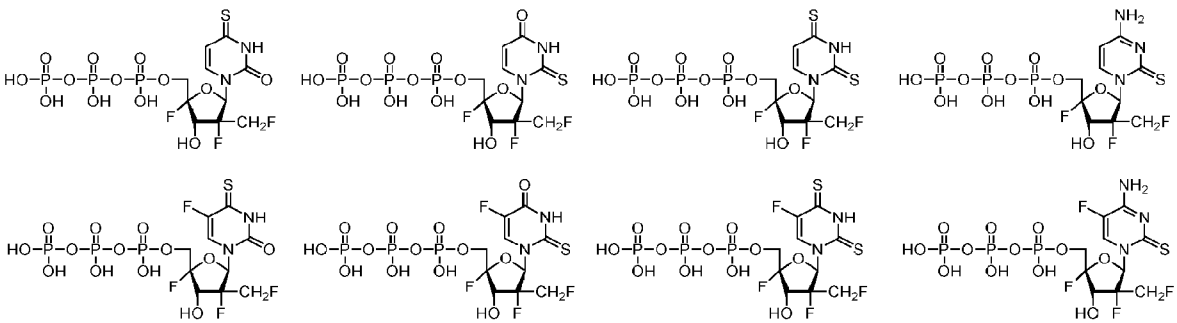


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is C≡CH. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

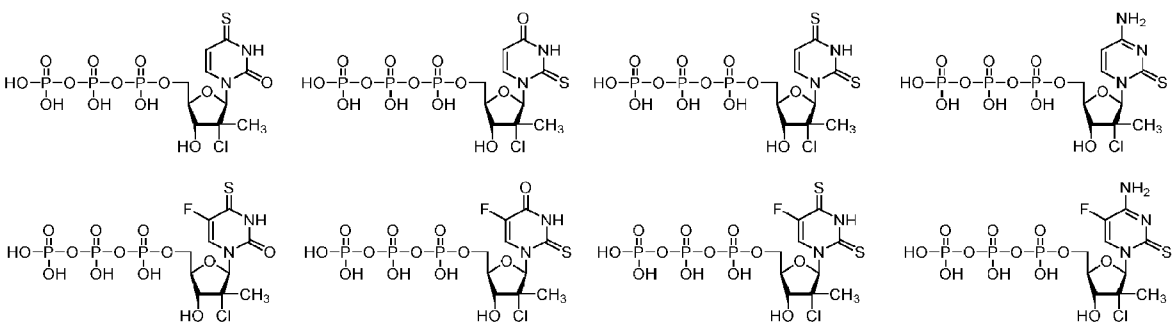
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In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is fluoro. In still another embodiment, R^6 is CH_2F. In yet another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

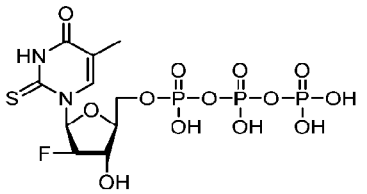
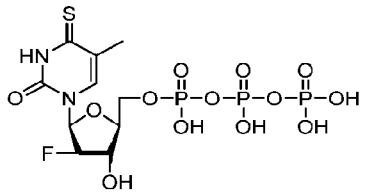
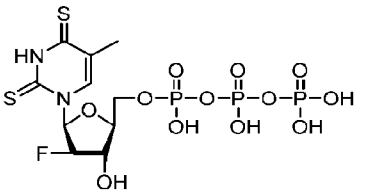


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In another embodiment, R^{10} is H. In still another embodiment, R^6 is CH_3. In yet another embodiment, R^7 is chloro. In exemplary embodiments, the compound is selected from the group consisting of:

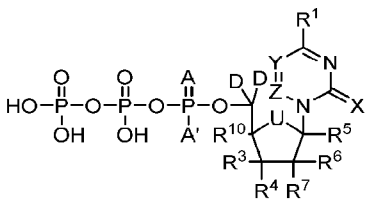
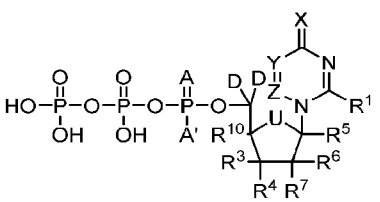
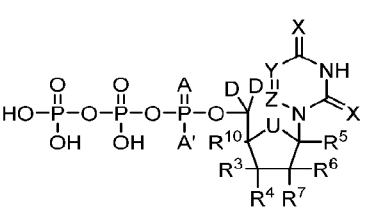


In one embodiment, R^3 is H. In another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In still another embodiment, R^6 is fluoro. In yet another embodiment, R^7 is H. In an still further embodiment, R^{10} is H.

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In certain embodiments, the disclosure relates to compounds of one of the following formulae:

Formula Ic' **Formula Id'** **Formula Ie'**

or a pharmaceutically acceptable salt thereof, wherein

Λ is O or S;

A' is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ic' and Id', either X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Ie', at least one X is S;

Y is CH, N, or CR^2;

Z is CH, N, or CR^2;

R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^8 is methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

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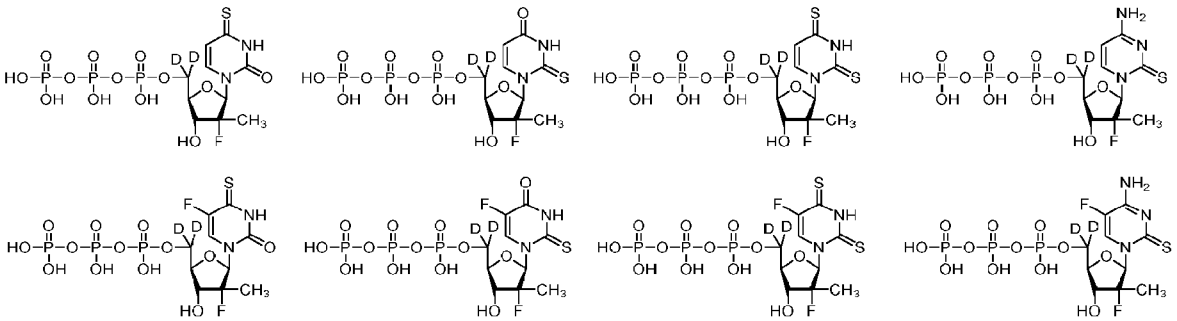
R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

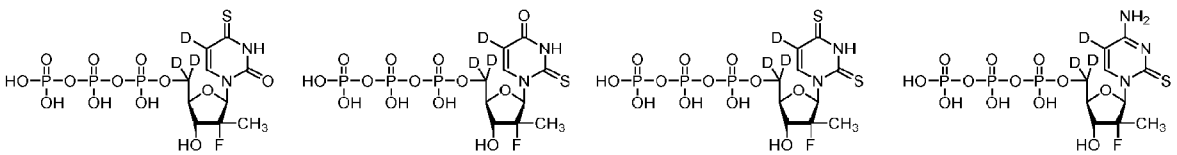
each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^2 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9.

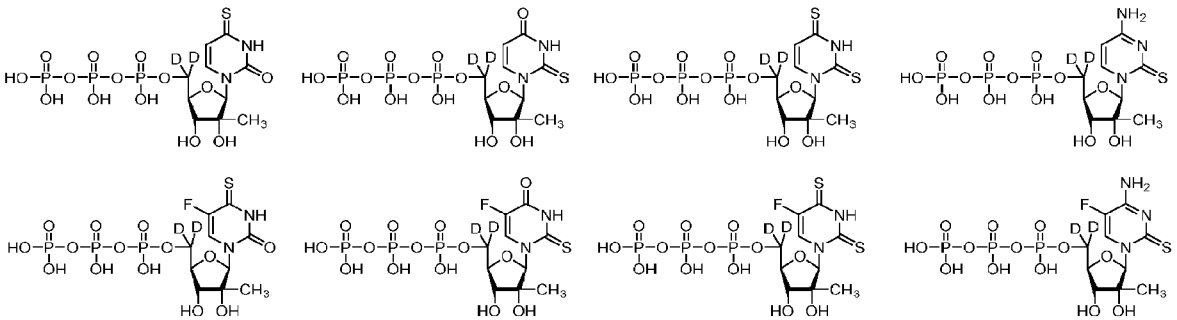
In exemplary embodiments, the compound is selected from the group consisting of:



In exemplary embodiments, the compound is selected from the group consisting of:

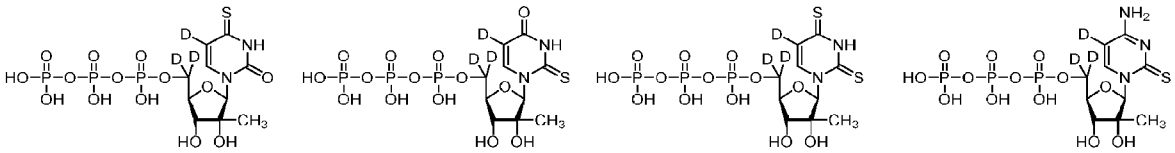


In exemplary embodiments, the compound is selected from the group consisting of:

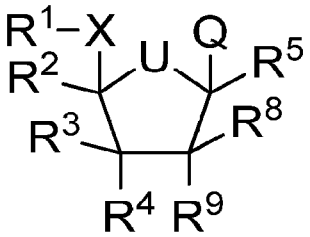


In exemplary embodiments, the compound is selected from the group consisting of:

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In certain embodiments, the disclosure relates to a compound of the following formula:



Formula If

or pharmaceutically acceptable salts thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is O, CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

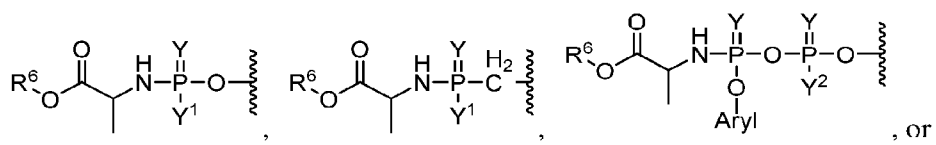
R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

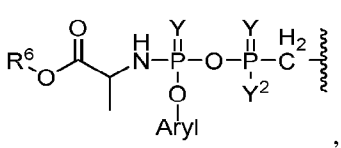
R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^8 and R^9 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

R^1 is one of the formula:



, or



,

Y is O or S;

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Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10}.

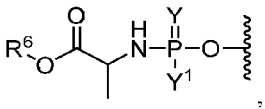
In certain exemplary embodiments, R^8 and R^9, with the carbon atom they are attached to, form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^{10}.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

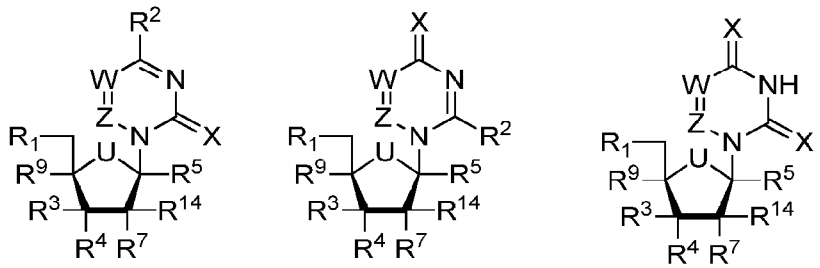
In certain embodiment, R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, CH_2OH, CH_2Cl, CCH, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In certain embodiment, U is O; X is CH_2; Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine; R^5 is H; and R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

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In certain embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In certain embodiments, the disclosure relates to a compound of the following formulae:



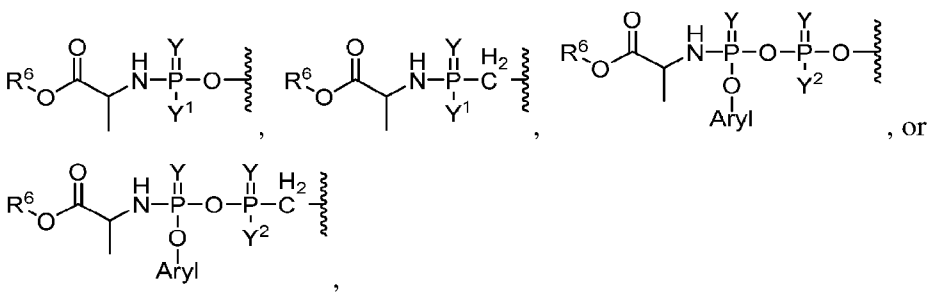
Formula Ig **Formula Ih** **Formula Ii**

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

R^1 is one of the formula:



Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

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wherein in Formula Ig and Ih, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Ii, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10}.

In certain embodiments, R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In certain embodiments, R^6 is *iso*-propyl.

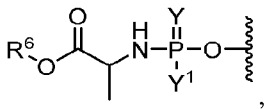
In certain exemplary embodiments, R^7 and R^{14}, with the carbon atom they are attached to, form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and can be optionally substituted with one or more, the same or different, R^{10}.

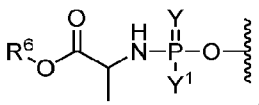
In certain embodiments, U is S and Y and Z are CH.

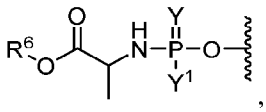
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In other embodiments, U is O and Y and Z are CH.

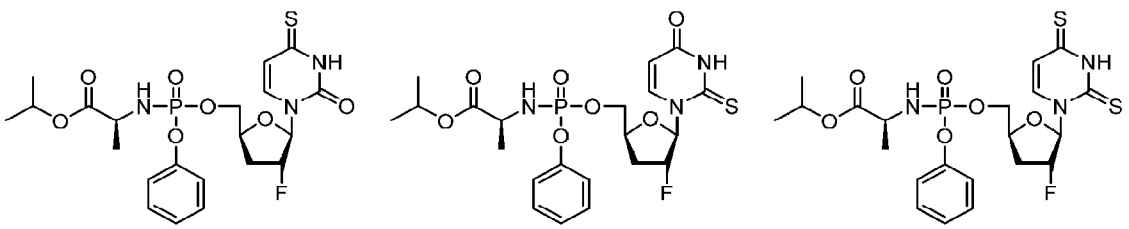
In certain embodiments, one X is O and the other X is S.

In one embodiment, R^5 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is H. In yet another embodiment, R^7 is F and R^{14} is H. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy and R^6 is *iso*-propyl.

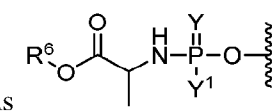
In certain embodiments, U is O; W and Z are CH; R^5 is H; R^1 is , wherein Y is O and Y^1 is phenoxy; and R^6 is alkyl.

In certain embodiments, R^5 is H, R^3 is H, R^4 is hydroxyl, R^7 is hyroxyl, R^{14} is methyl, R^1 is , Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

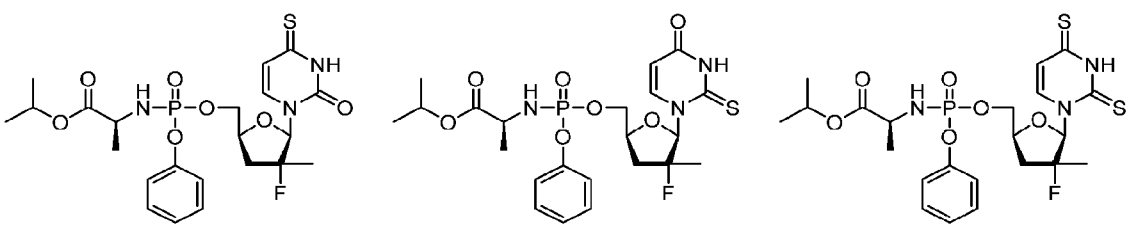
In exemplary embodiments, the compound is selected from:



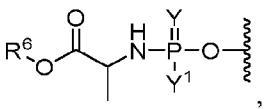
.

In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is H. In yet another embodiment, R^7 is F and R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

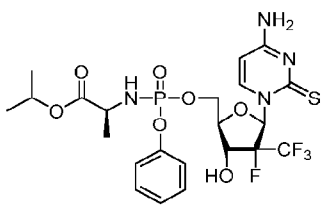
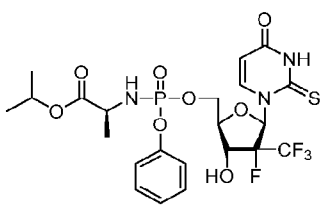
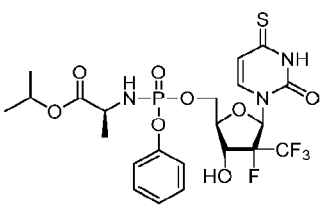
In exemplary embodiments, the compound is selected from:

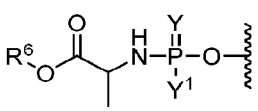


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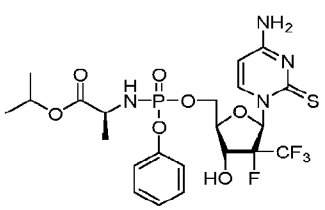
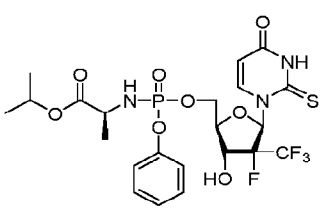
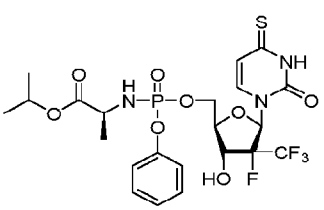
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is H. In yet another embodiment, R^7 is F and R^{14} is trifluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

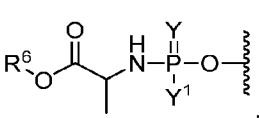
In exemplary embodiments, the compound is selected from:

In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is F. In another embodiment, R^{14} is trifluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

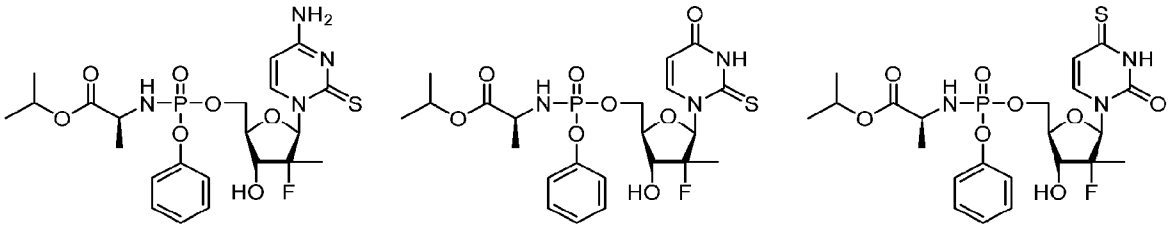
In exemplary embodiments, the compound is selected from:

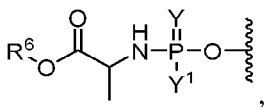




In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is F. In another embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

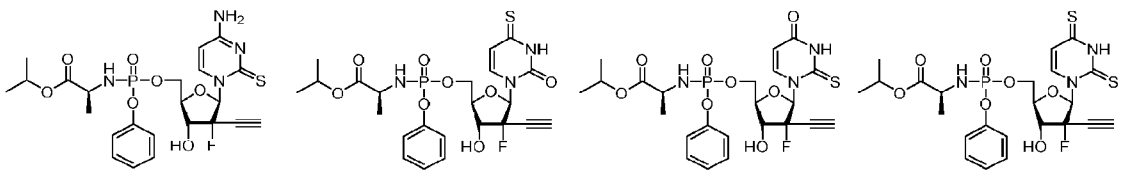
In exemplary embodiments, the compound is selected from:

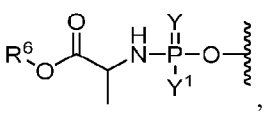
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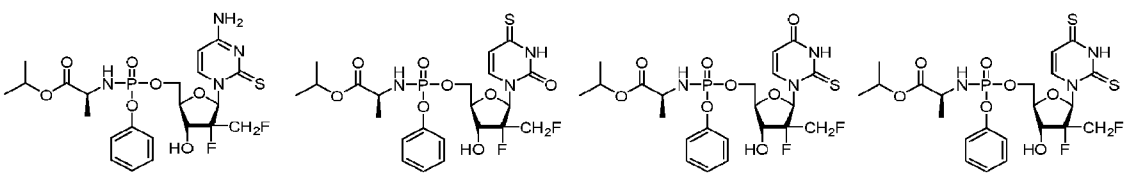
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is OH. In yet another embodiment, R^7 is F and R^{14} is ethynyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:



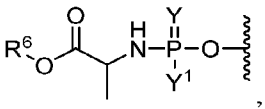
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is OH. In yet another embodiment, R^7 is F and R^{14} is monofluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

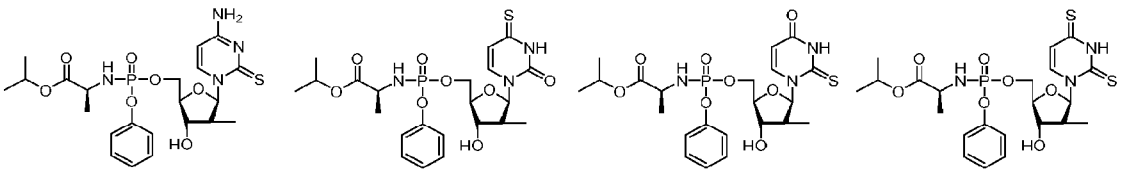


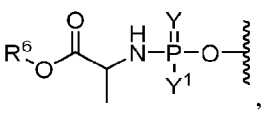
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is H. In another embodiment,

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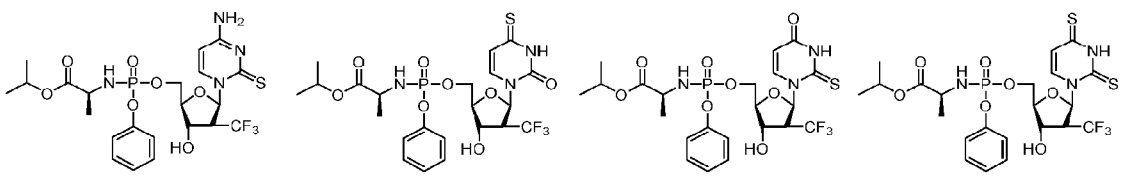
R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

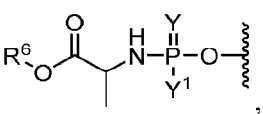
In exemplary embodiments, the compound is selected from:



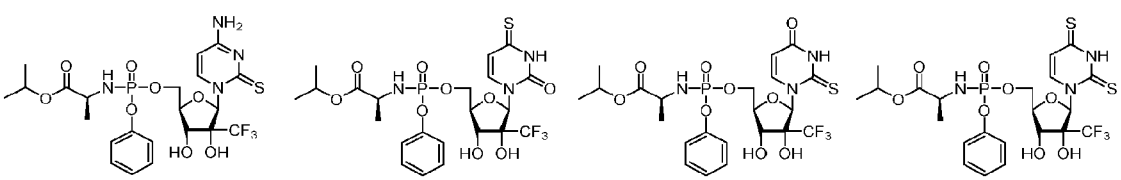
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is OH. In yet another embodiment, R^7 is H and R^{14} is trifluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

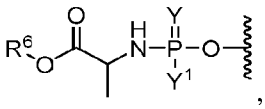


In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is trifluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

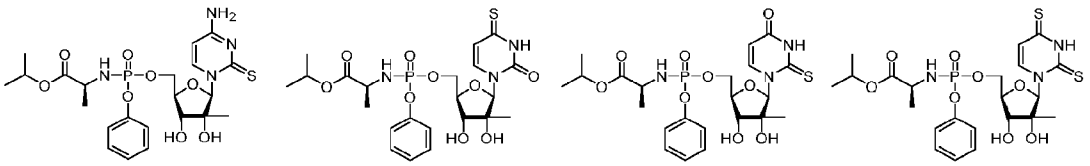
In exemplary embodiments, the compound is selected from:

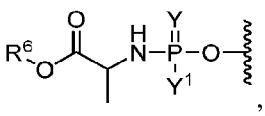


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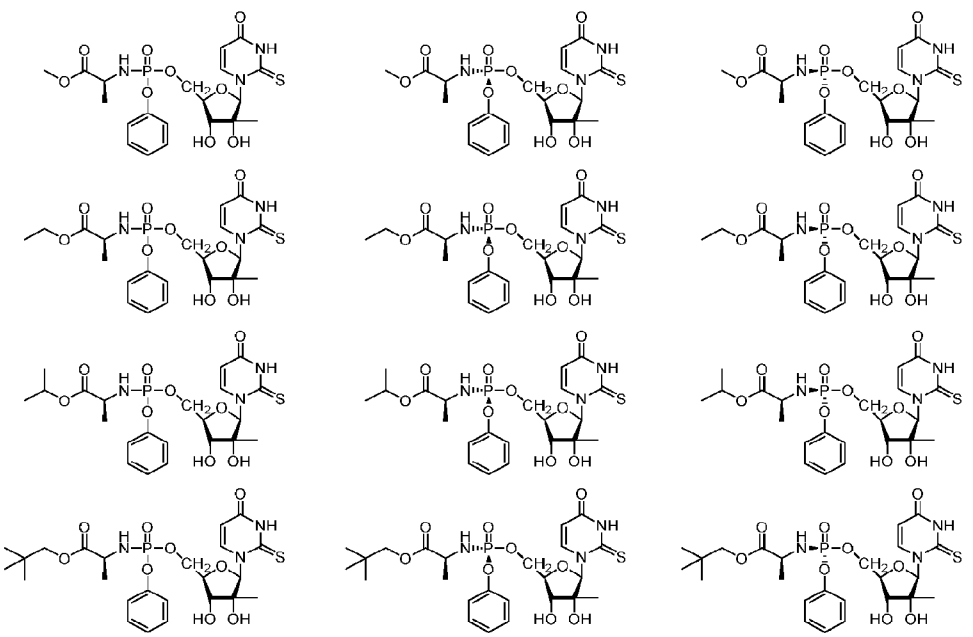
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

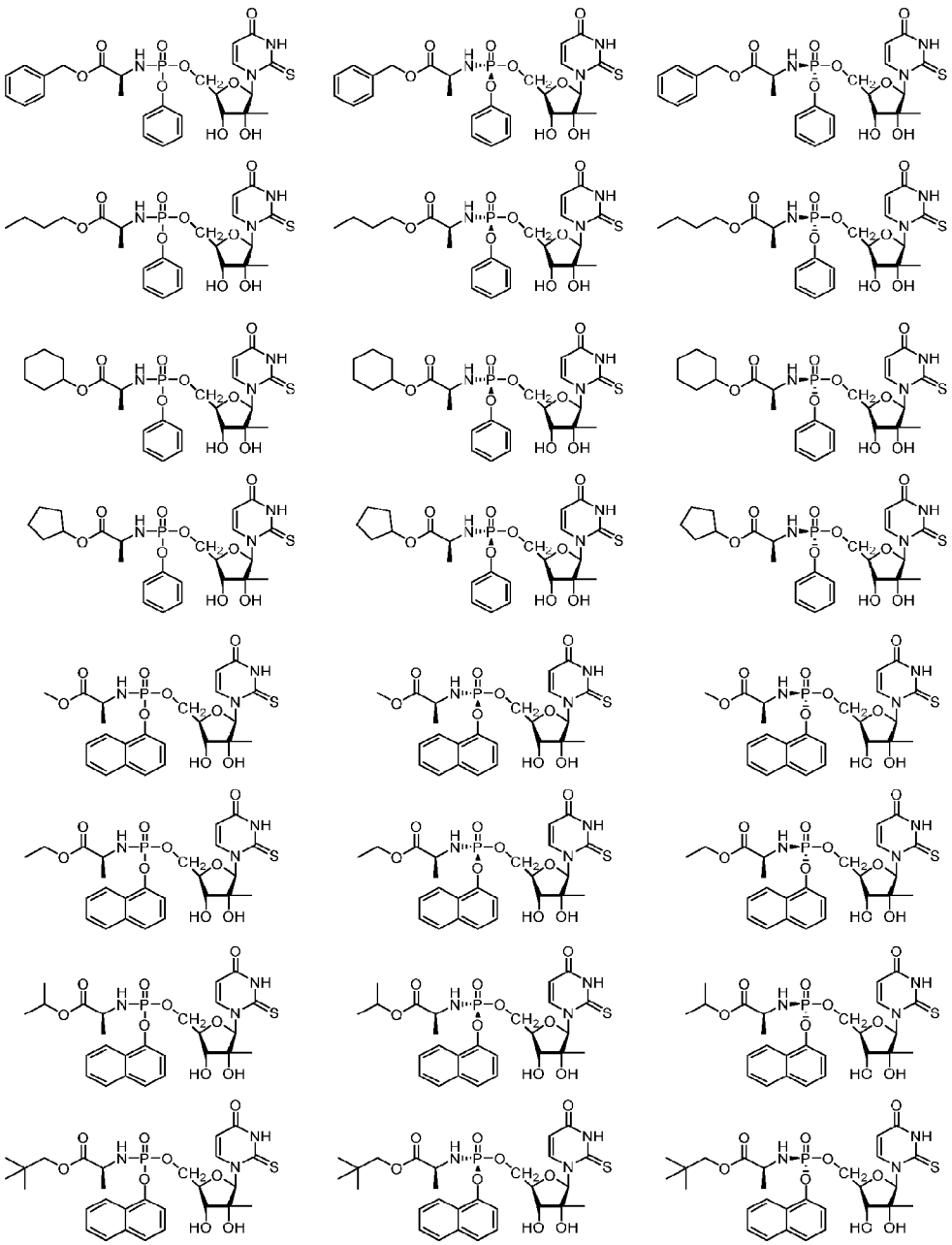


In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O.

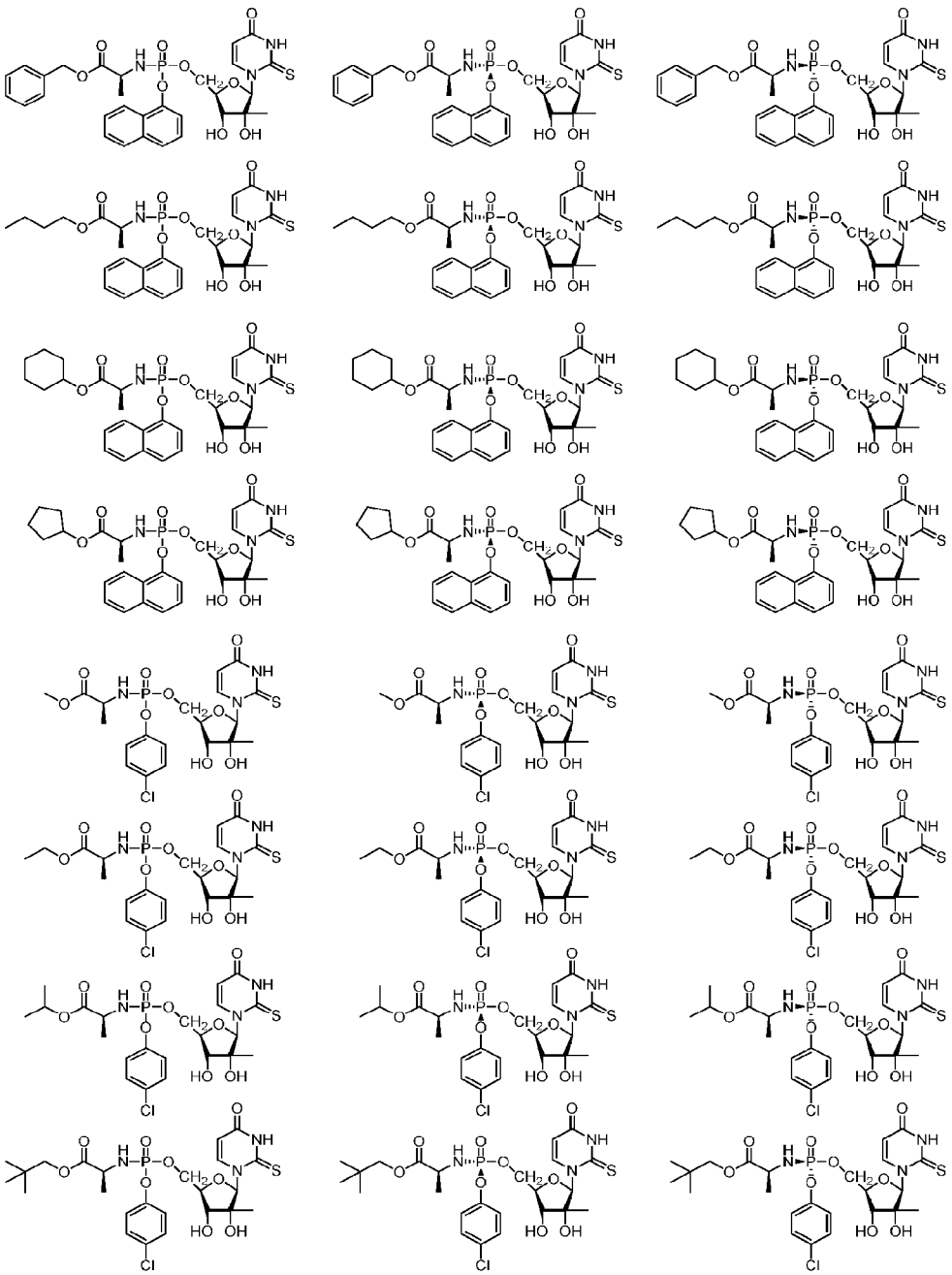
In exemplary embodiments, the compound is selected from:



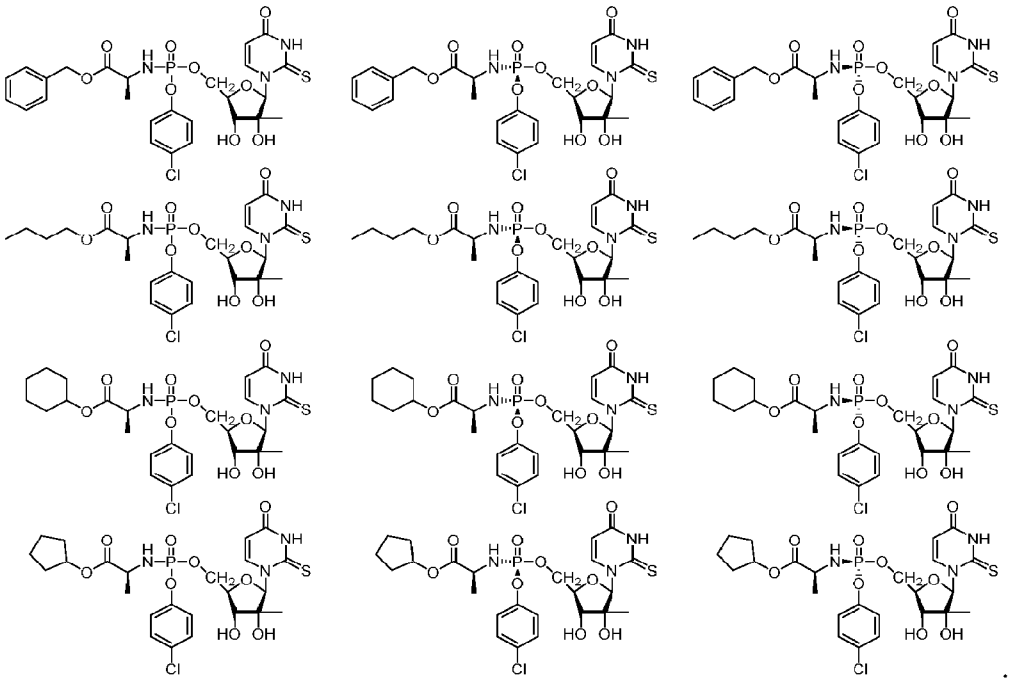
CA 03216679 2023-10-25



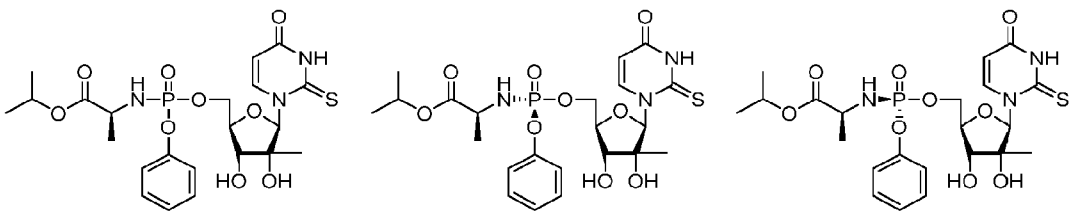
CA 03216679 2023-10-25

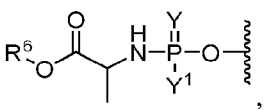


CA 03216679 2023-10-25

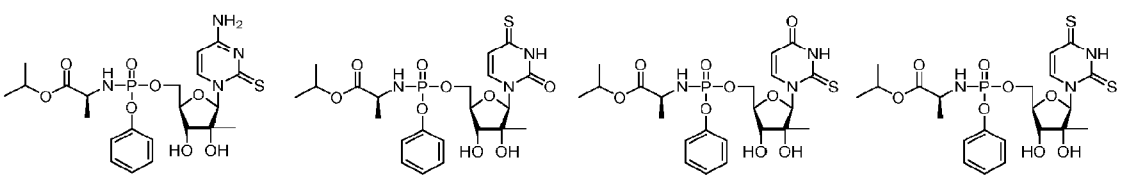


In a more preferred embodiment, a compound of the present disclosure is selected from one or more of the following:



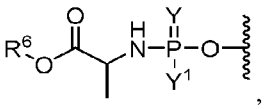
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is ethynyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

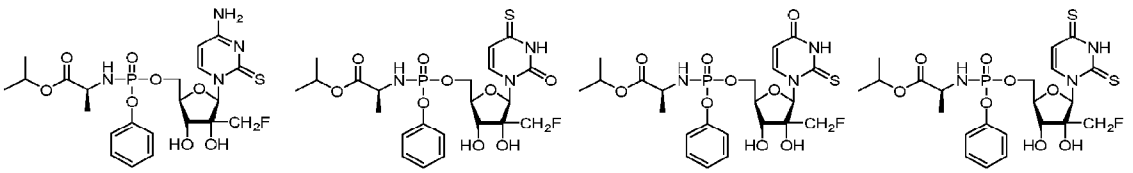


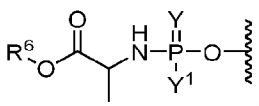
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another

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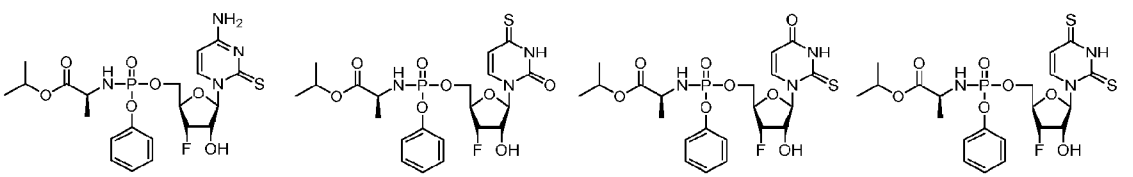
embodiment, R^{14} is monofluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

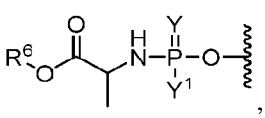
In exemplary embodiments, the compound is selected from:



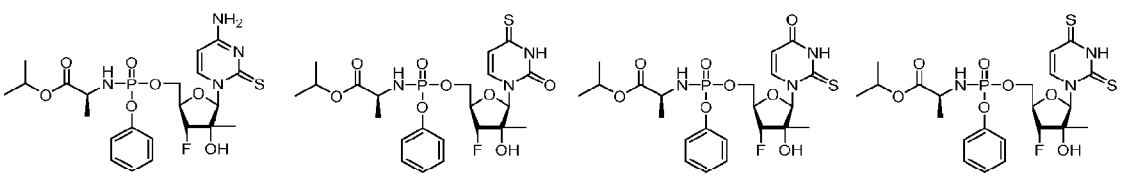
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is fluoro. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is H. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:



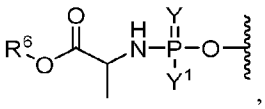
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is fluoro. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

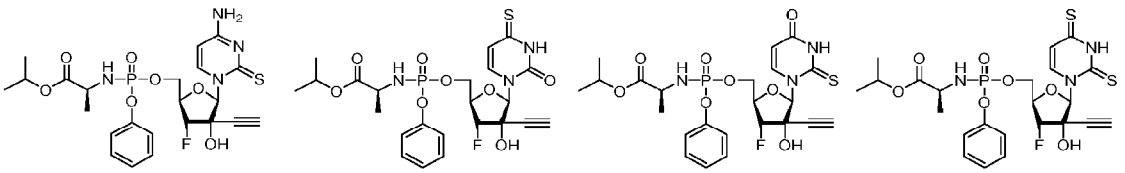


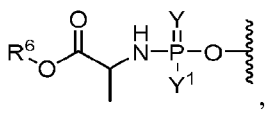
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is fluoro. In yet another embodiment, R^7 is hydroxyl. In another

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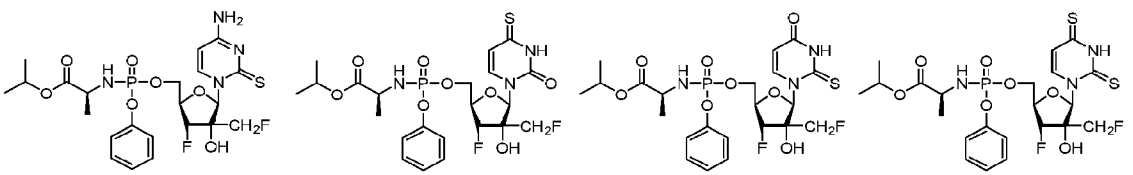
embodiment, R^{14} is ethynyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

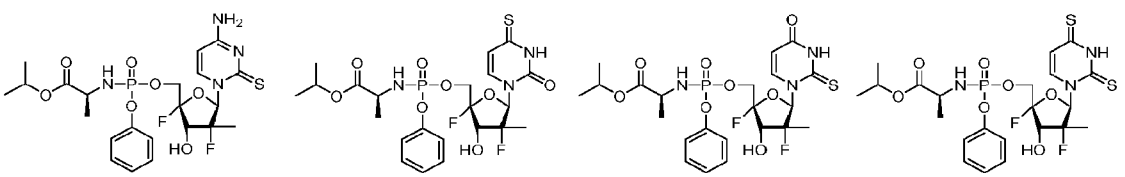


In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is fluoro. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is monofluoromethyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

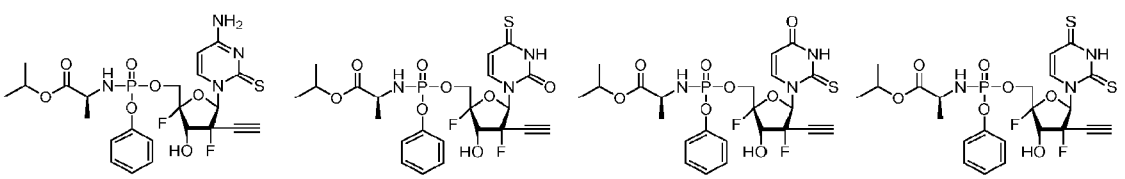
In exemplary embodiments, the compound is selected from:



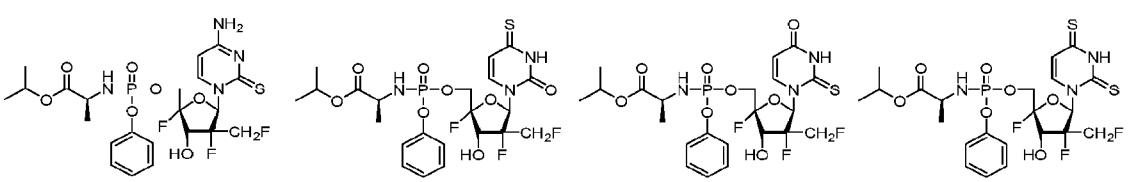
In exemplary embodiments, the compound is selected from:



In exemplary embodiments, the compound is selected from:

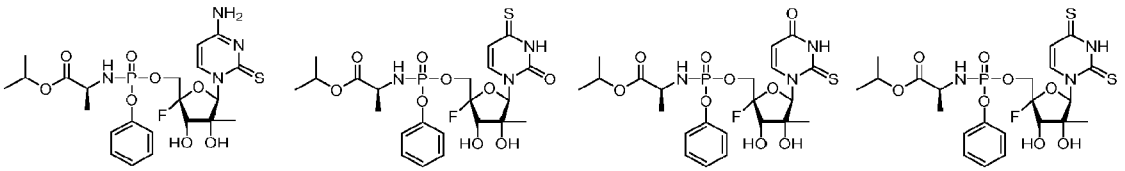


In exemplary embodiments, the compound is selected from:

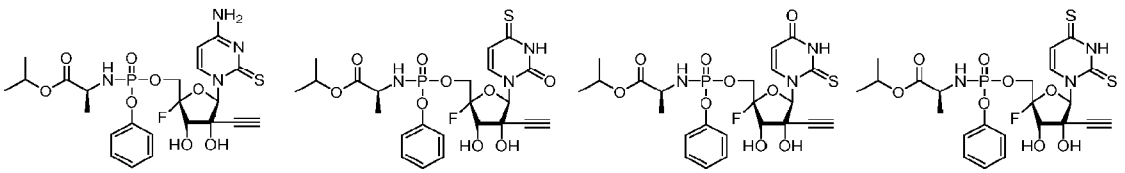


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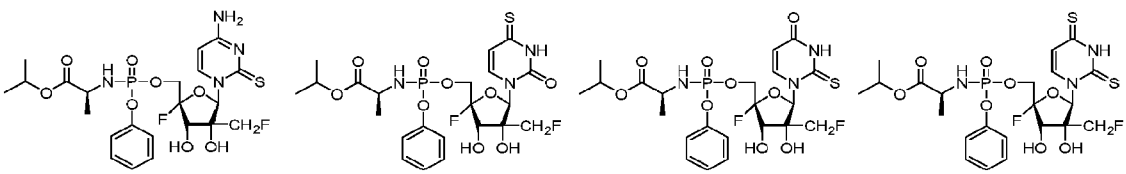
In exemplary embodiments, the compound is selected from:



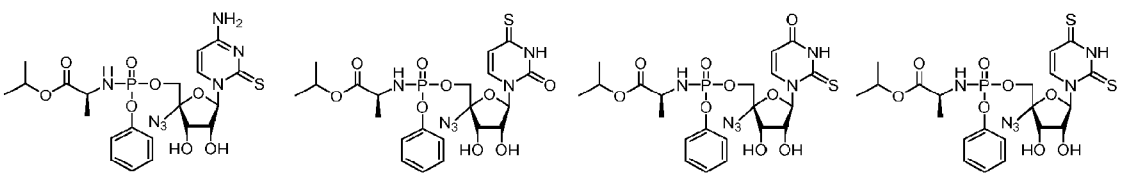
In exemplary embodiments, the compound is selected from:



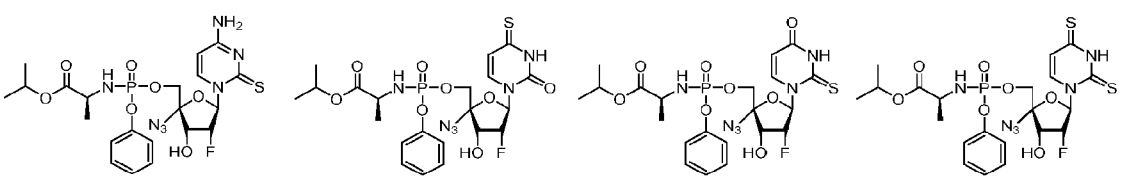
In exemplary embodiments, the compound is selected from:



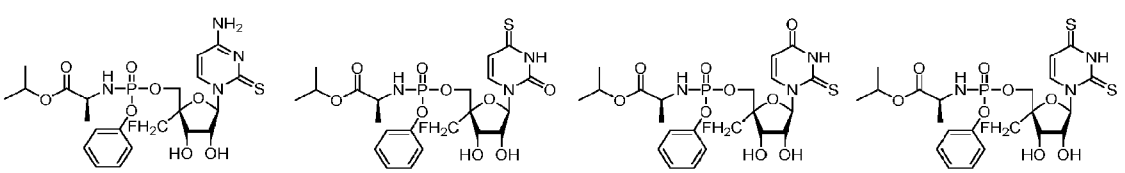
In exemplary embodiments, the compound is selected from:



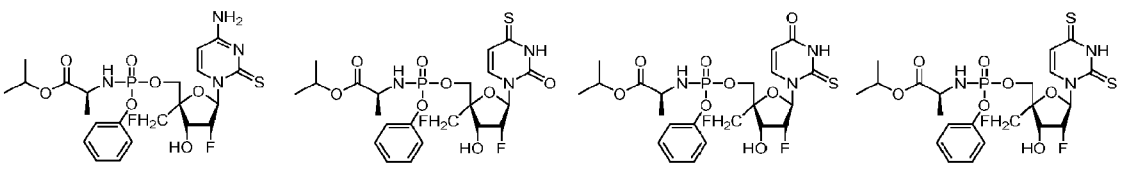
In exemplary embodiments, the compound is selected from:



In exemplary embodiments, the compound is selected from:

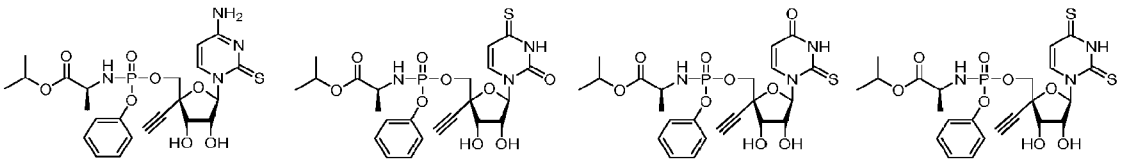


In exemplary embodiments, the compound is selected from:

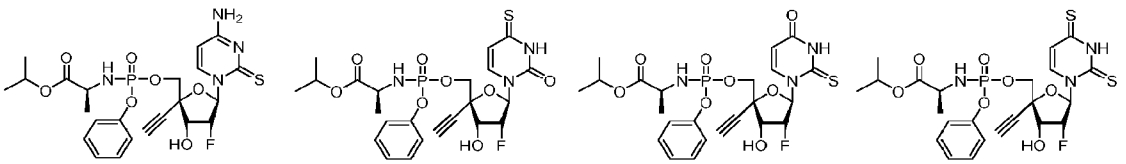


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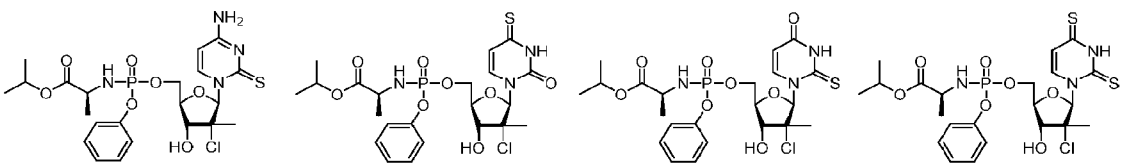
In exemplary embodiments, the compound is selected from:



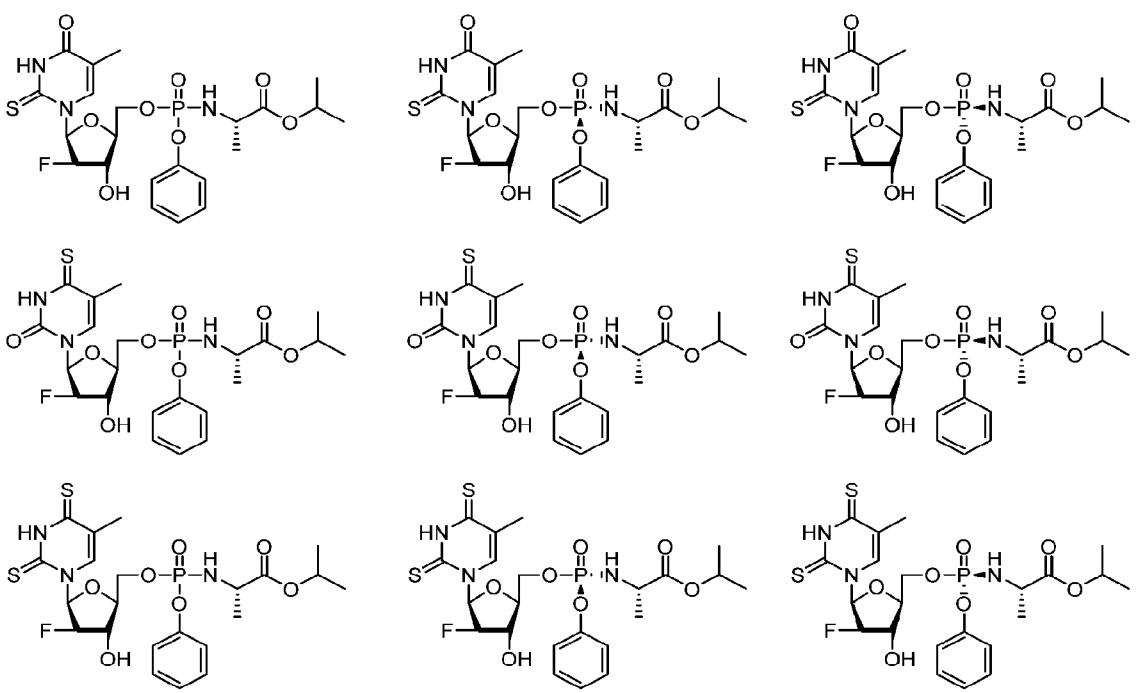
In exemplary embodiments, the compound is selected from:



In exemplary embodiments, the compound is selected from:

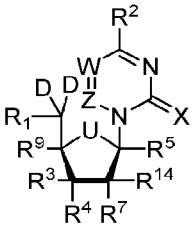
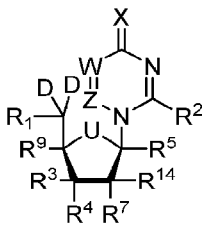
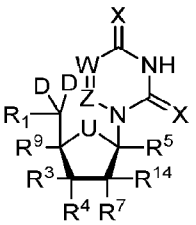


In exemplary embodiments, the compound is selected from:



In certain embodiments, the disclosure relates to a compound of the following formulac:

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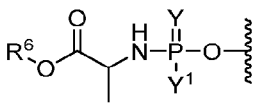
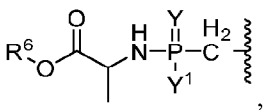
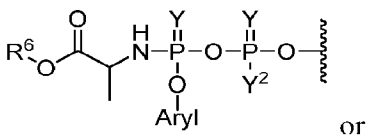
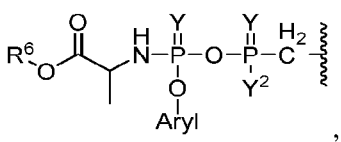
Formula Ij **Formula Ik** **Formula Il**

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

R^1 is one of the formula:




or


Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ij and Ik, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Il, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different R^{10};

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

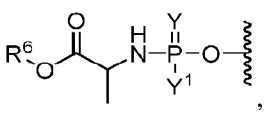
Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

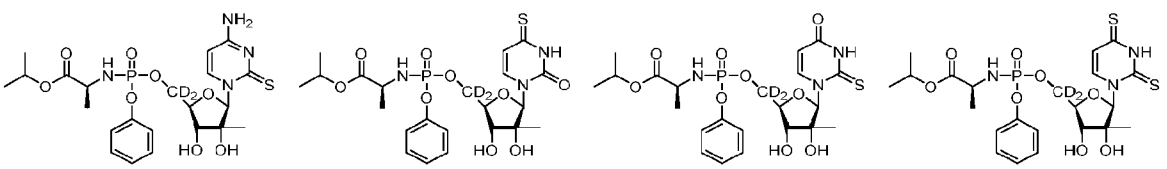
R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10}.

In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

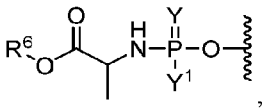
In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O, Y^1 is phenoxy, and R^6 is *iso*-propyl.

In exemplary embodiments, the compound is selected from:

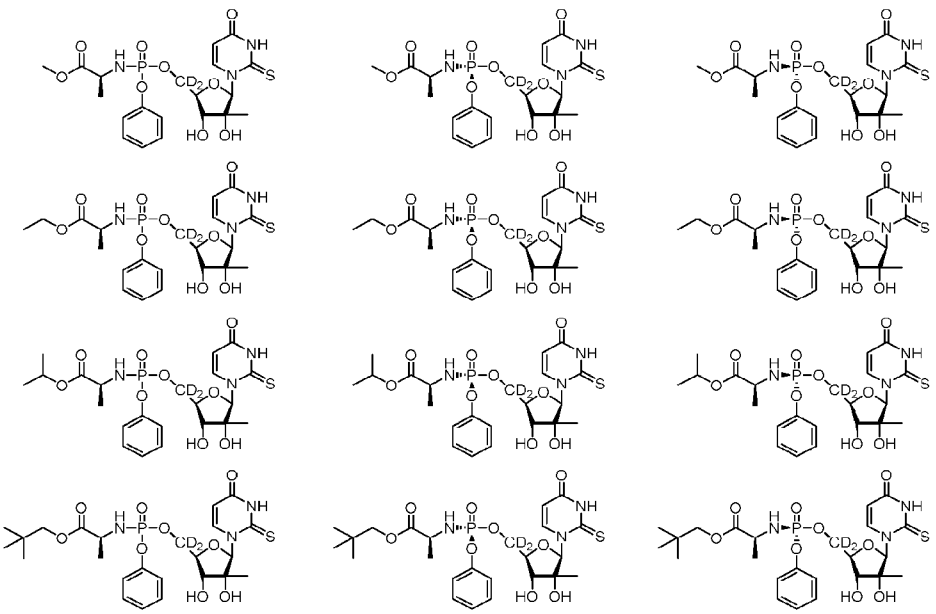


In one embodiment, R^5 is H. In another embodiment, R^3 is H. In yet another embodiment, R^4 is hydroxyl. In yet another embodiment, R^7 is hydroxyl. In another

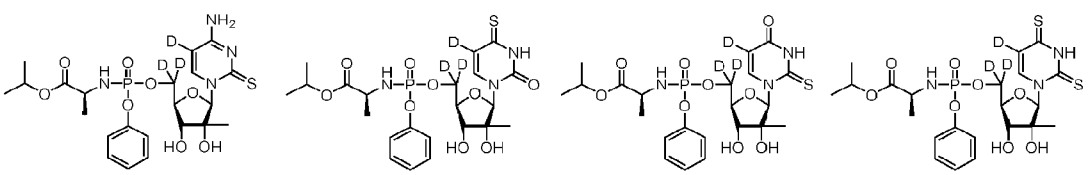
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embodiment, R^{14} is methyl. In a further embodiment, R^1 is , wherein Y is O and Y^1 is O-aryl.

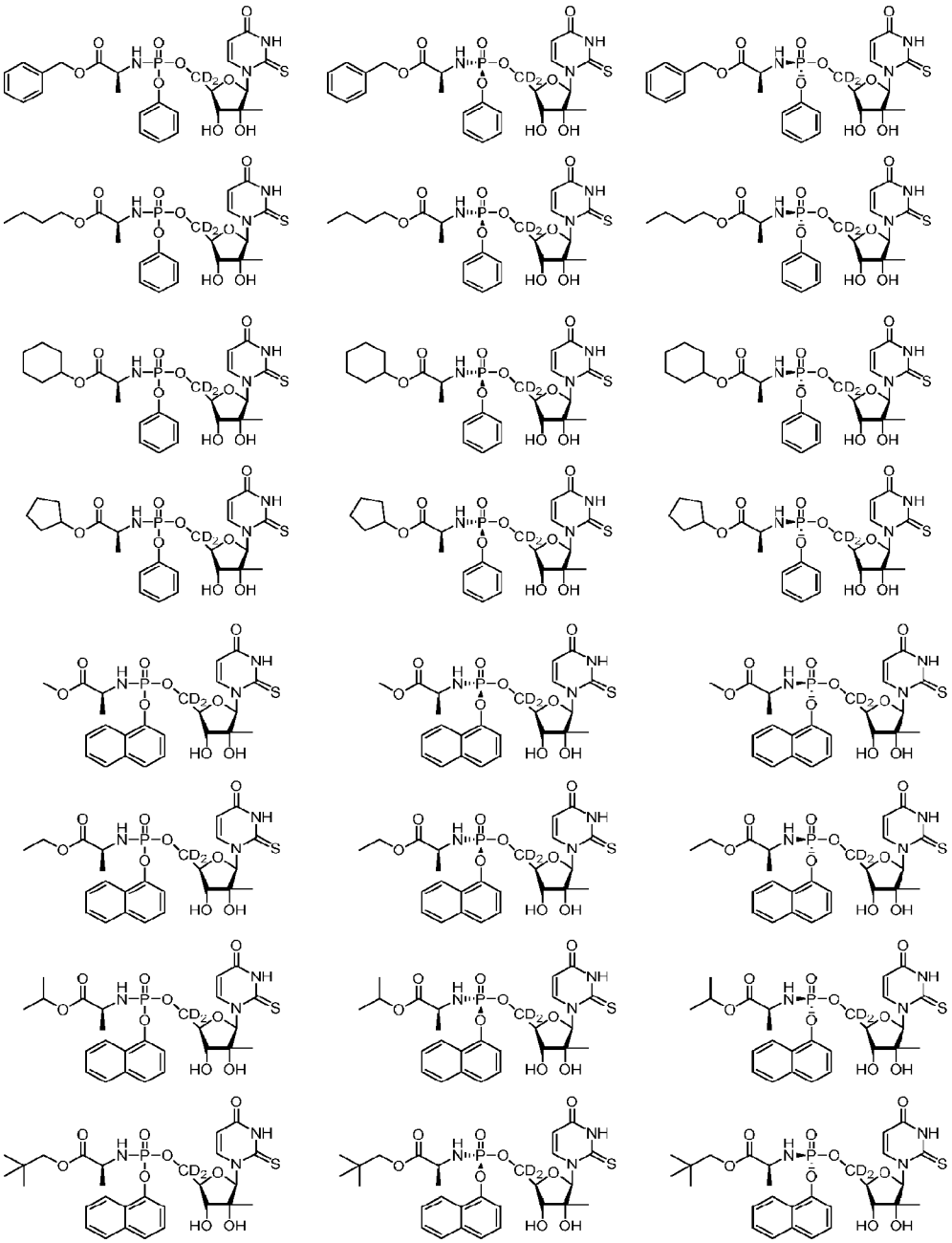
In exemplary embodiments, the compound is selected from:



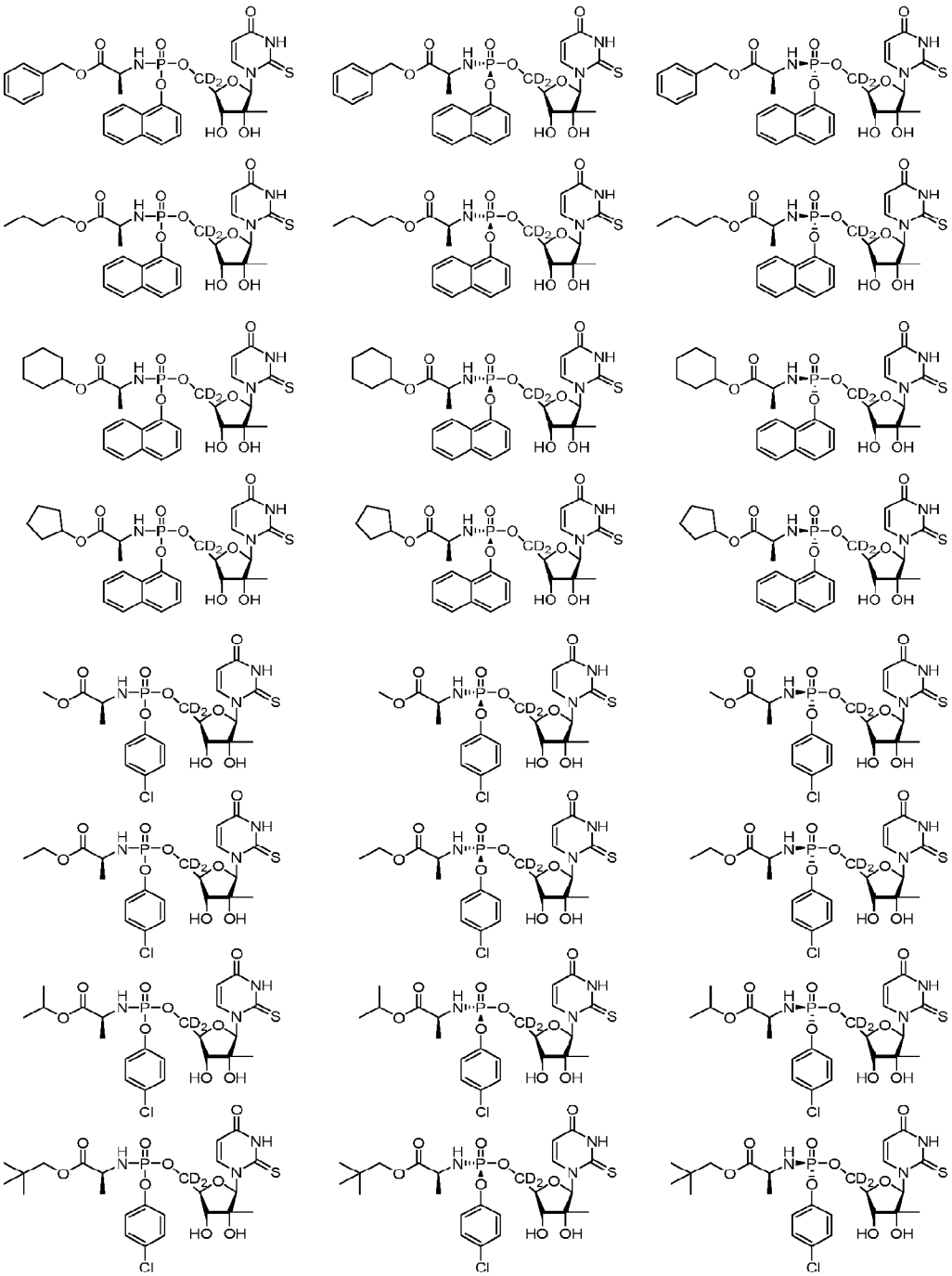
In exemplary embodiments, the compound is selected from:



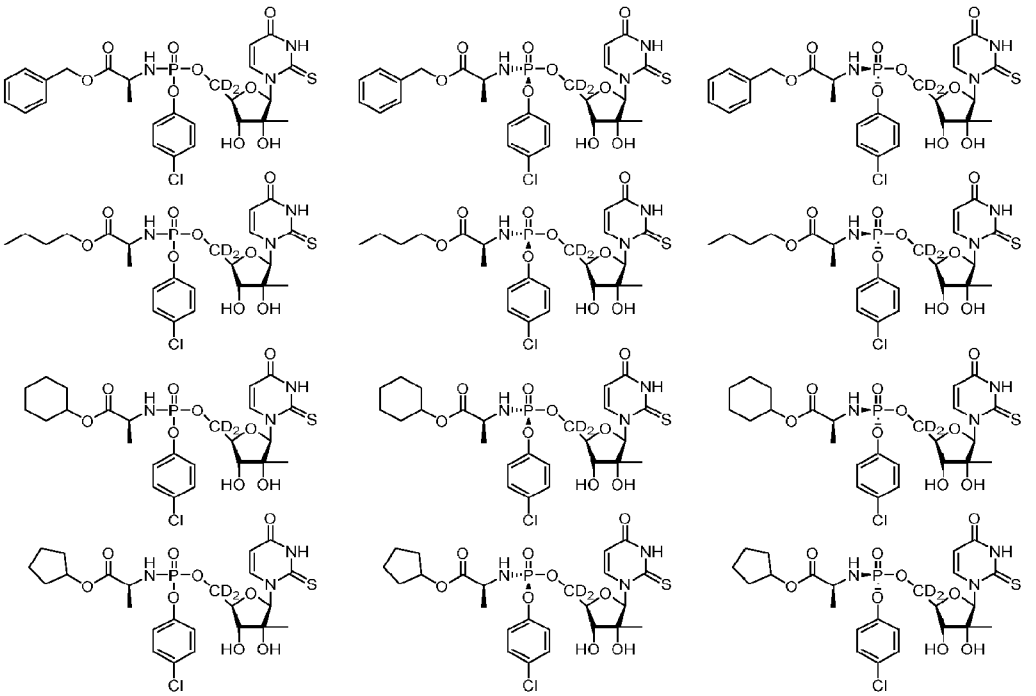
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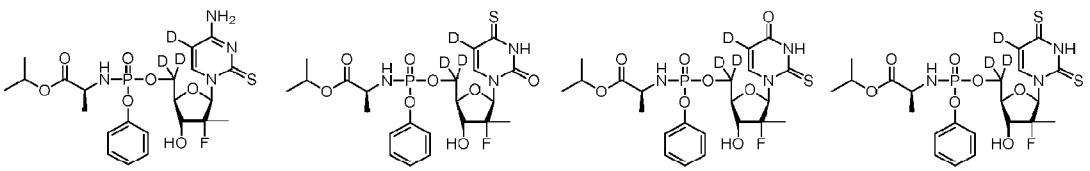
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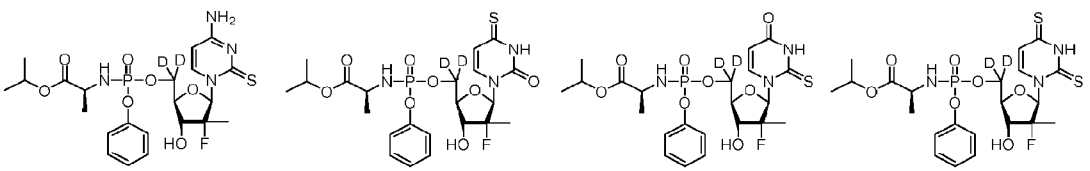
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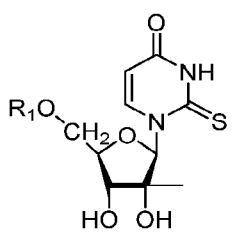
In exemplary embodiments, the compound is selected from:



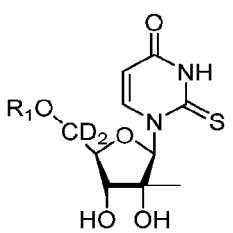
In exemplary embodiments, the compound is selected from:



In preferred embodiments, the nucleoside conjugated to a phosphorus moiety has the following structure:



Formula Im

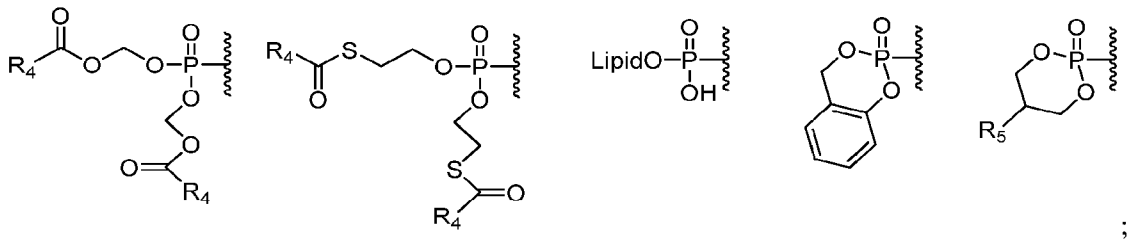


Formula In

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or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

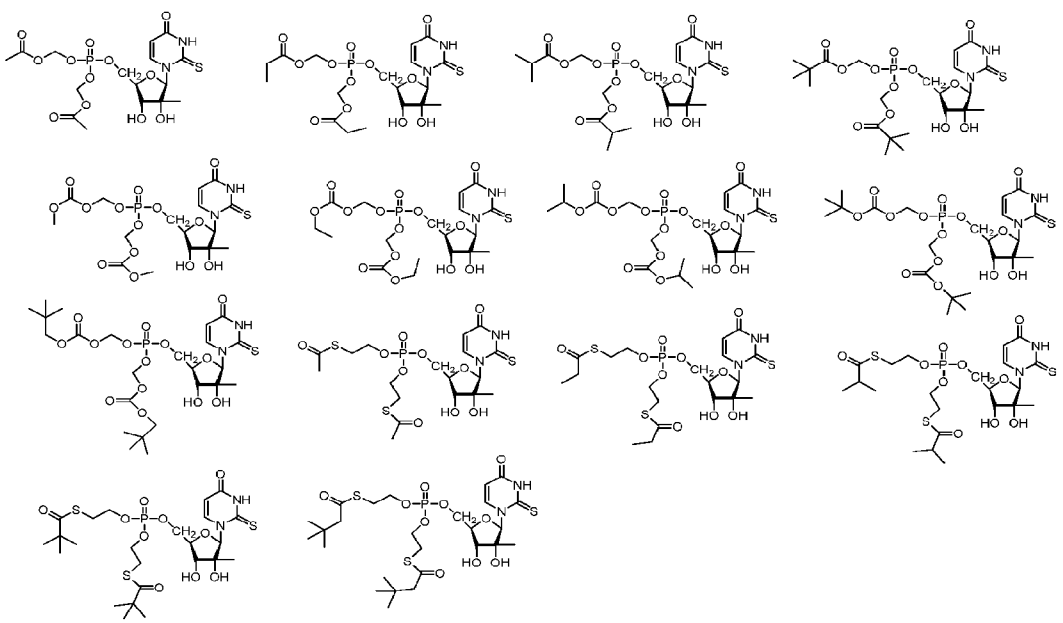


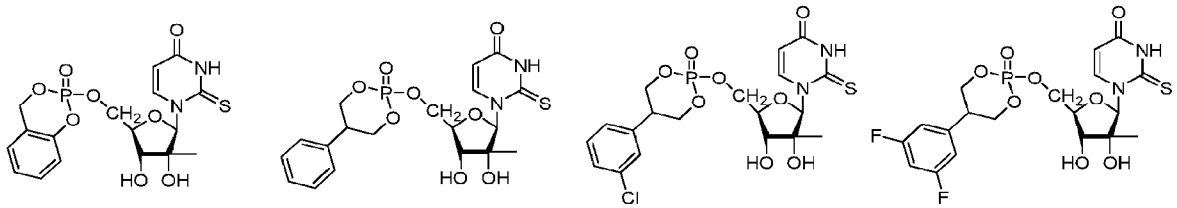
;

R_4 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

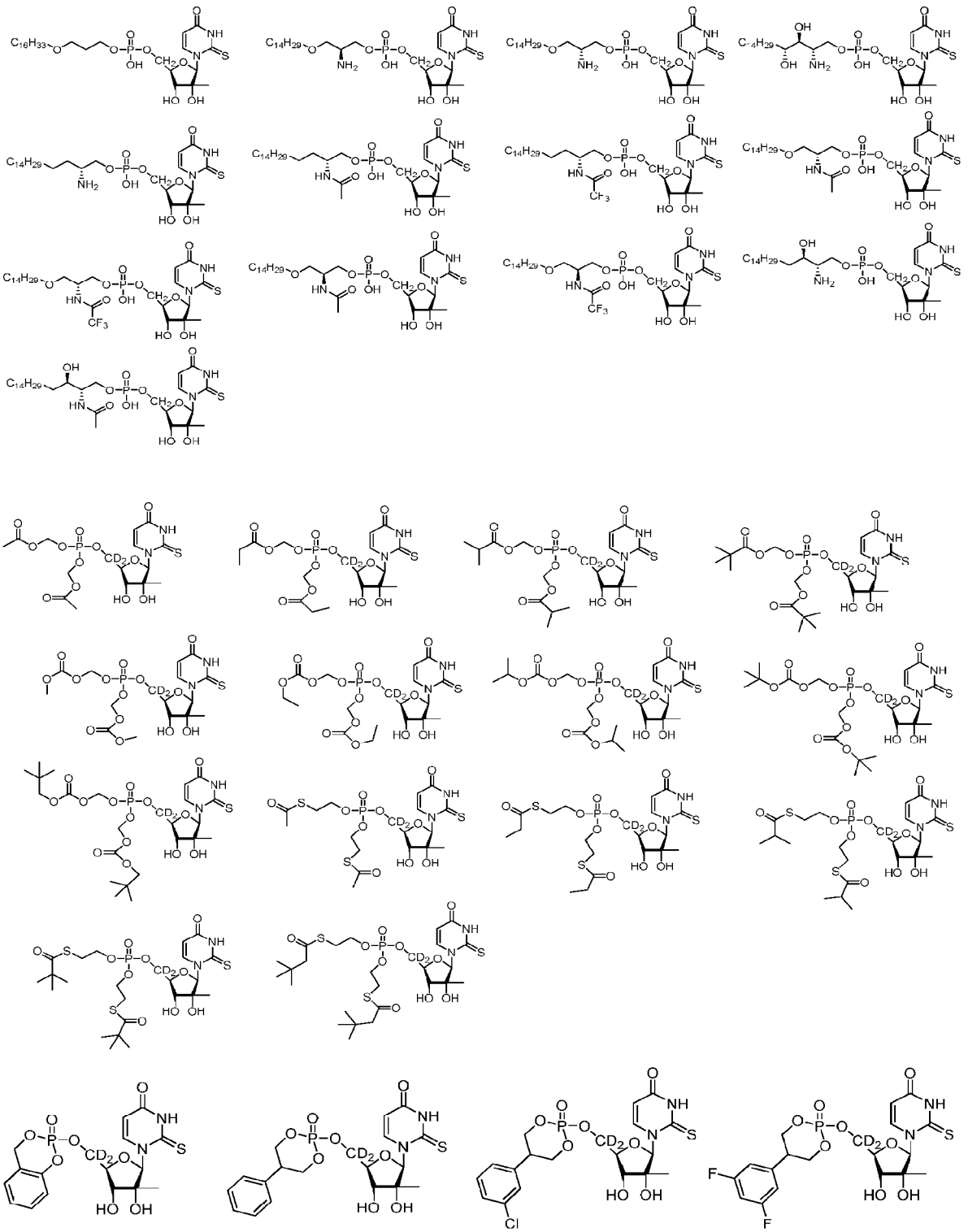
R_5 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

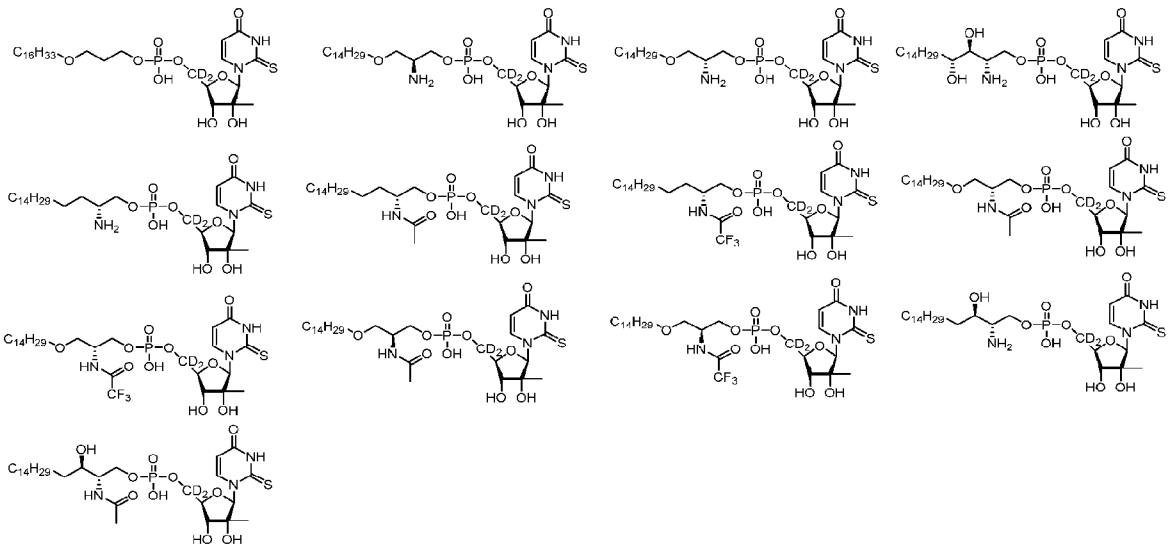
In exemplified embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



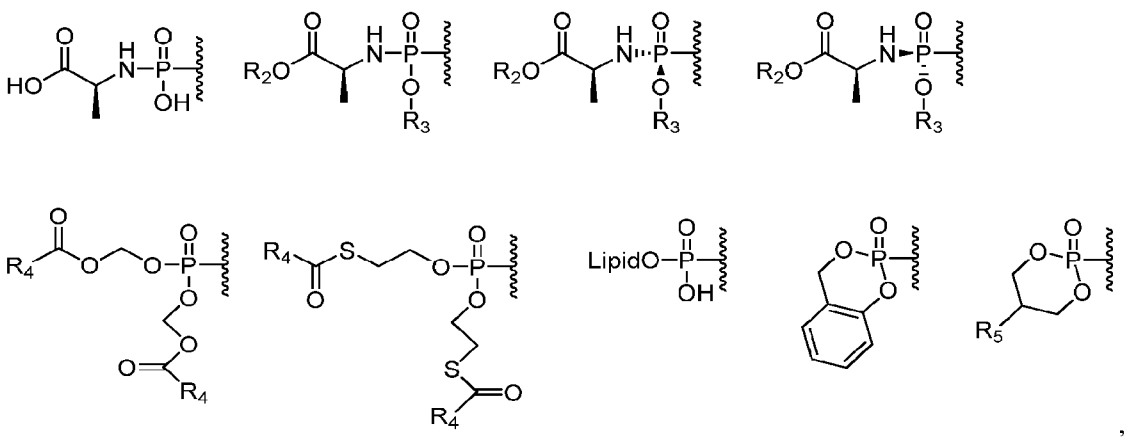


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In other embodiments, R_1 of Formula Im or In is selected from one of the following:



wherein

R_2 is alkyl, branched alkyl, or cycloalkyl;

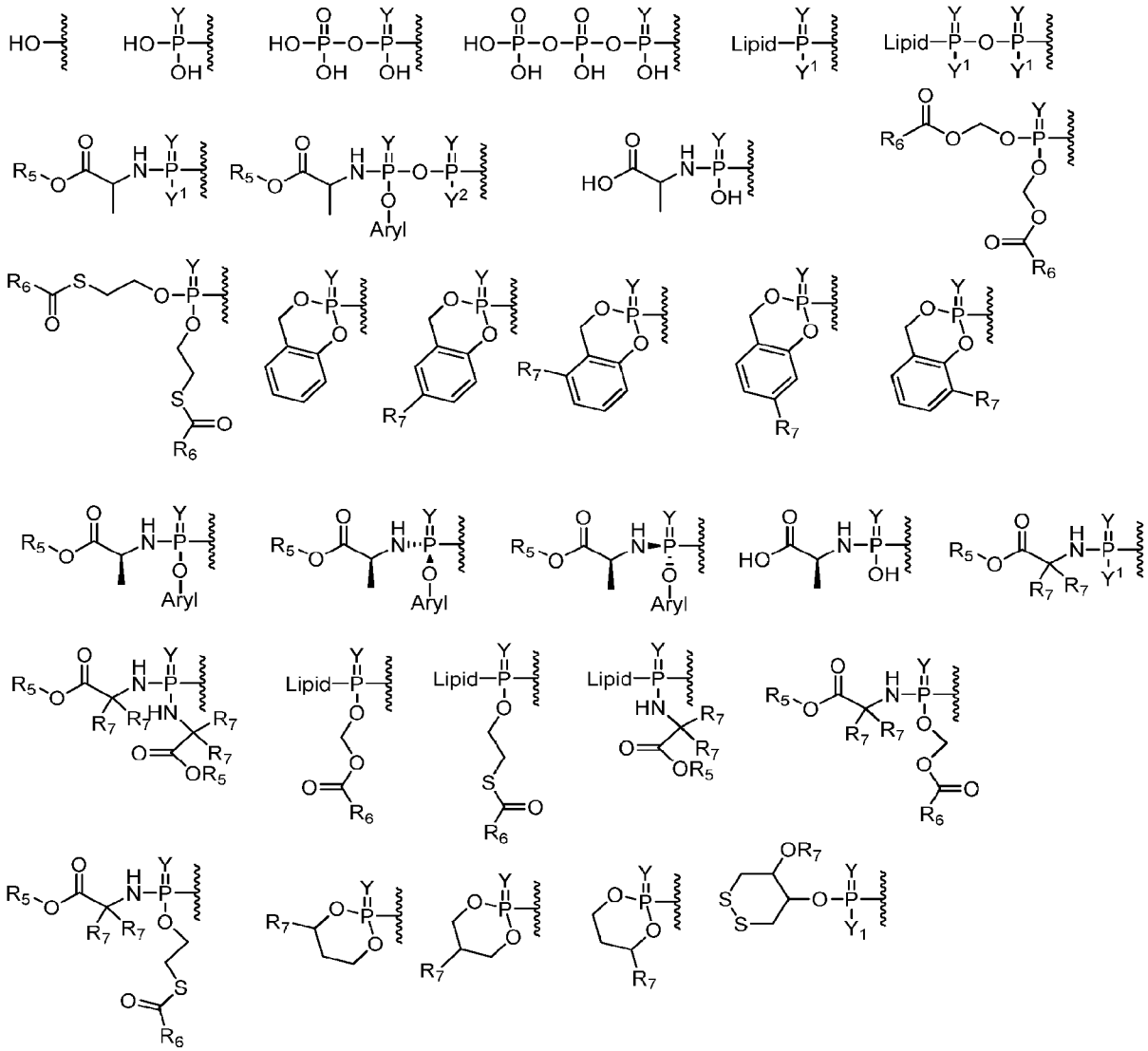
R_3 is aryl, biaryl, or substituted aryl;

R_4 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_5 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In other embodiments, R_1 of Formula Im or In is selected from one of the following:

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Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_5 is alkyl, branched alkyl, or cycloalkyl;

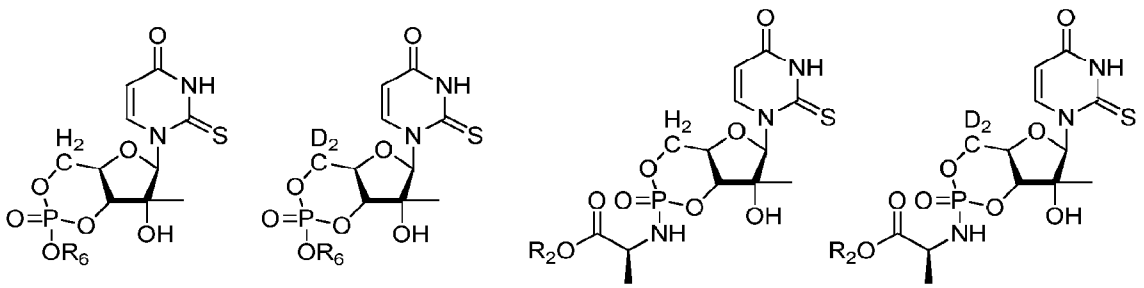
Aryl is as described herein;

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R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

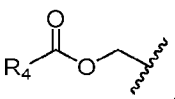
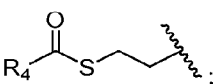
R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



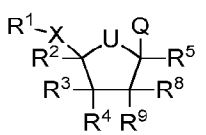
,

R_2 is selected from C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl;

R_6 is lipid, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, pivaloyloxymethyl, cycloalkyl, or selected from , ;

wherein R_4 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy.

In certain embodiments, the disclosure relates to a compound of the following formula:



Formula Io

or pharmaceutically acceptable salts thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is O, CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

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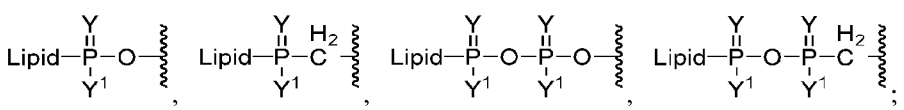
R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^8 and R^9 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^1 is one of the formula:



;

Y is O or S;

Y^1 is OH, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

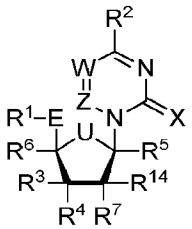
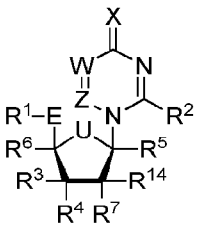
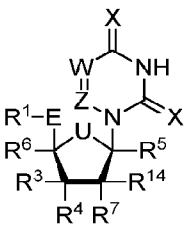
R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl; and

Lipid is as described herein.

In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.In certain embodiments, the disclosure relates to a compound of the following formulae:

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Formala Ip **Formula Iq** **Formula Ir**

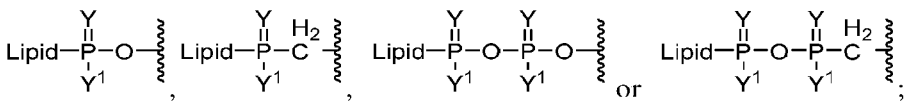
or pharmaceutically acceptable salts thereof, wherein

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

E is O, CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^1 is one of the formula:



Y is O or S;

Y^1 is OH, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Lipid is as described herein;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ip and Iq, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Ir, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3, R^4, R^6, R^7 and R^{14} are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

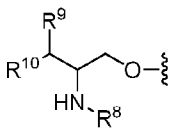
In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

In certain embodiments, E is CH_2; U is O; and Y and Z are CH.

In certain embodiments, the lipid is hexadecyloxypropyl, 2-aminohexadecyloxypropyl, 2-aminoarachidyl, lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, or lignoceryl.

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

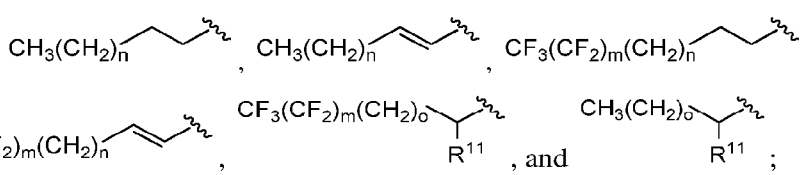


wherein,

R^8 of the sphingolipid is hydrogen, alkyl, $C(=O)R^{12}$, $C(=O)OR^{12}$, or $C(=O)NHR^{12}$;

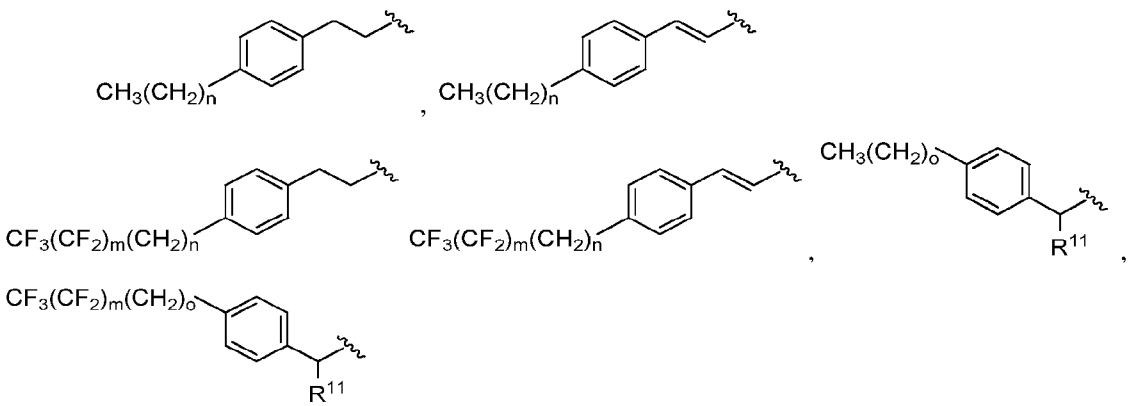
R^9 of the sphingolipid is hydrogen, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{10} 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:

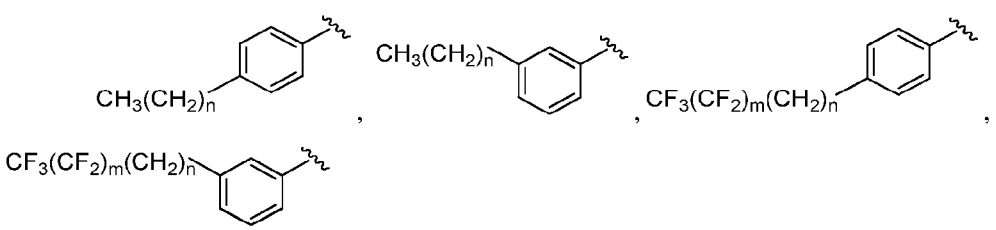


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n is 8 to 14 or less than or equal to 8 to less than or equal to 14, o is 9 to 15 or less than or equal to 9 to less than or equal to 15, the total or m and n is 8 to 14 or less than or equal to 8 to less than or equal to 14, the total of m and o is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



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



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^{11} of the sphingolipid is OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{12} of the sphingolipid is hydrogen, a branched or strait chain C_{1-12}alkyl, C_{13-22}alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{13}; and

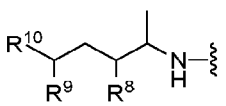
R^{13} of the sphingolipid is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl,

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methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R^{12} of the sphingolipid is H, alkyl, methyl, ethyl, propyl, n-butyl, branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, phenyl, monosubstituted phenyl, disubstituted phenyl, trisubstituted phenyl, or saturated or unsaturated C12-C19 long chain alkyl.

In certain embodiments, the sphingolipid has the formula:

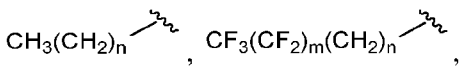


wherein,

R^8 of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^9 of the sphingolipid is hydrogen, hydroxy, fluoro, OR^{12}, $OC(=O)R^{12}$, $OC(=O)OR^{12}$, or $OC(=O)NHR^{12}$;

R^{10} 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:



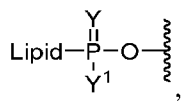
n is 8 to 14 or less than or equal to 8 to less than or equal to 14, the total or m and n is 8 to 14 or less than or equal to 8 to less than or equal to 14;

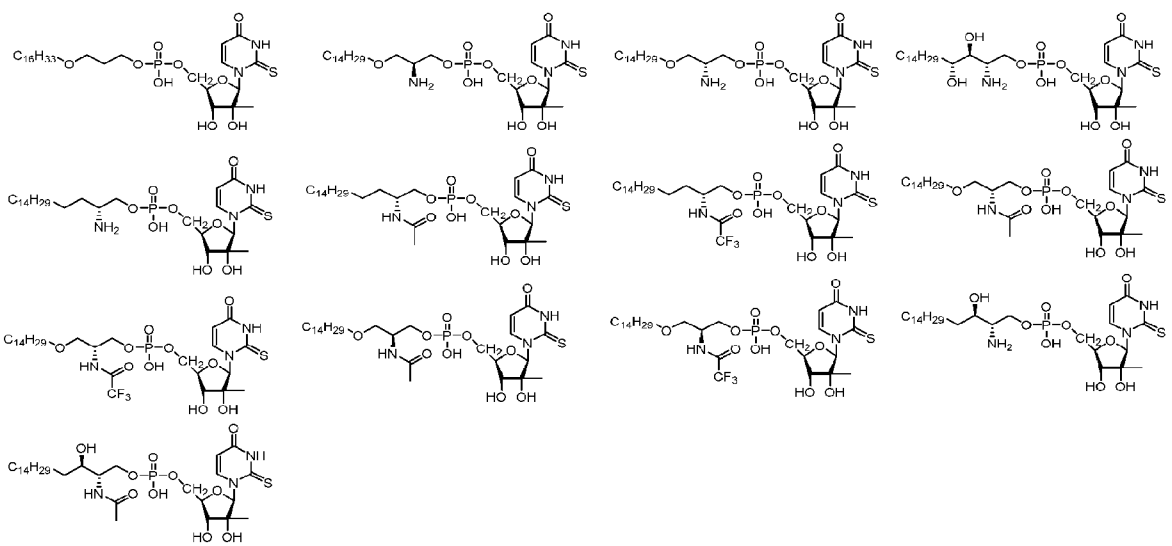
R^{12} of the sphingolipid is hydrogen, a branched or strait chain $C_{1\text{-}12}$alkyl, $C_{13\text{-}22}$alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{13}; and

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R^{13} of the sphingolipid is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

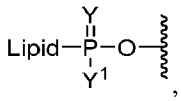
In certain embodiments, R^{12} of the sphingolipid is H, alkyl, methyl, ethyl, propyl, n-butyl, branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl,1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, phenyl, monosubstituted phenyl, disubstituted phenyl, trisubstituted phenyl, or saturated or unsaturated C_{12}-C_{19} long chain alkyl.

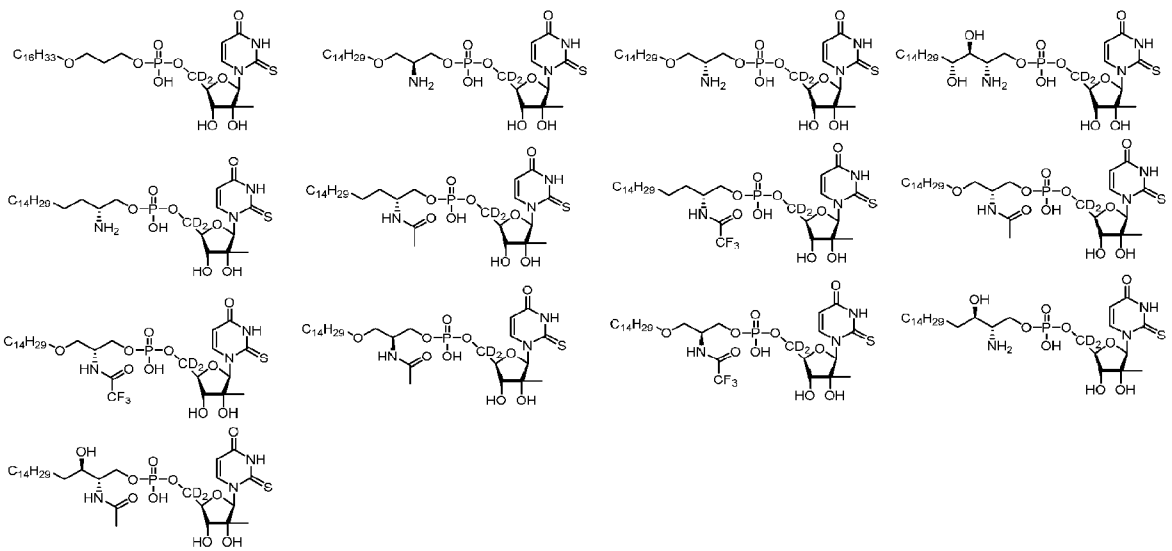
In one embodiment, R^5 is H. In another embodiment, R^4 is hydroxyl. In still another embodiment, R^7 is hydroxyl. In yet another embodiment, R^{14} is methyl. In a further embodiment, R^3 is hydrogen. In another embodiment, R^1 is , wherein Y is O, Y^1 is –OH and lipid is a sphingolipid. In another embodiment, E is CH_2. In exemplary embodiments, the compound is selected from:



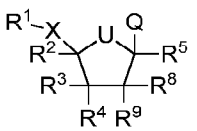
In one embodiment, R^5 is H. In another embodiment, R^4 is hydroxyl. In still another embodiment, R^7 is hydroxyl. In yet another embodiment, R^{14} is methyl. In a further

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embodiment, R^3 is hydrogen. In another embodiment, R^1 is , wherein Y is O, Y^1 is –OH and lipid is a sphingolipid. In another embodiment, E is CD_2. In exemplary embodiments, the compound is selected from:



In certain embodiments, the disclosure relates to a compound of the following formula:



Formula Is

or pharmaceutically acceptable salts thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

R^1 is hydroxyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^8 and R^9 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

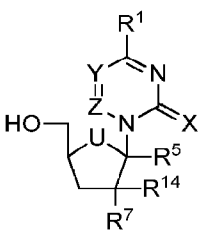
each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

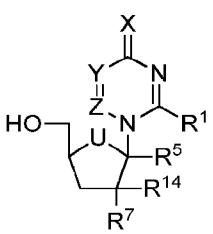
In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In certain embodiments, R^8 and R^9 are selected from H, fluoro, methyl, fluoromethyl, hydroxymethyl, difluoromethyl, trifluoromethyl, acetylenyl, ethyl, vinyl and cyano.

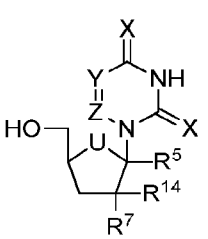
In certain embodiments, the disclosure relates to compounds of the following formulae:



Formula It



Formula Iu



Formula Iv

or a pharmaceutically acceptable salt thereof wherein,

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

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R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula It and Iu, one of X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Iv, at least one X is S;

Y is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^7 and R^{14} are each independently selected from are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^7 and $R1^4$ with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

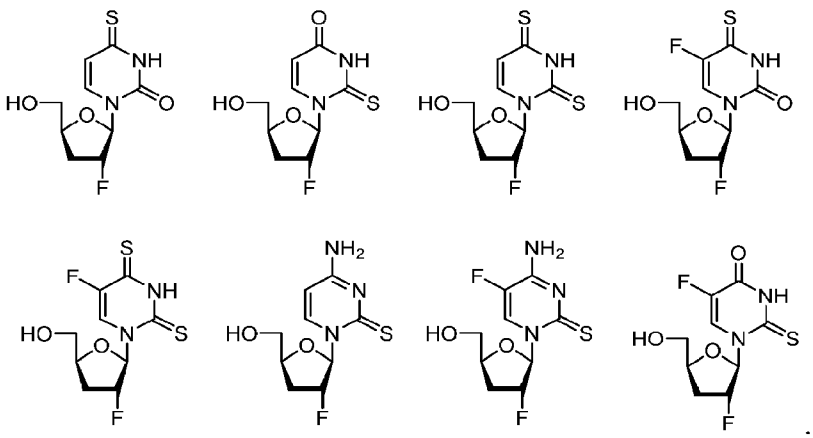
each R^8 is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

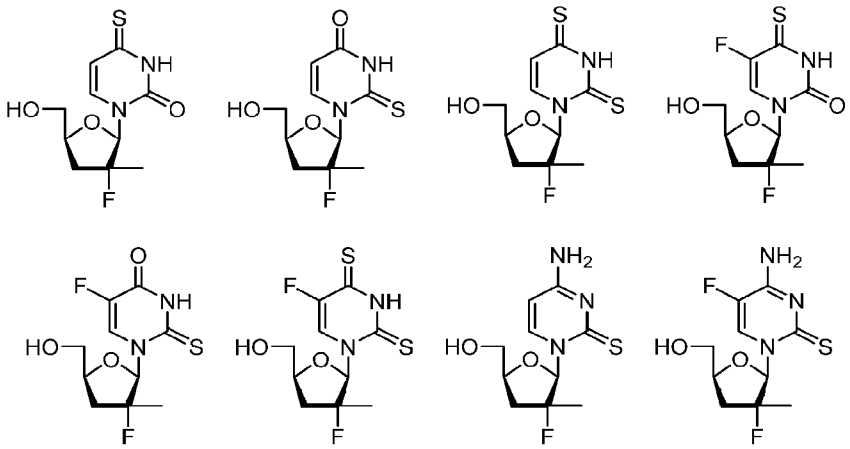
In certain embodiments, R^5 is H. In other embodiments, R^7 is F and R^{14} is H. In exemplary embodiments, the compound is selected from:



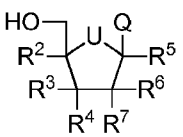
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In certain embodiments, R^5 is H. In other embodiments, R^7 is F and R^{14} is methyl. In exemplary embodiments, the compound is selected from:



In certain embodiments, the disclosure relates to compounds of the following formula:



Formula Iw

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

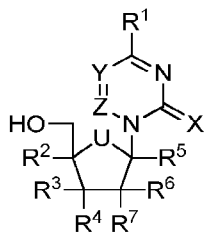
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and R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl.

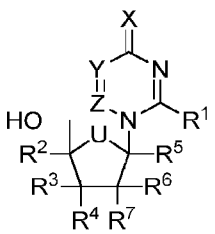
In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

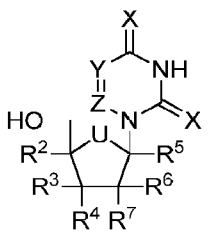
In certain embodiments, the disclosure relates to compounds of one of the following formulae:



Formula Ix



Formula Iy



Formula Iz

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ix and Iy, one of X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Iz, at least one X is S;

Y is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^8 is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

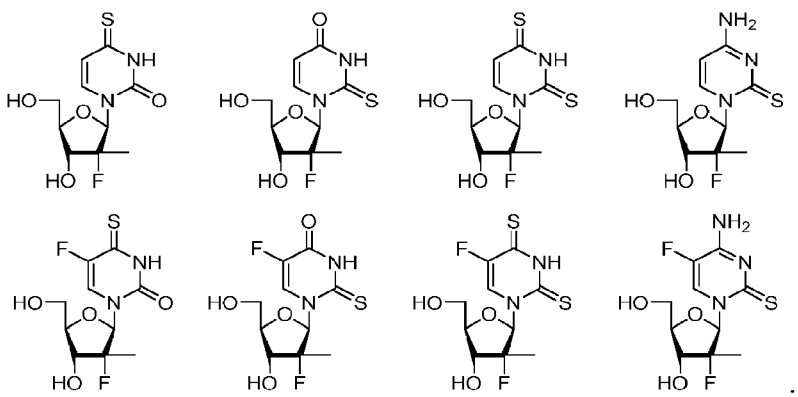
each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

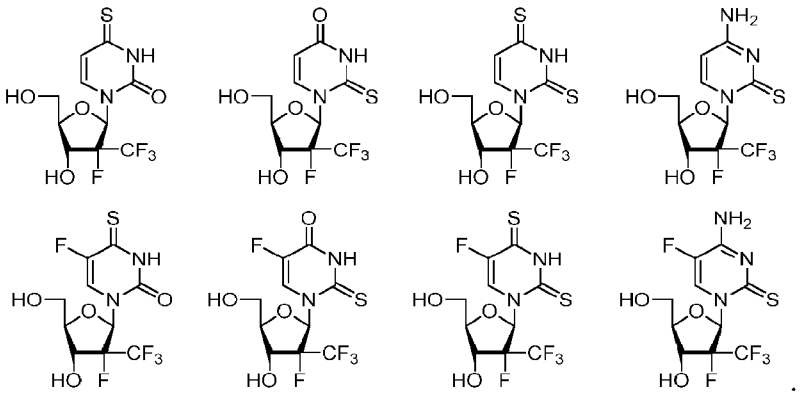
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is fluoro.

In exemplary embodiments, the compound is selected from the group consisting of:

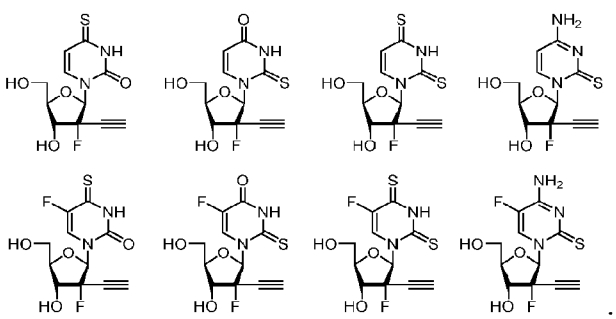


In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is trifluoromethyl. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

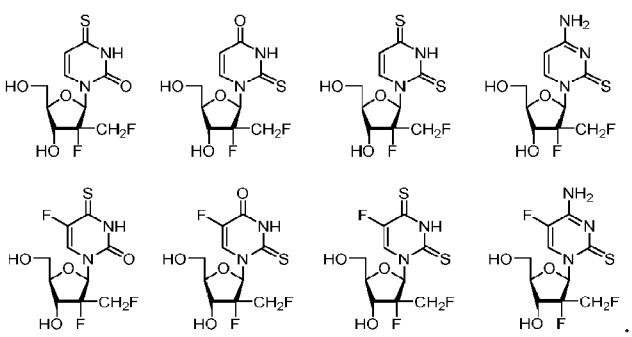
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In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is C≡CH. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

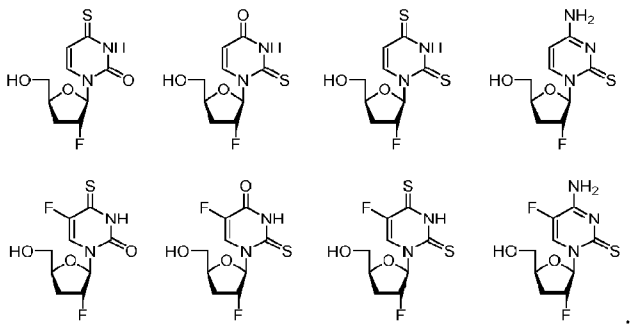


In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is CH_2F. In a still further another embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

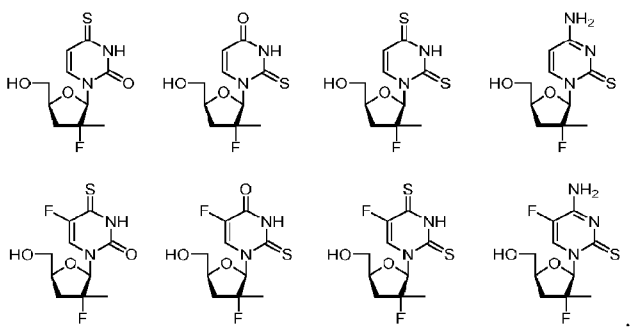


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In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is H. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

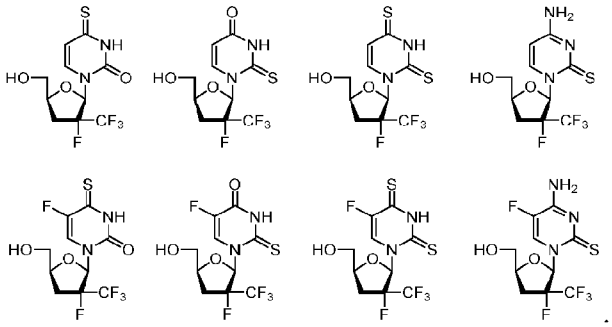


In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is H. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

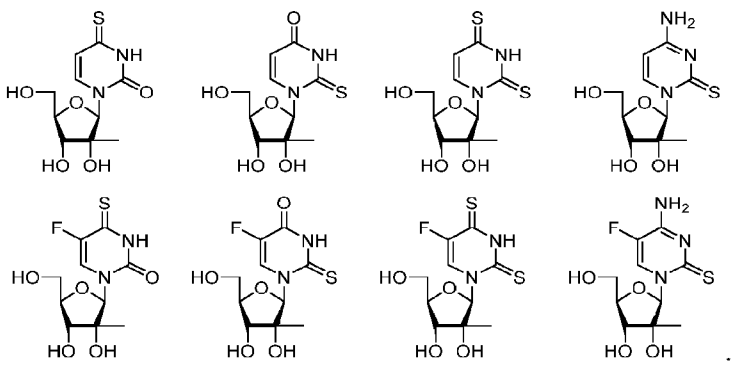


In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is H. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is trifluoromethyl. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

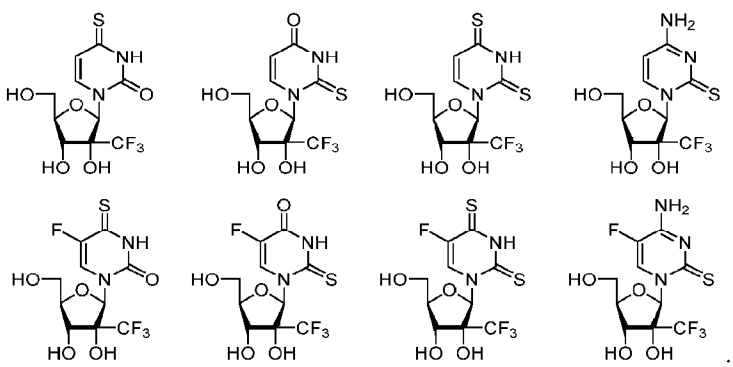
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In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



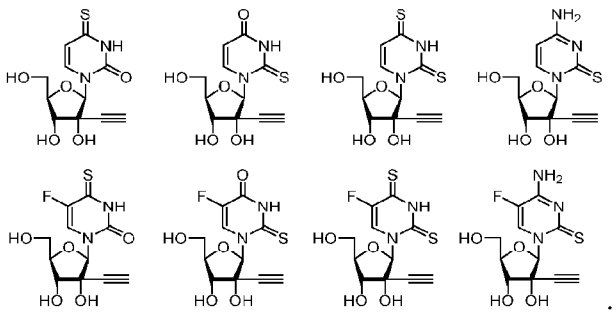
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is trifluoromethyl. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



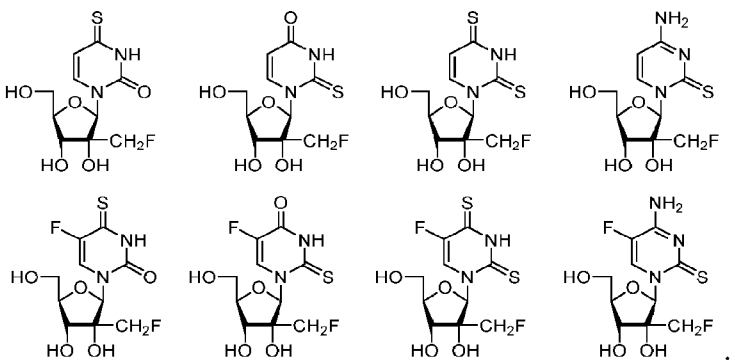
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment,

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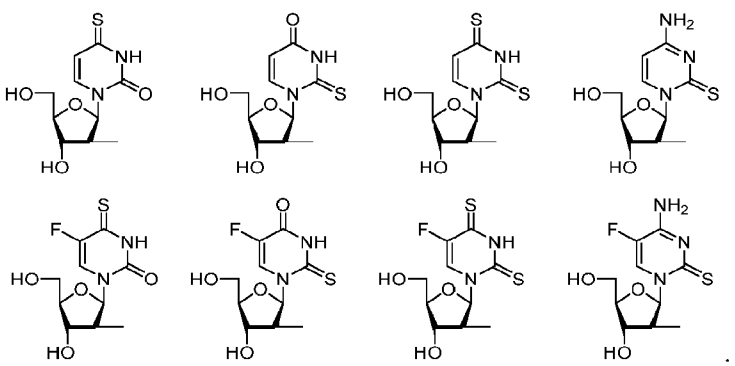
R^6 is C≡CH. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is CH_2F. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

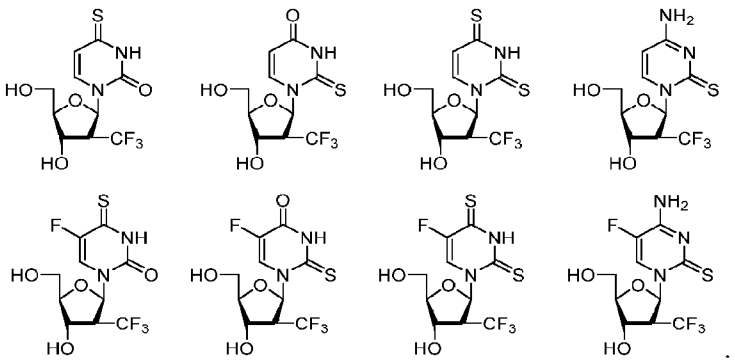


In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is H. In exemplary embodiments, the compound is selected from the group consisting of:

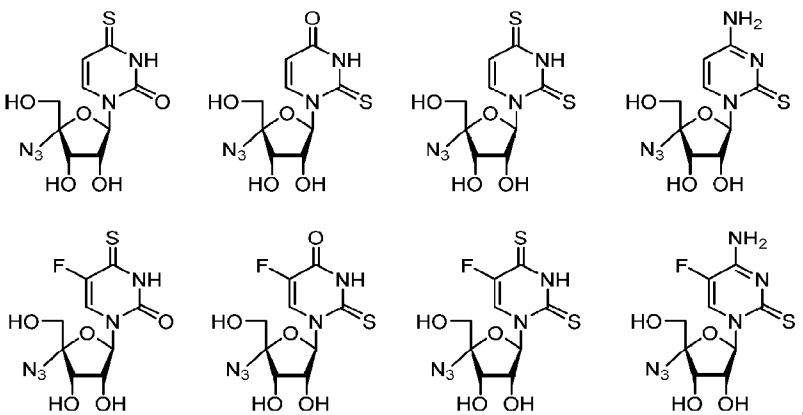


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In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is trifluoromethyl. In a still further embodiment, R^7 is H. In exemplary embodiments, the compound is selected from the group consisting of:

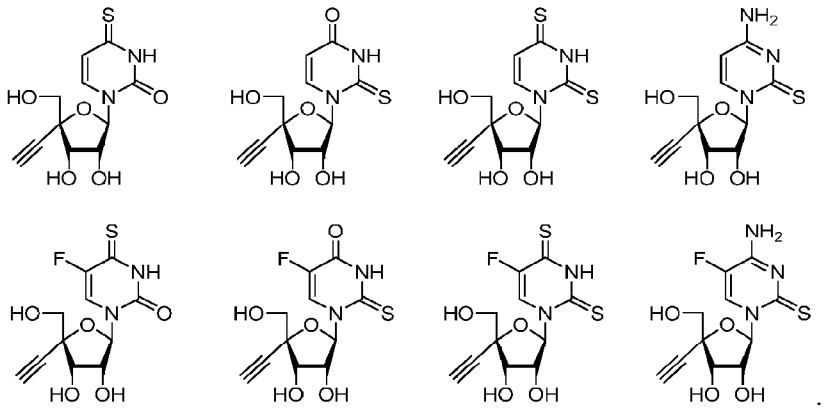


In one embodiment, R^2 is N_3. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

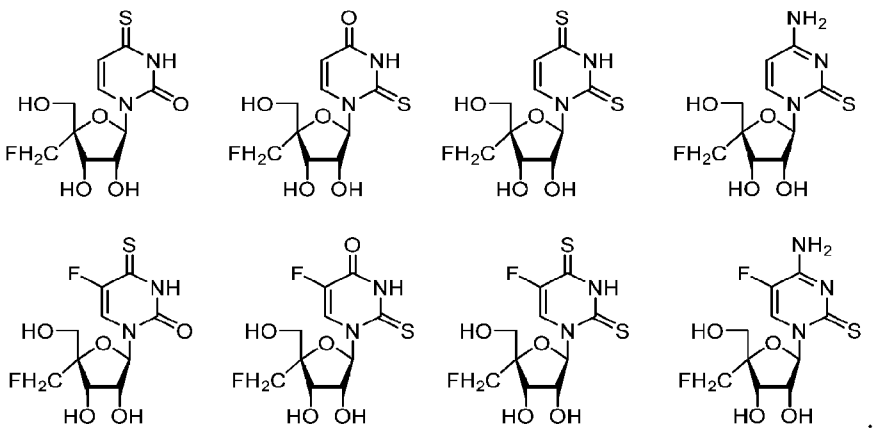


In one embodiment, R^2 is C≡CH. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

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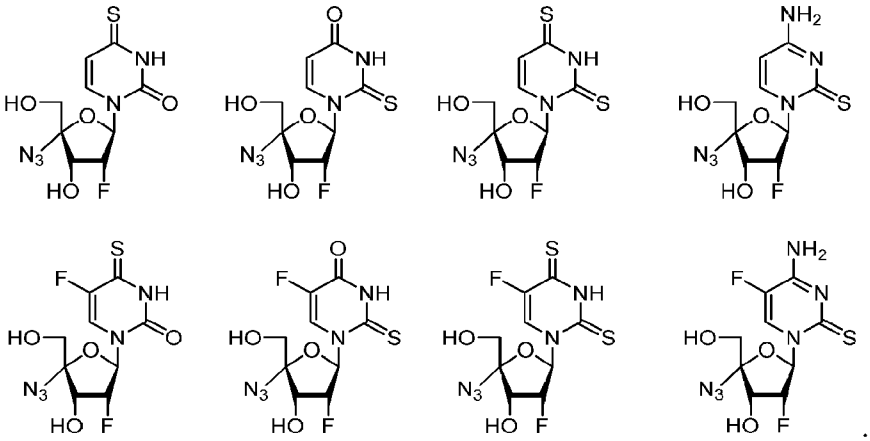


In one embodiment, R^2 is CH_2F. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

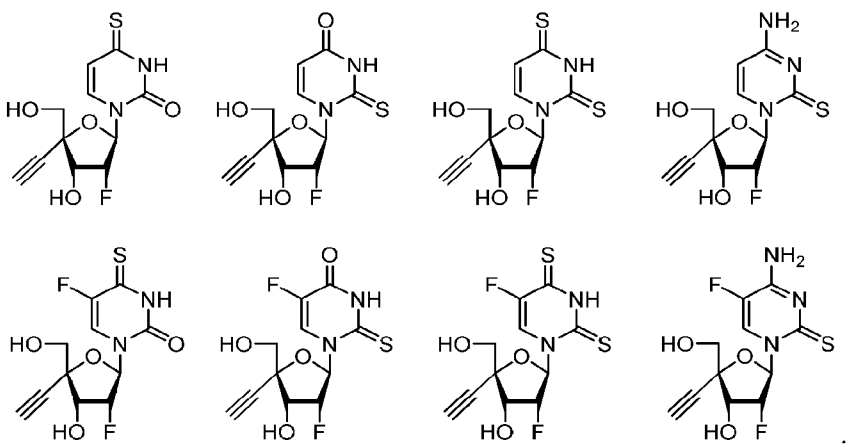


In one embodiment, R^2 is N_3. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

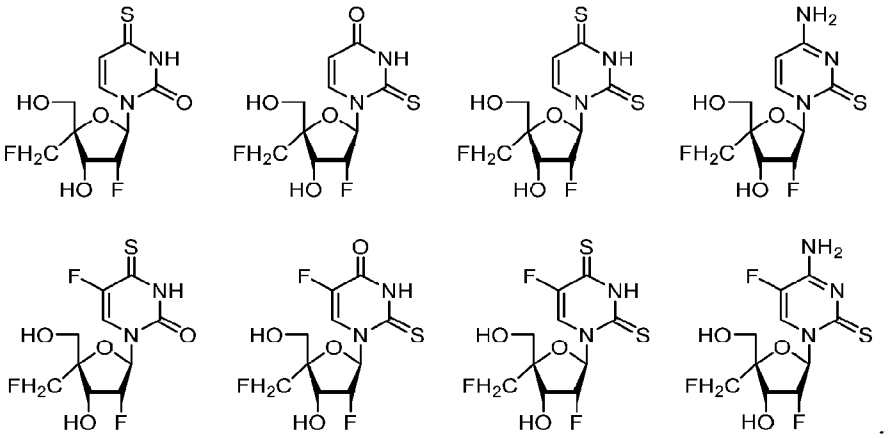
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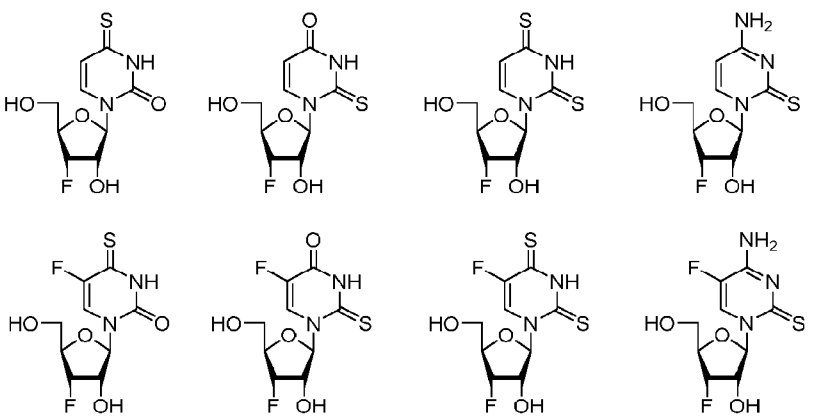
In one embodiment, R^2 is C≡CH. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:



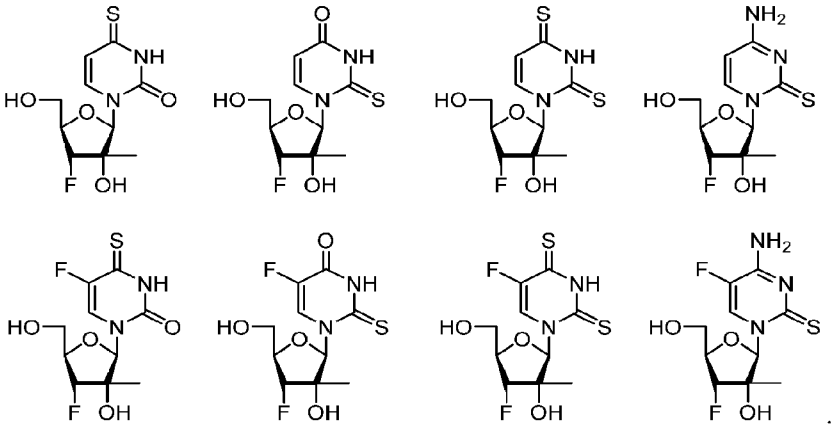
In one embodiment, R^2 is CH_2F. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:



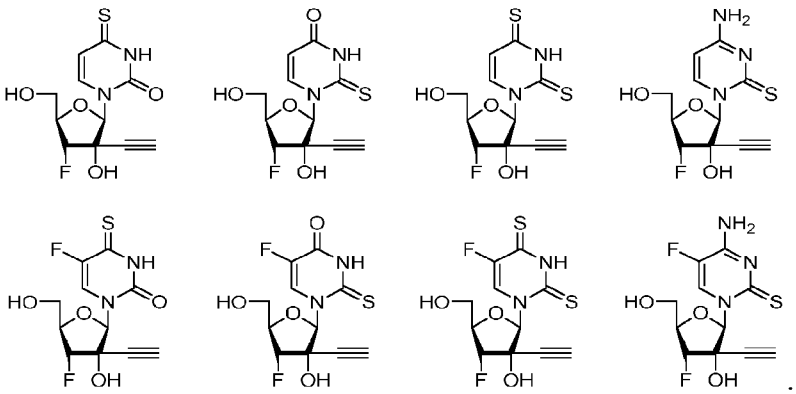
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is H. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



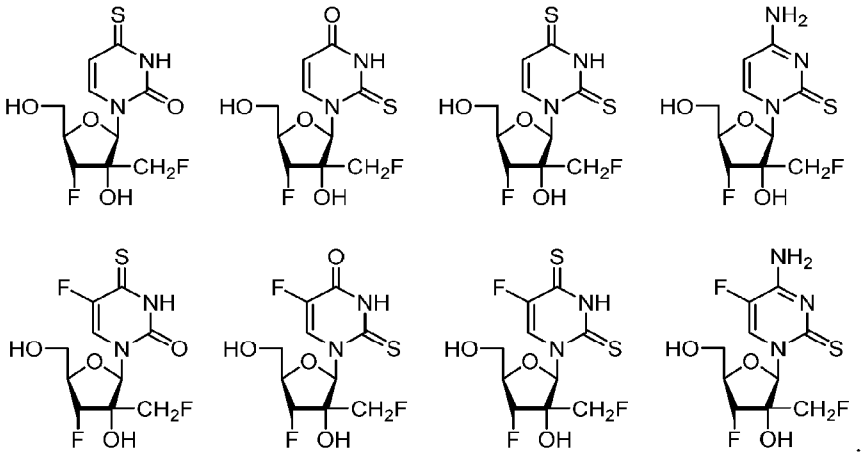
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



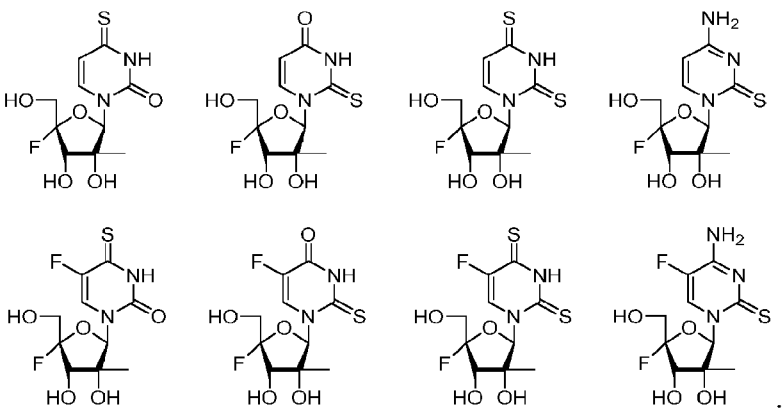
In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is C≡CH. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:



In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is fluoro. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is CH_2F. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

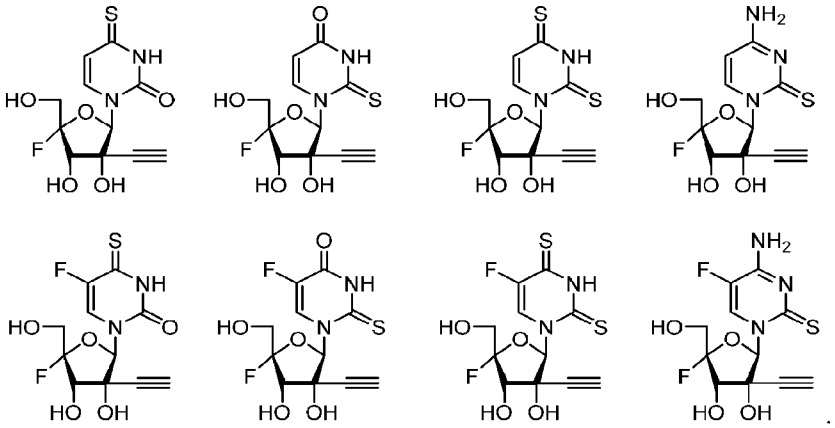


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further another embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

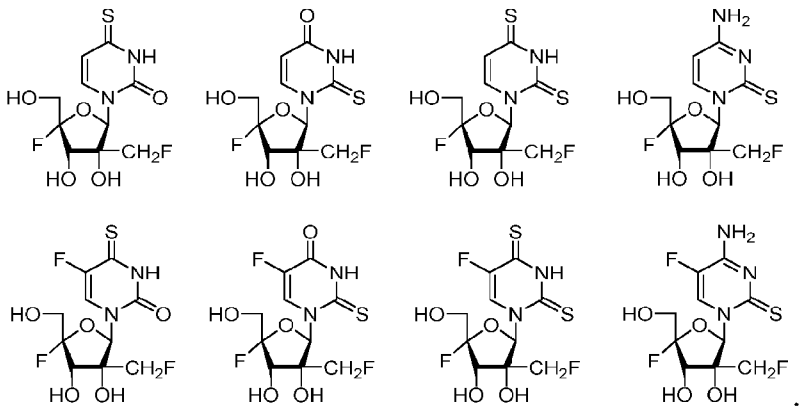


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is C≡CH. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

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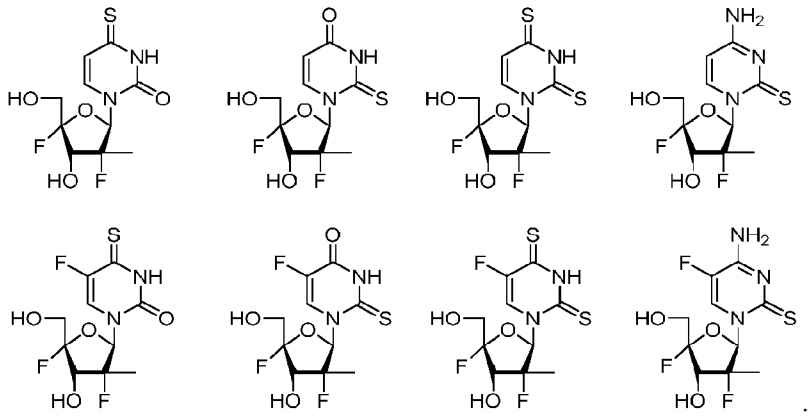


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is CH_2F. In a still further embodiment, R^7 is hydroxyl. In exemplary embodiments, the compound is selected from the group consisting of:

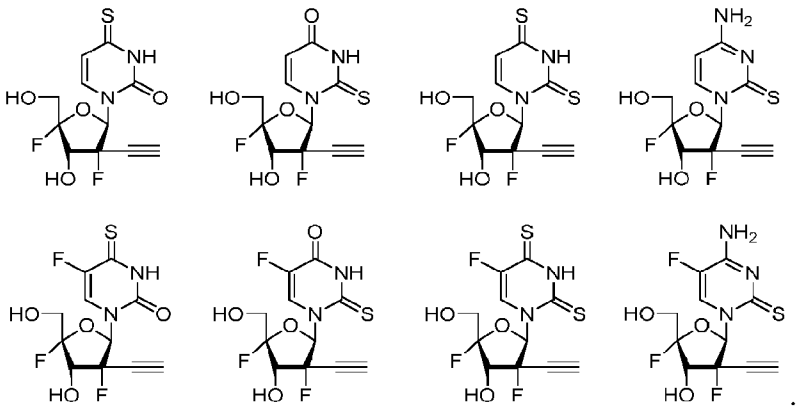


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is methyl. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

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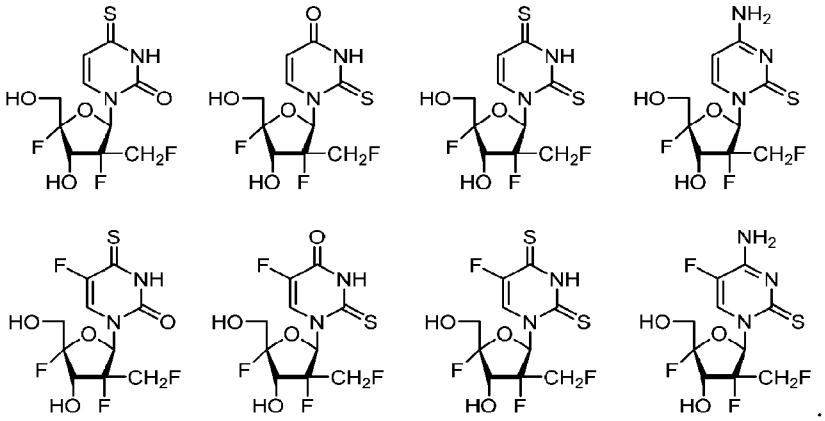


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is C≡CH. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

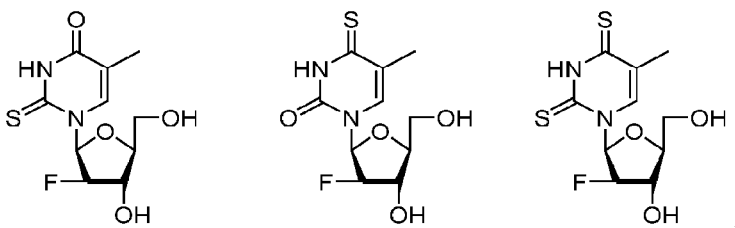


In one embodiment, R^2 is fluoro. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is CH_2F. In a still further embodiment, R^7 is fluoro. In exemplary embodiments, the compound is selected from the group consisting of:

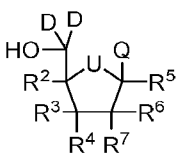
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In one embodiment, R^2 is H. In another embodiment, R^3 is H. In still another embodiment, R^4 is hydroxyl. In a further embodiment, R^5 is H. In yet another embodiment, R^6 is fluoro. In a still further embodiment, R^7 is H. In exemplary embodiments, the compound is selected from the group consisting of:



In certain embodiments, the disclosure relates to compounds of the following formula:



Formula Iw

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

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R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

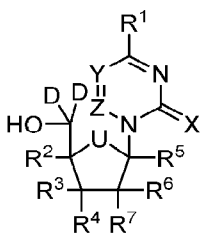
each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

and R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl.

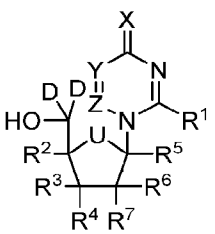
In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

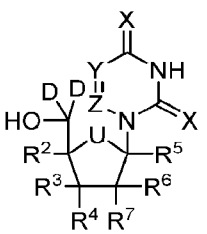
In certain embodiments, the disclosure relates to compounds of one of the following formulae:



Formula Ix



Formula Iy



Formula Iz

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

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wherein in Formula Ix and Iy, one of X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Iz, at least one X is S;

Y is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

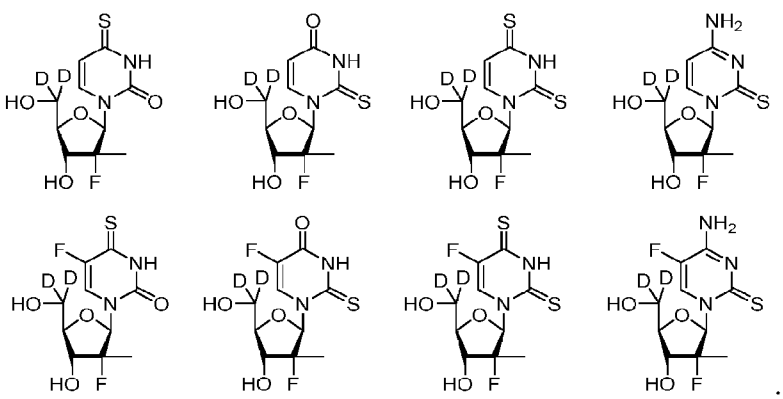
R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^8 is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

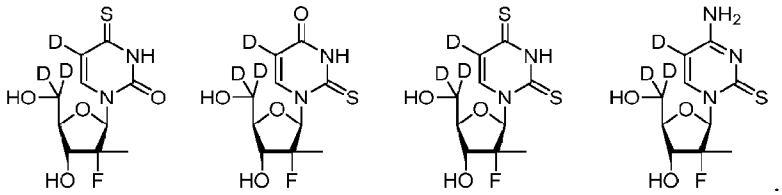
each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In exemplary embodiments, the compound is selected from the group consisting of:

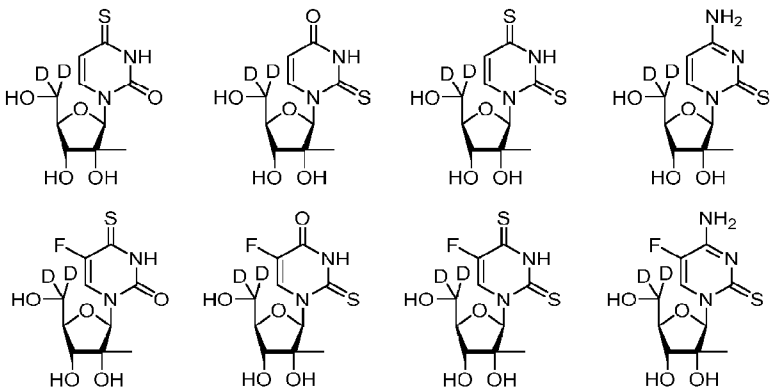


In exemplary embodiments, the compound is selected from the group consisting of:

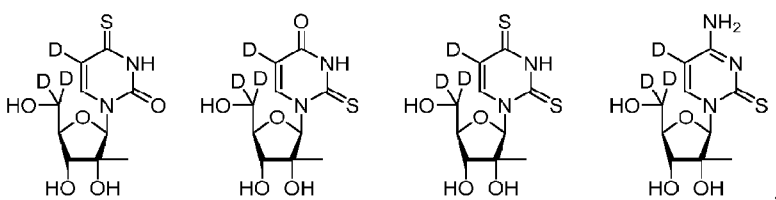
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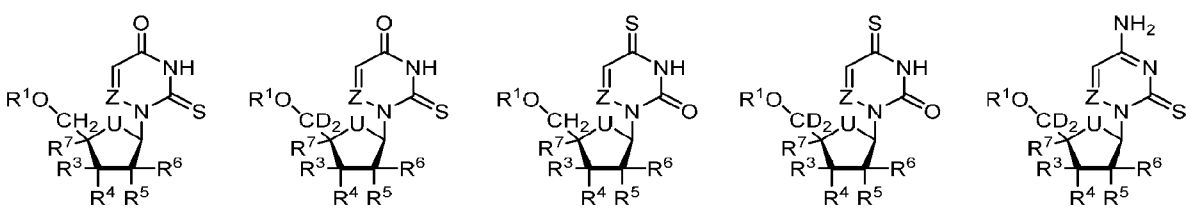
In exemplary embodiments, the compound is selected from the group consisting of:



In exemplary embodiments, the compound is selected from the group consisting of:



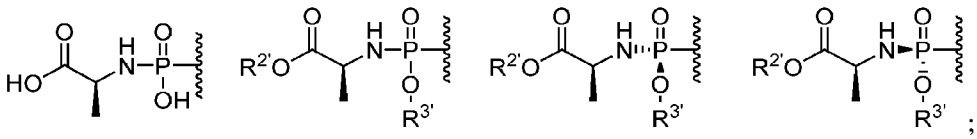
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



Formula Iaa **Formula Iab** **Formula Iac** **Formula Iad** **Formula ae**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^7 is H, D, N_3, ethynyl, vinyl, fluoro, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, CD_3, hydroxymethyl or cyano;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl or vinyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

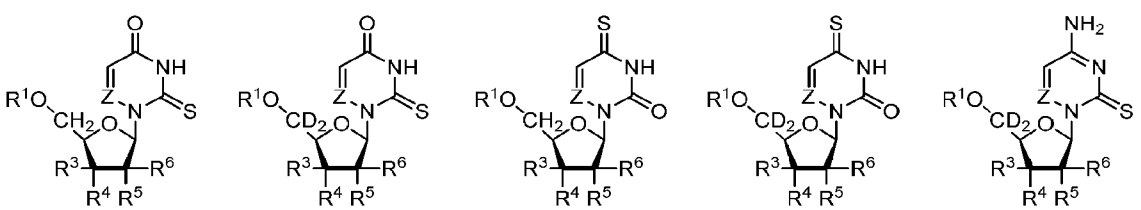
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl or vinyl.

In certain embodiments of any of the formula described herein, Z is CD.

In certain embodiments, U is S and Z is CH.

In other embodiments, U is O and Z is CH.

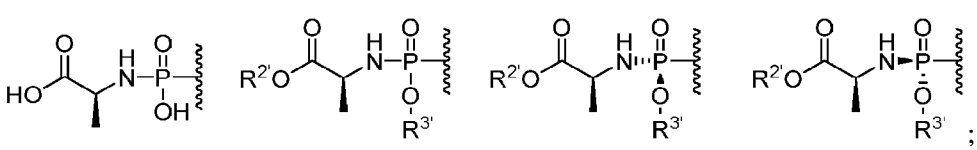
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



Formula Iaf **Formula Iag** **Formula Iah** **Formula Iai** **Formula Iaj**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

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$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

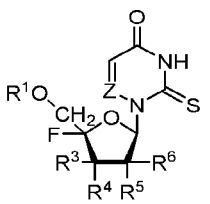
R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

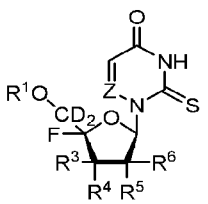
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

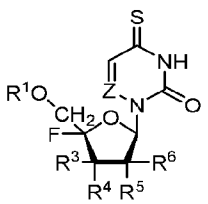
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formula:



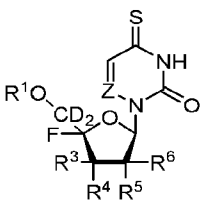
Formula Iak



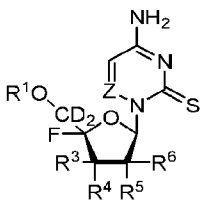
Formula Ial



Formula Iam



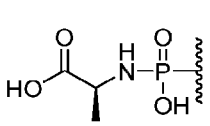
Formula Ian

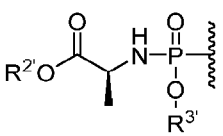


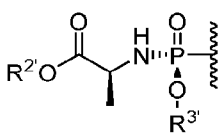
Formula Iao

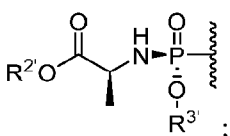
or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:









;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

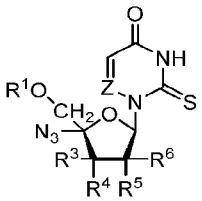
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

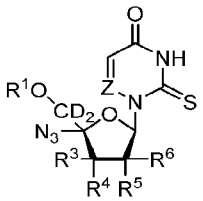
In certain embodiments, Z is CH.

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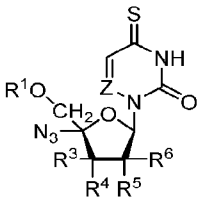
In preferred embodiments, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



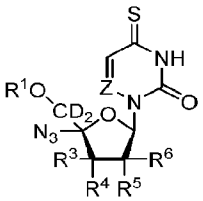
Formula Iap



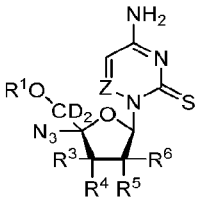
Formula Iaq



Formula Iar



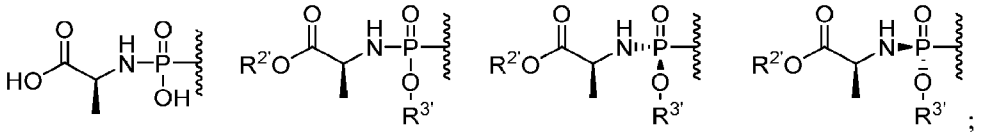
Formula Ias



Formula Iat

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

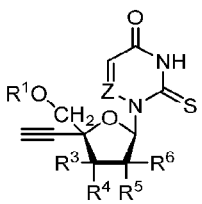
R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

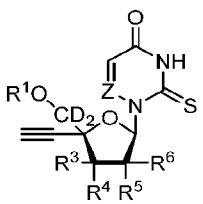
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

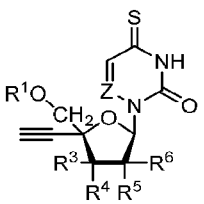
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



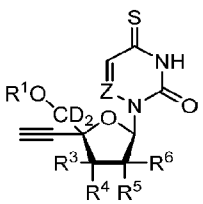
Formula Iau



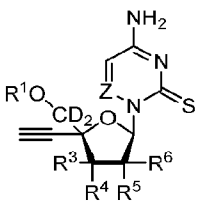
Formula Iav



Formula Iaw



Formula Iax

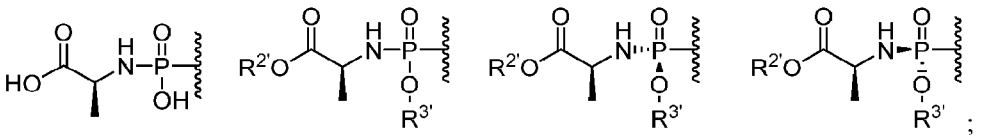


Formula Iay

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or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D,methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

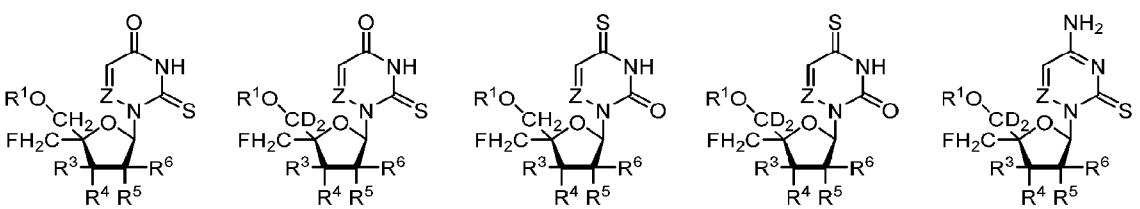
R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

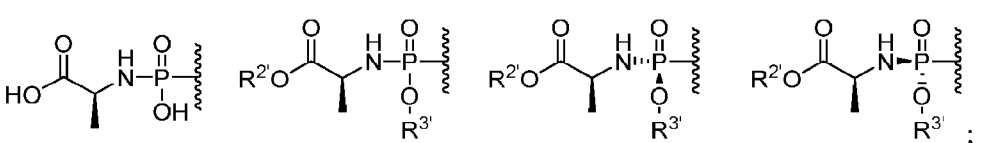
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



Formula Iaz **Formula Iba** **Formula Ibb** **Formula Ibc** **Formula Ibd**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

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R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

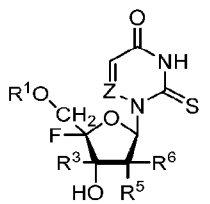
R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

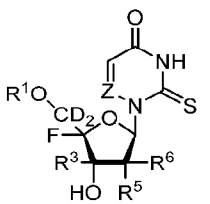
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

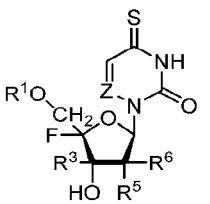
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



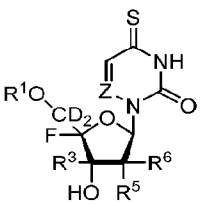
Formula Ibc



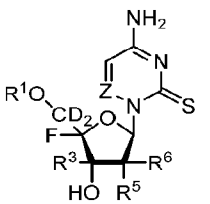
Formula Ibf



Formula Ibg



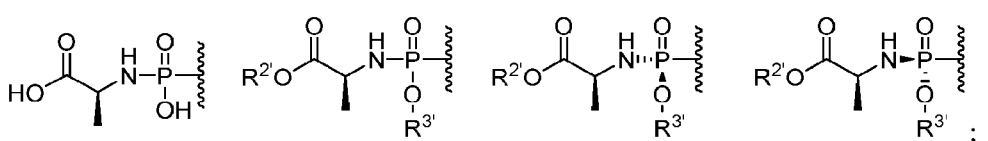
Formula Ibh



Formula Ibi

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

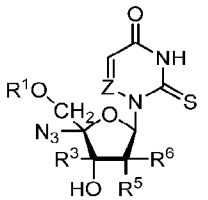
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

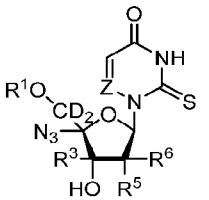
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

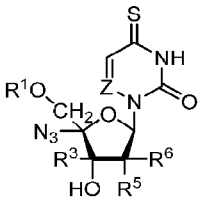
In certain embodiments, Z is CH.

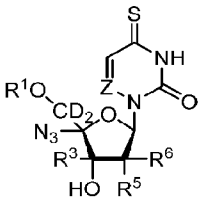
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:

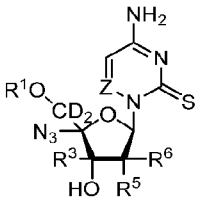
CA 03216679 2023-10-25


Formula Ibj


Formula Ibk

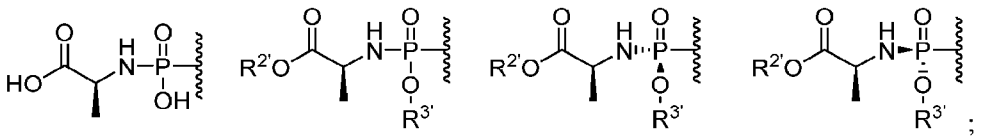

Formula Ibl


Formula Ibm


Formula Ibn

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

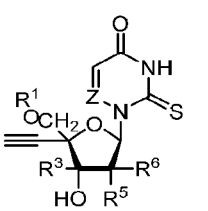
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

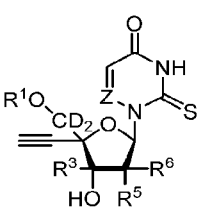
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

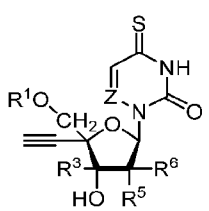
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

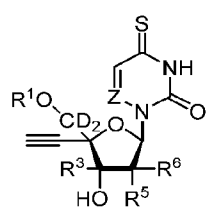
In certain embodiments, Z is CH.

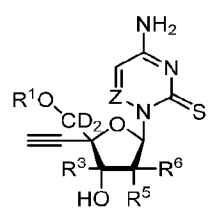
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formuale:


Formula Ibo


Formula Ibp


Formula Ibq

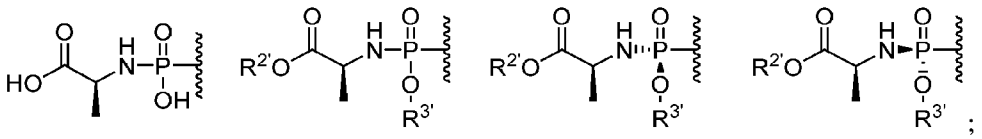

Formula Ibr


Formula Ibs

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:

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$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

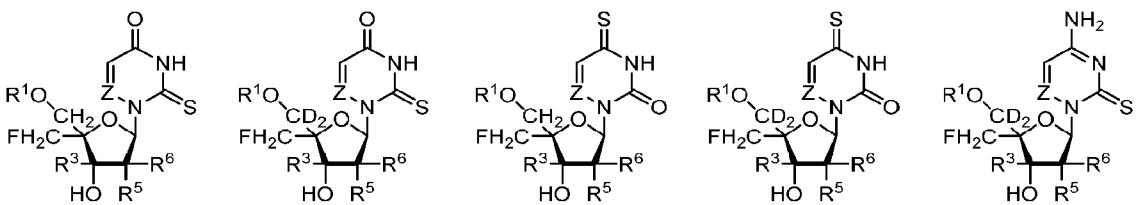
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

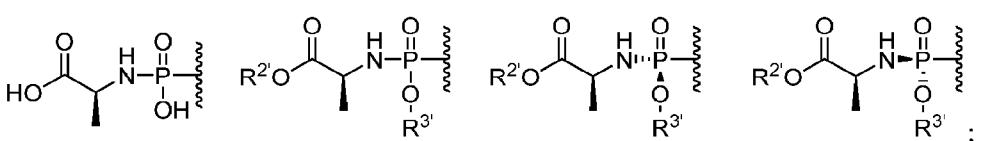
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



Formula Ibt **Formula Ibu** **Formula Ibv** **Formula Ibw** **Formula Ibx**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

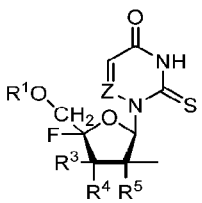
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

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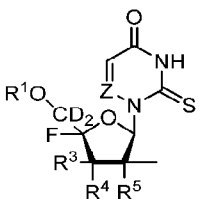
R^6 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl.

In certain embodiments, Z is CH.

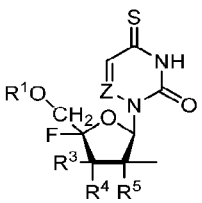
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



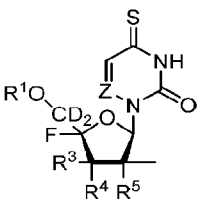
Formula Iby



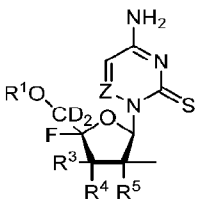
Formula Ibz



Formula Ica



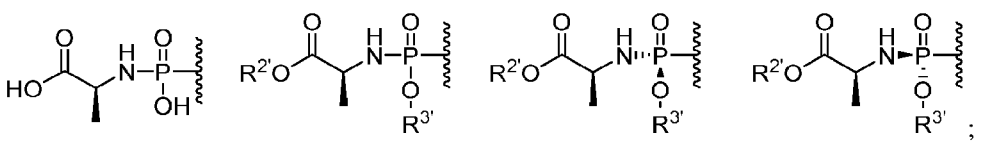
Formula Icb



Formula Icc

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

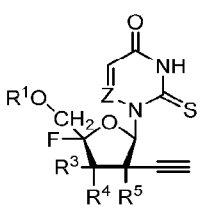
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

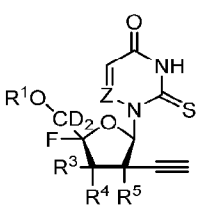
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

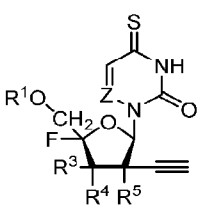
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



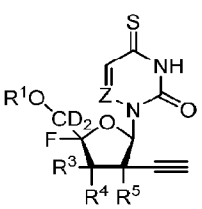
Formula Icd



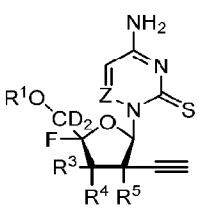
Formula Ice



Formula Icf



Formula Icg

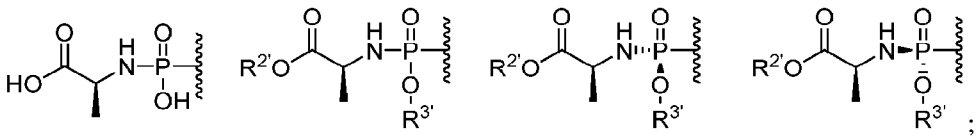


Formula Ich

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or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

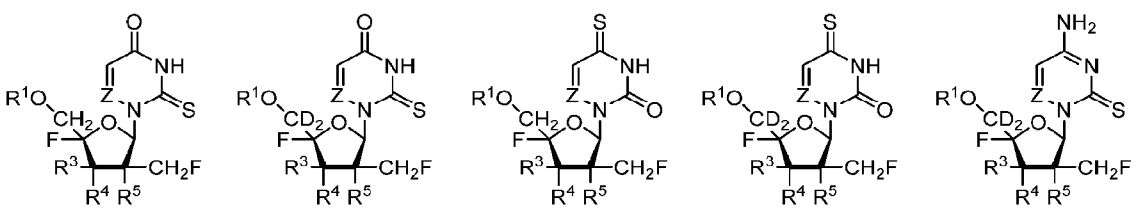
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CII.

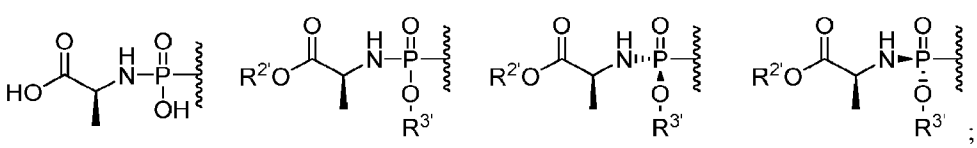
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formuale:



Formula Ici **Formula Icj** **Formula Ick** **Formula Icl** **Formula Icm**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

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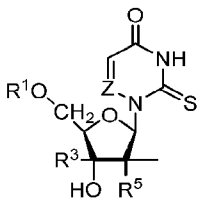
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

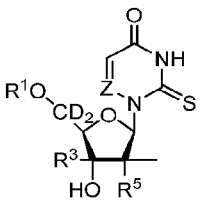
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

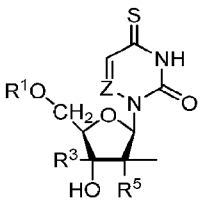
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



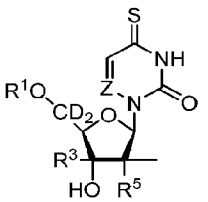
Formula Icn



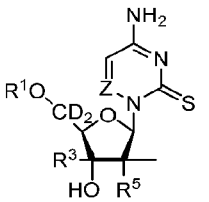
Formula Ico



Formula Icp



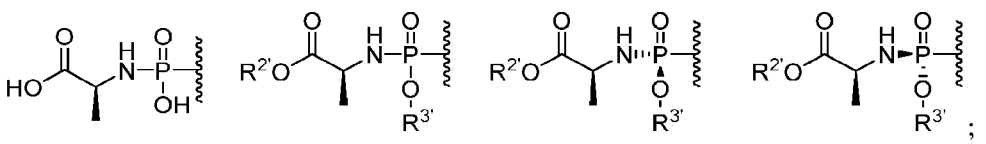
Formula Icq



Formula Icr

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

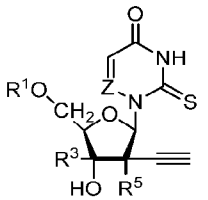
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

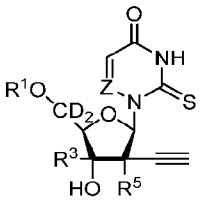
In certain embodiments, Z is CH.

In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:

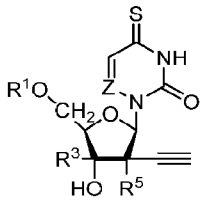
CA 03216679 2023-10-25



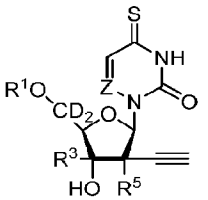
Formula Ics



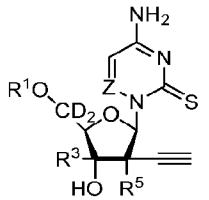
Formula Ict



Formula Icu



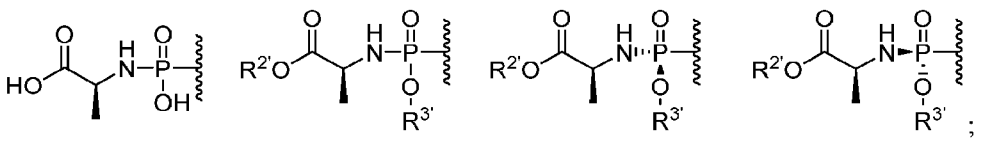
Formula Icv



Formula Icw

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

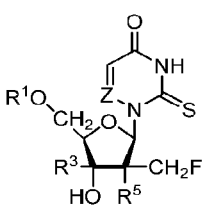
Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

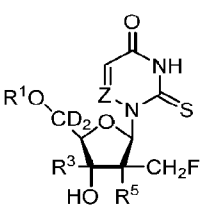
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

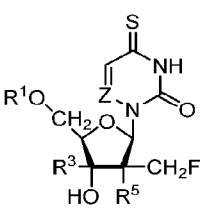
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



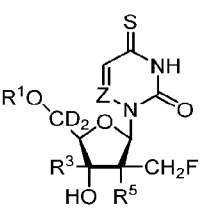
Formula Icx



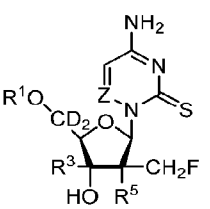
Formula Icy



Formula Icz



Formula Ida

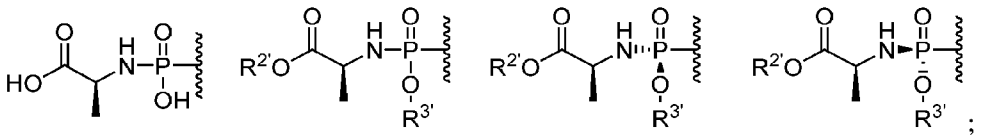


Formula Idb

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:

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$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

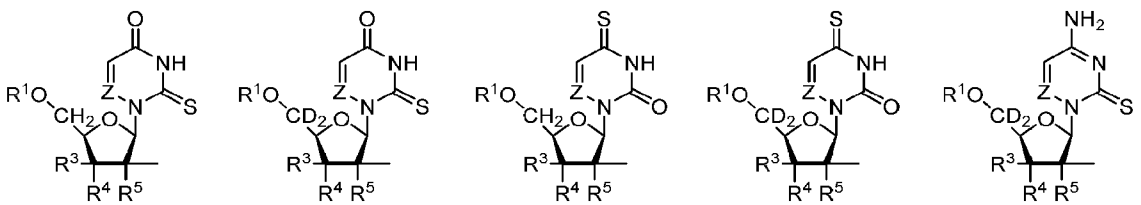
Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

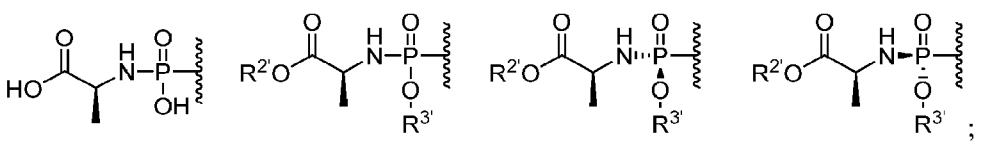
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



Formula Idc **Formula Idd** **Formula Ide** **Formula Idf** **Formula Idg**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

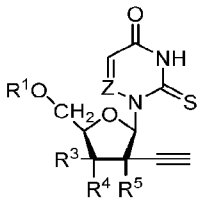
R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

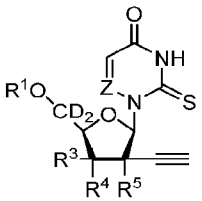
In certain embodiments, Z is CH.

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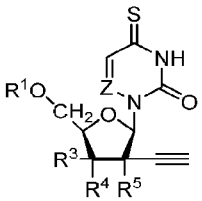
In one embodiment, the nucleoside conjugated to a phosphorus moiety is of the following formulae:



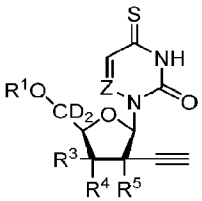
Formula Idh



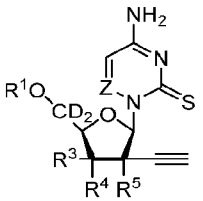
Formula Idi



Formula Idj



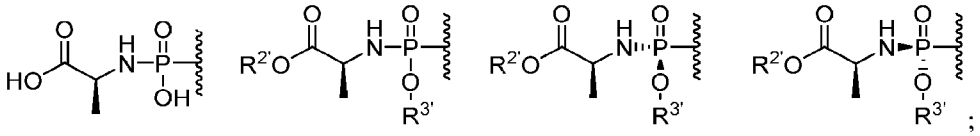
Formula Idk



Formula Idl

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

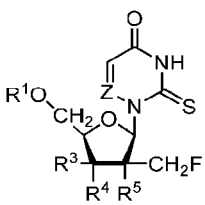
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

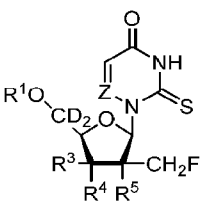
R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

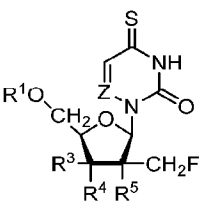
In one embodiment, the nucleoside conjugated to a phosphorus moiety is a compound of the following formulae:



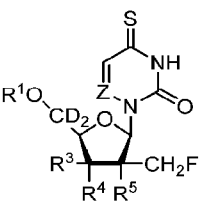
Formula Idm



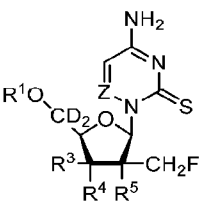
Formula Idn



Formula Ido



Formula Idp

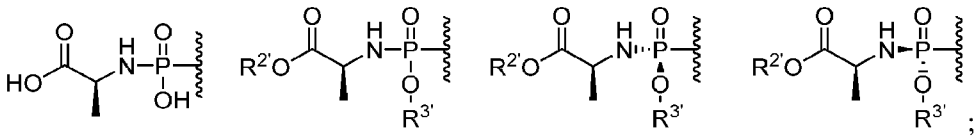


Formula Idq

or a pharmaceutically acceptable salt thereof, wherein

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R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:



;

$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl;

$R^{3'}$ is aryl, biaryl, or substituted aryl;

Z is CH, CD, or N;

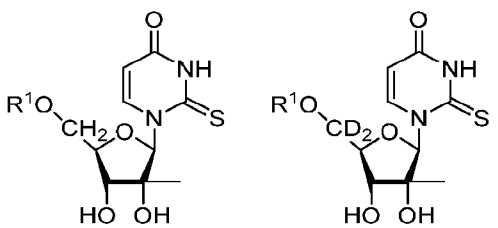
R^3 is H, D, methyl, CD_3, ethynyl, cyano, fluoro, chloro, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, vinyl or allyl;

R^4 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH;

R^5 is H, D, hydroxyl, methoxy, azido, amino, fluoro, chloro or SH.

In certain embodiments, Z is CH.

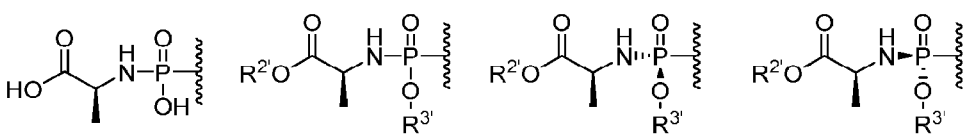
In one embodiment, the nucleoside conjugated to a phosphorus moiety is a compound of the following formulae:



Formula Idr **Formula Ids**

or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:

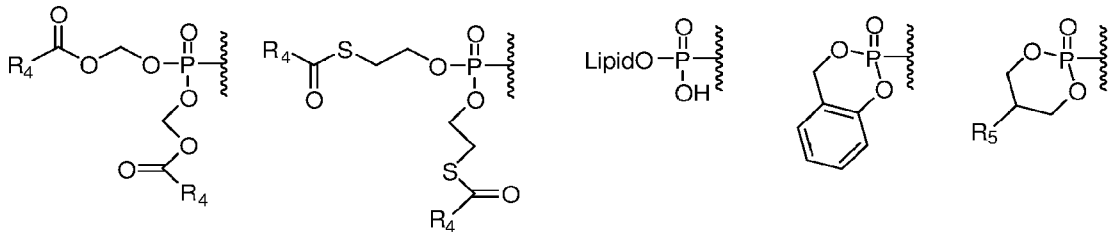


$R^{2'}$ is alkyl, branched alkyl, or cycloalkyl and

$R^{3'}$ is aryl, biaryl, or substituted aryl.

In another embodiment, R^1 is selected from one of the following:

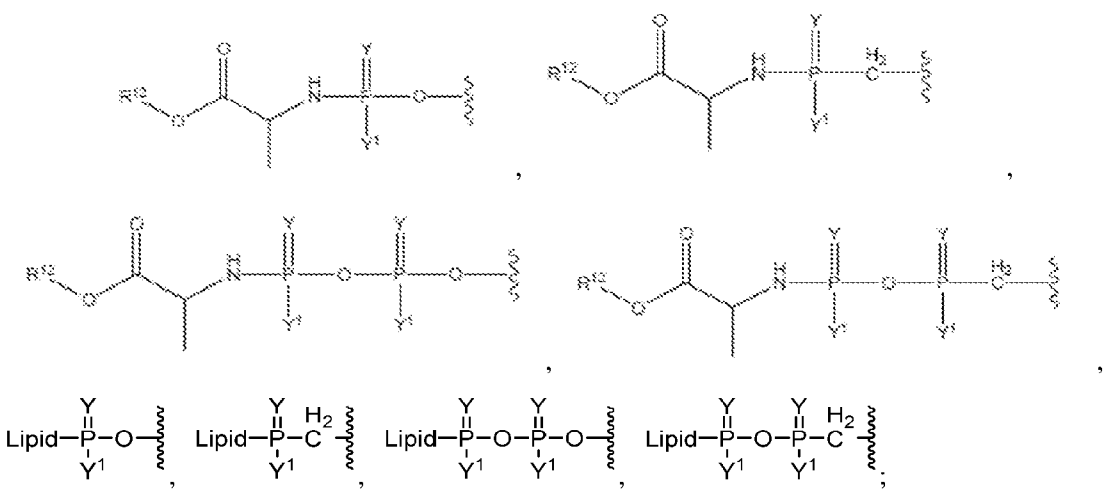
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R_4 is alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_5 is aryl, heteroaryl, substituted aryl, or substituted heteroaryl.

In certain embodiments of Formula I, X is methylene (CH_2) and R^1 is one of the following:



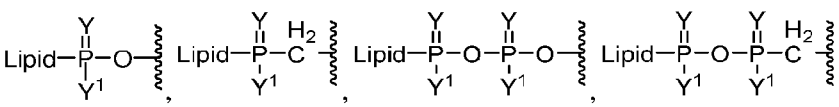
wherein R^{12} $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, branched alkyl, or cycloalkyl;Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl; and

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl.

In certain embodiments, X is methylene (CH_2) and R^1 is one of the following:



wherein

Y is O or S;

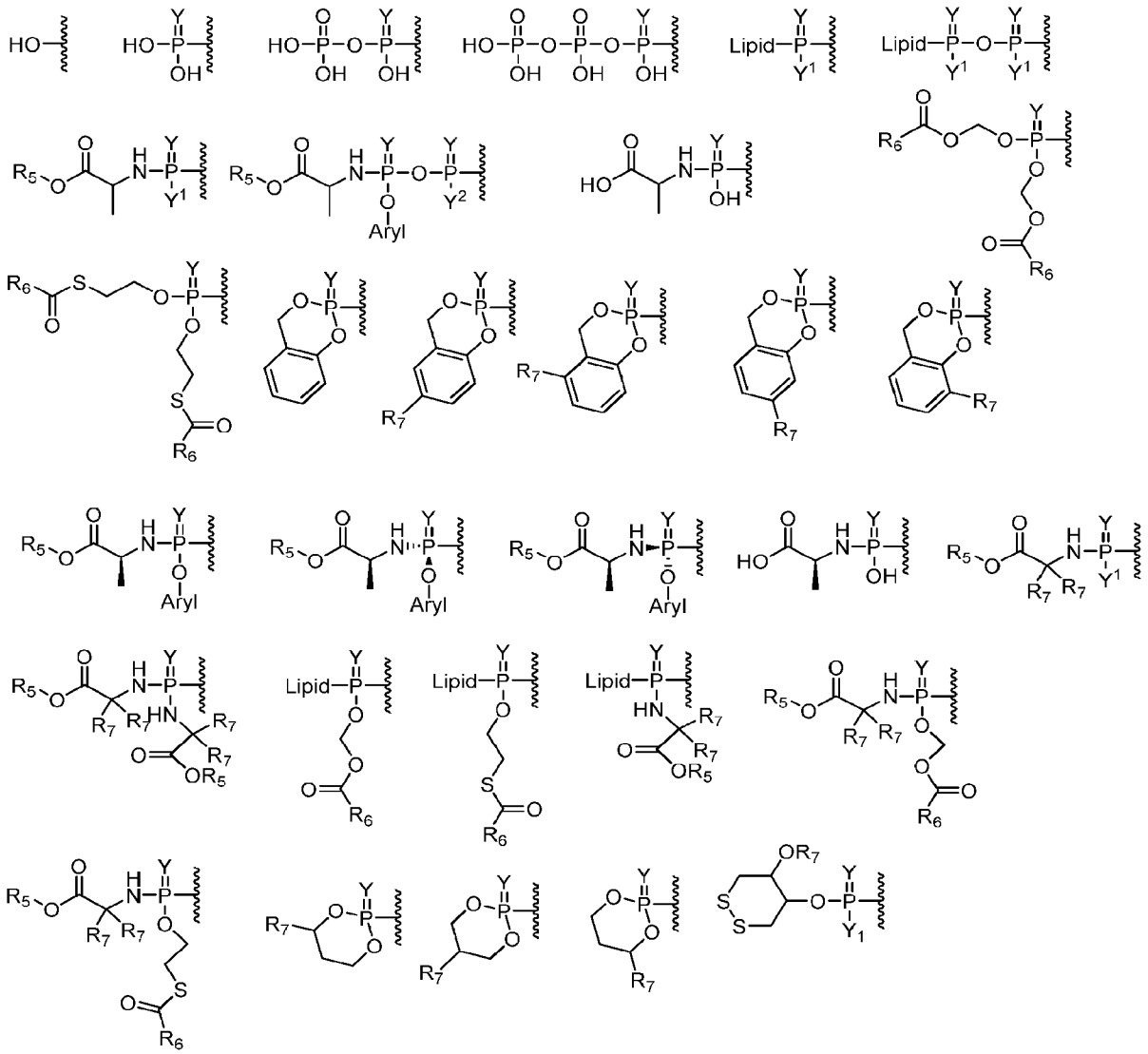
Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

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R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl; and

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl.

In another embodiment, R^1 is selected from one of the following:



Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

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Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

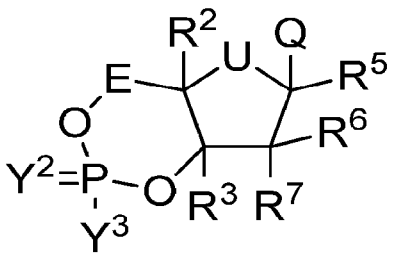
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In certain embodiments, the present disclosure relates to a compound of the following formula:

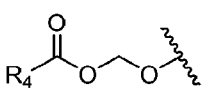


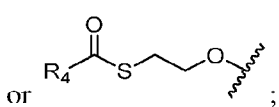
Formula II

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

Y^2 is O or S;

Y^3 is OH, OR^{10},SR^{10}, NHR^{10}, NR^{10}_2, lipid, BH_3-M^+ or selected from 

or ;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

R^2, R^3, R^6 and R^7 are independently selected from are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{11};

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R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{11};

R^{10} is aryl, heteroaryl, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl;

R^4 is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl; and

each R^{11} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain exemplary embodiments, Y^3 is selected from the group consisting of OH, SR^{10}, NHR^{10}, and $NR^{10}{}_2$.

In certain exemplary embodiments, E is selected from the group consisting of CHMe, CMe_2, CHF, and CF_2

In certain embodiments, the Q heterocyclyl is selected from pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

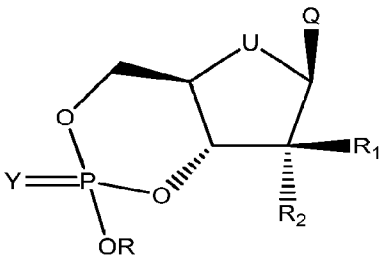
In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In other certain embodiments, R^2, R^3, R^6 and R^7 are independently selected from the group consisting of H, D, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

In still other certain embodiments, R^{10} is alkyl, methyl, ethyl, propyl, n-butyl, branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl,cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or 2-butyl.

In certain embodiments, the disclosure relates to compounds of the following formula:

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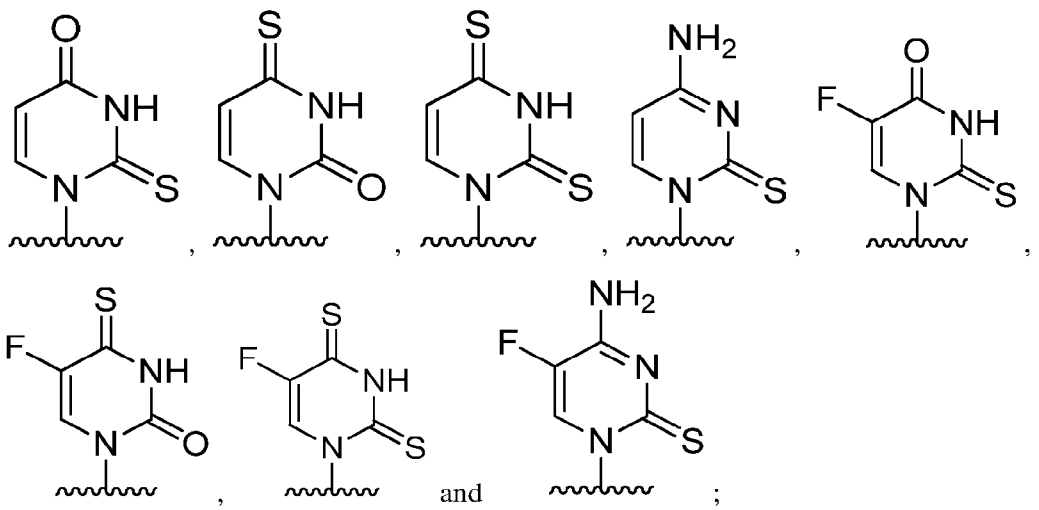
Formula IIa

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

wherein R_1 and R_2 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^8;

each R^8 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Q is selected from



and

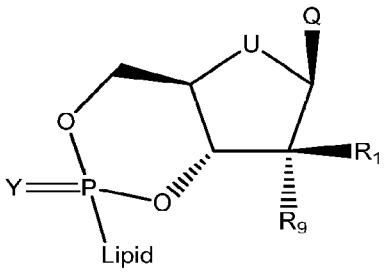
;

Y is O or S; and

R is straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; benzyl, aryl, or heteroaryl.

In certain embodiments, the disclosure relates to compounds of the formula:

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Formula IIb

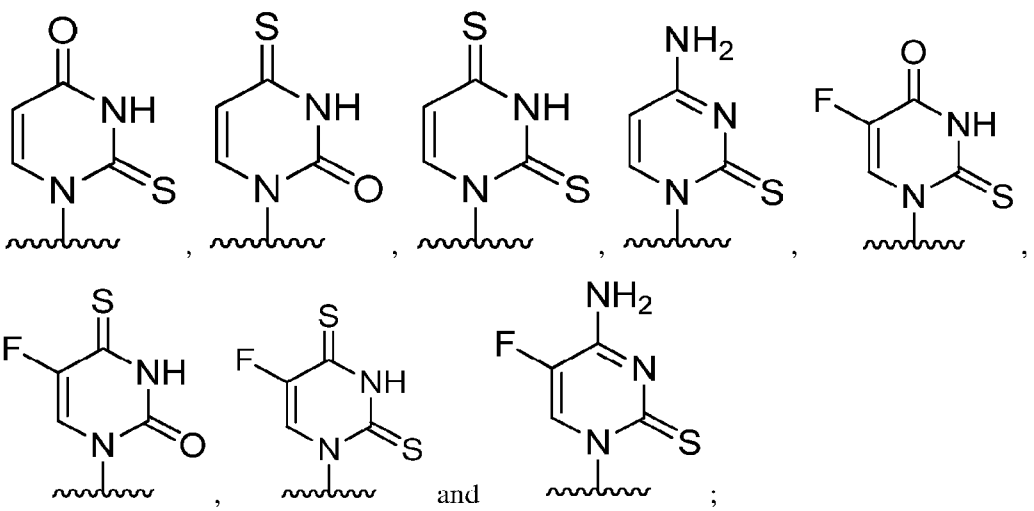
or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

wherein R_1 and R_9 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

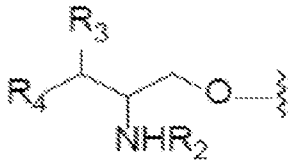
Q is selected from



, , , , , , and ;

Y is O or S;

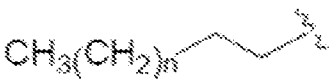
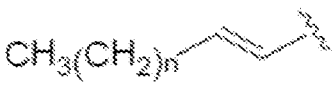
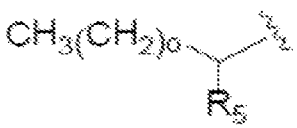
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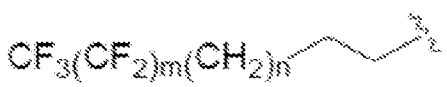
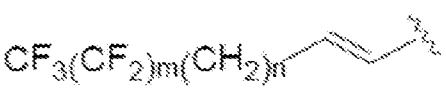
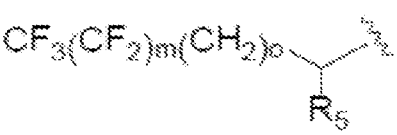
Lipid is  ;

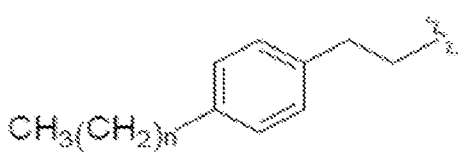
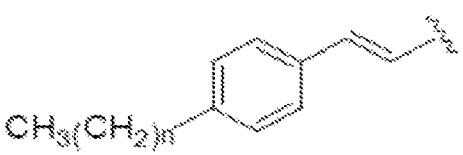
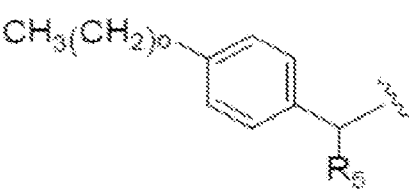
wherein R_2 is H; alkyl, e.g. methyl; C(O)R'; C(O)OR'; or C(O)NHR';

R_3 is H; hydroxyl; fluoro; OR'; OC(O)R'; OC(O)OR'; OC(O)NHR';

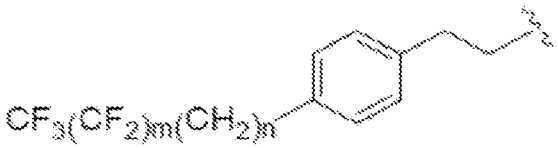
R' is H; straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; benzyl; phenyl; monosubstituted phenyl; disubstituted phenyl or trisubstituted phenyl;

R^4 is a C_{11-17} long alkyl chain, e.g. , , , or , wherein n is 8-14 and o is 9-15; or

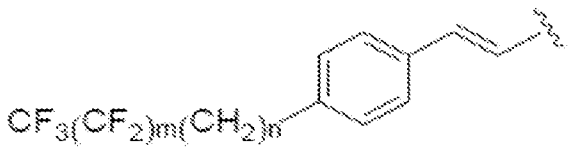
, , or , wherein "m+n" is 8-14 and "m+o" is 9-15; or

, , or , wherein n is 4-10 and o is 5-11; or

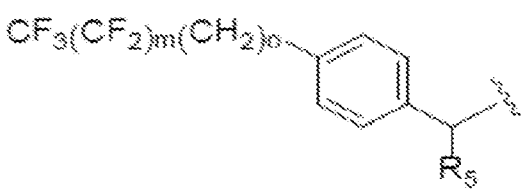
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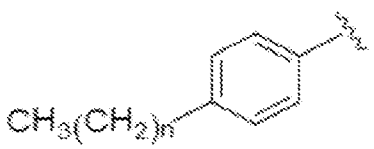
,



, or



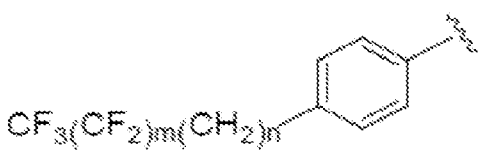
, wherein "m+n" is 4-10 and "m+o" is 5-11; or



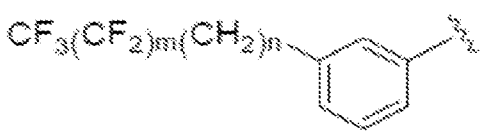
, or



, wherein n is 6-12; or



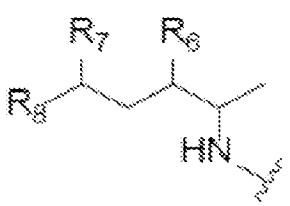
, or



,

wherein "m+n" is 6-12; and

R_5 is H, hydroxyl, fluoro, OR', OC(O)R', OC(O)OR', or OC(O)NHR'.



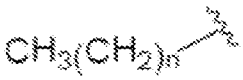
In an alternative embodiment, Lipid is ;

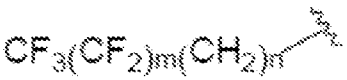
wherein R_6 is H; hydroxyl; fluoro; OR'; OC(O)R'; OC(O)OR'; or OC(O)NHR';

R_7 is H; hydroxyl; fluoro; OR'; OC(O)R'; OC(O)OR'; or OC(O)NHR';

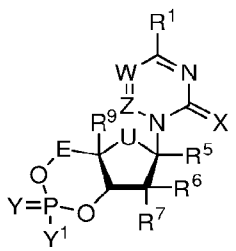
R' is H; straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; benzyl; phenyl; monosubstituted phenyl; disubstituted phenyl; trisubstituted phenyl;

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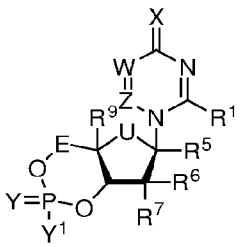
R_8 is a C_{9-15} alkyl chain, e.g.  wherein n is 8-14 or

 wherein "m+n" is 8-14.

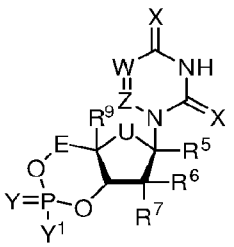
In certain embodiments, the disclosure relates to compounds of the formulae:



Formula IIc



Formula IId



Formula IIe

or a pharmaceutically salt thereof, wherein

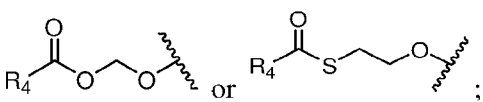
R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y is O or S;

Y^1 is OH, OR^{40}, SR^{40}, NHR^{40}, $NR^{40}{}_2$, lipid, $BH_3{}^-M^+$ or selected from

;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula IIc and IId, one of X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula IIe at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^6, R^7, and R^9 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different R^8;

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R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^8; and

each R^8 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

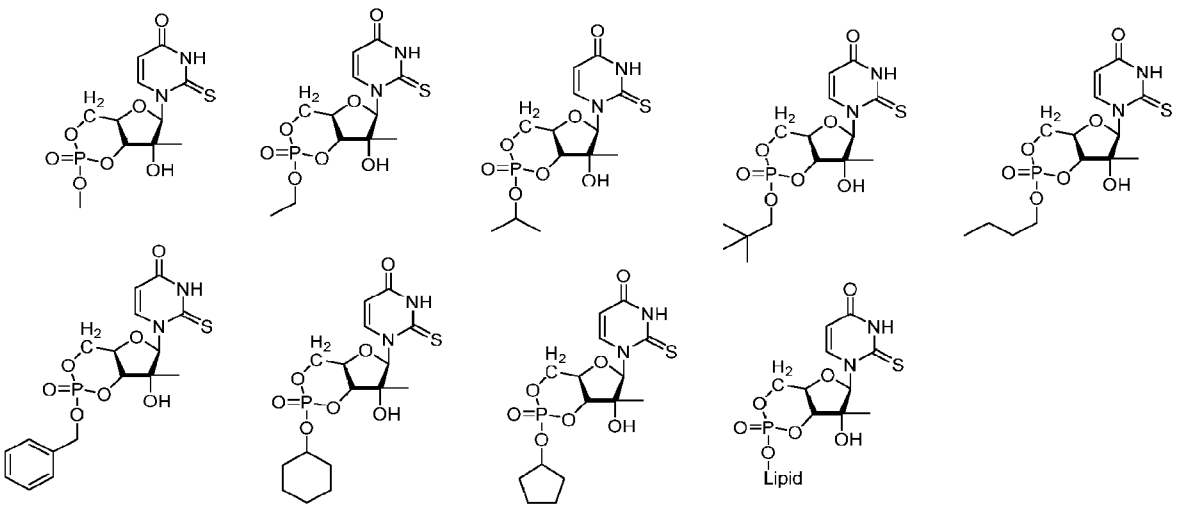
R^{40} is aryl, heteroaryl, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl;

R^4 is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl.

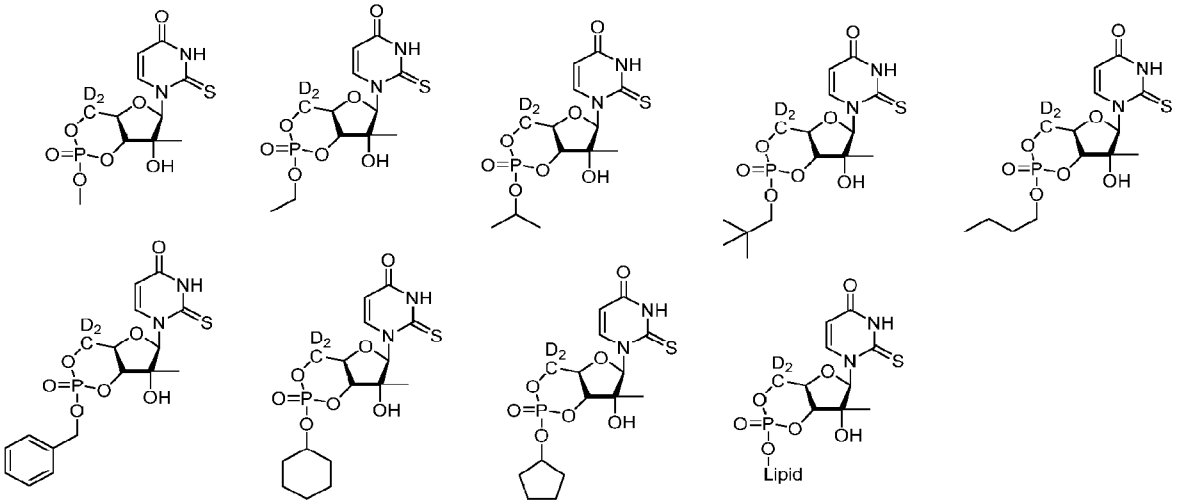
In certain embodiments, U is S and Y and Z are CH.

In other embodiments, U is O and Y and Z are CH.

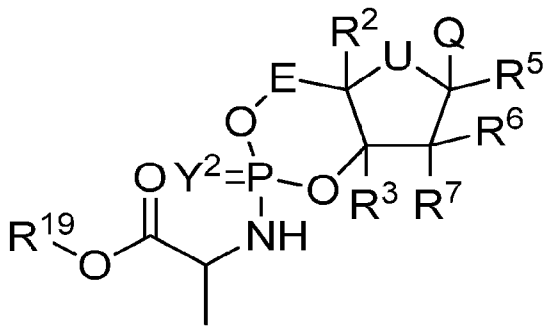
In exemplary embodiments, the compound is selected from:



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In certain embodiments, the present disclosure relates to a compound of the following formula:



Formula III

or pharmaceutically acceptable salts thereof wherein,

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

Y^2 is O or S;

R^2, R^3, R^6 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^8;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^8; and

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Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

each R^8 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

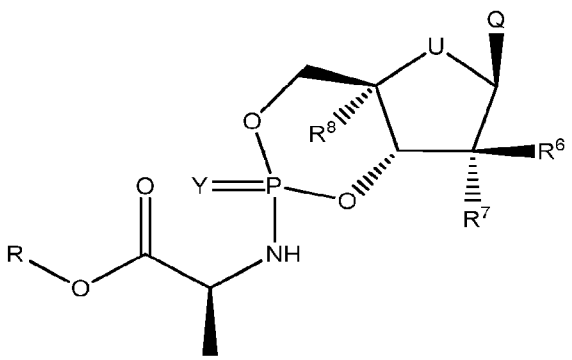
R^{19} is $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, branched alkyl, or cycloalkyl.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In certain embodiments, R^6 is selected from hydrogen, methyl, fluoromethyl, hydroxymethyl, difluoromethyl, trifluoromethyl, acetylenyl, ethyl, vinyl, or cyano.

In certain embodiments, R^{19} is selected from is alkyl, methyl, ethyl, propyl, n-butyl , branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or 2-butyl.

In certain embodiments, the disclosure relates to compounds of formula:



Formula IIIa

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

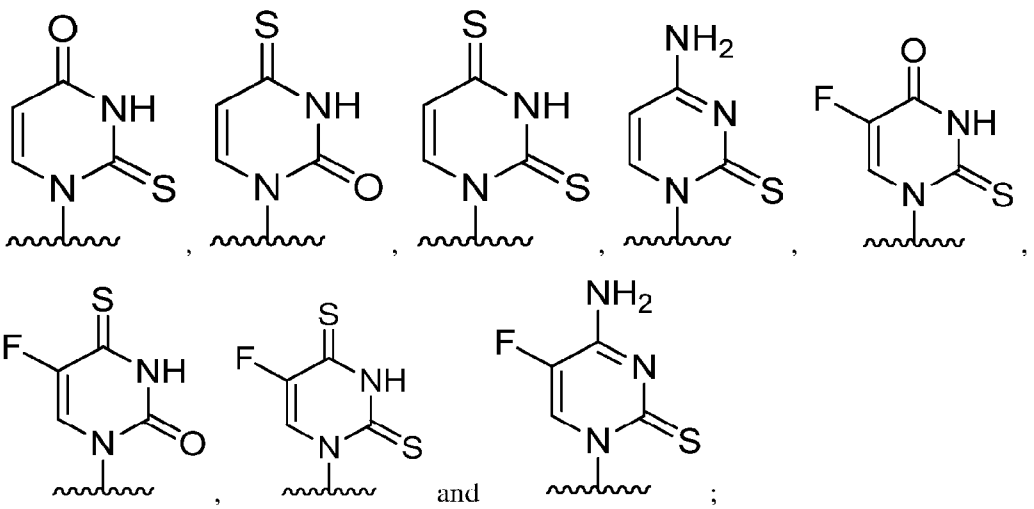
R^6 and R^7 are each independently selected from are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

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R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

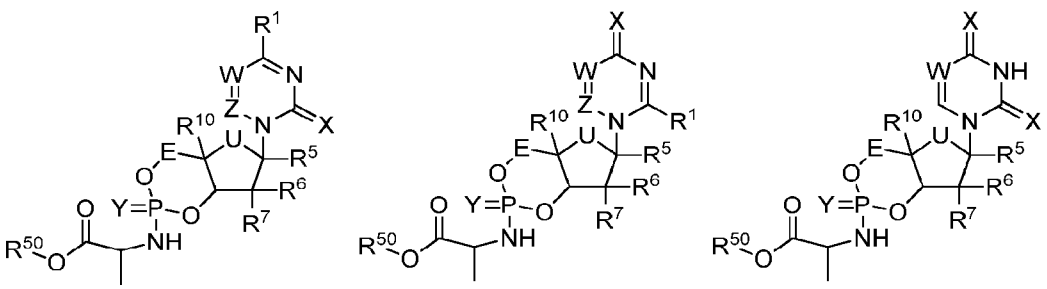
Q is selected from



; Y is O or S;

R is straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or benzyl.

In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula IIIb **Formula IIIc** **Formula IIId**

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or a pharmaceutically acceptable salt thereof, wherein

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y is O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula IIIb and IIIc, one of X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula IIId at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

wherein R^6, R^7 and R^{10} are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{50} is $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, branched alkyl, or cycloalkyl.

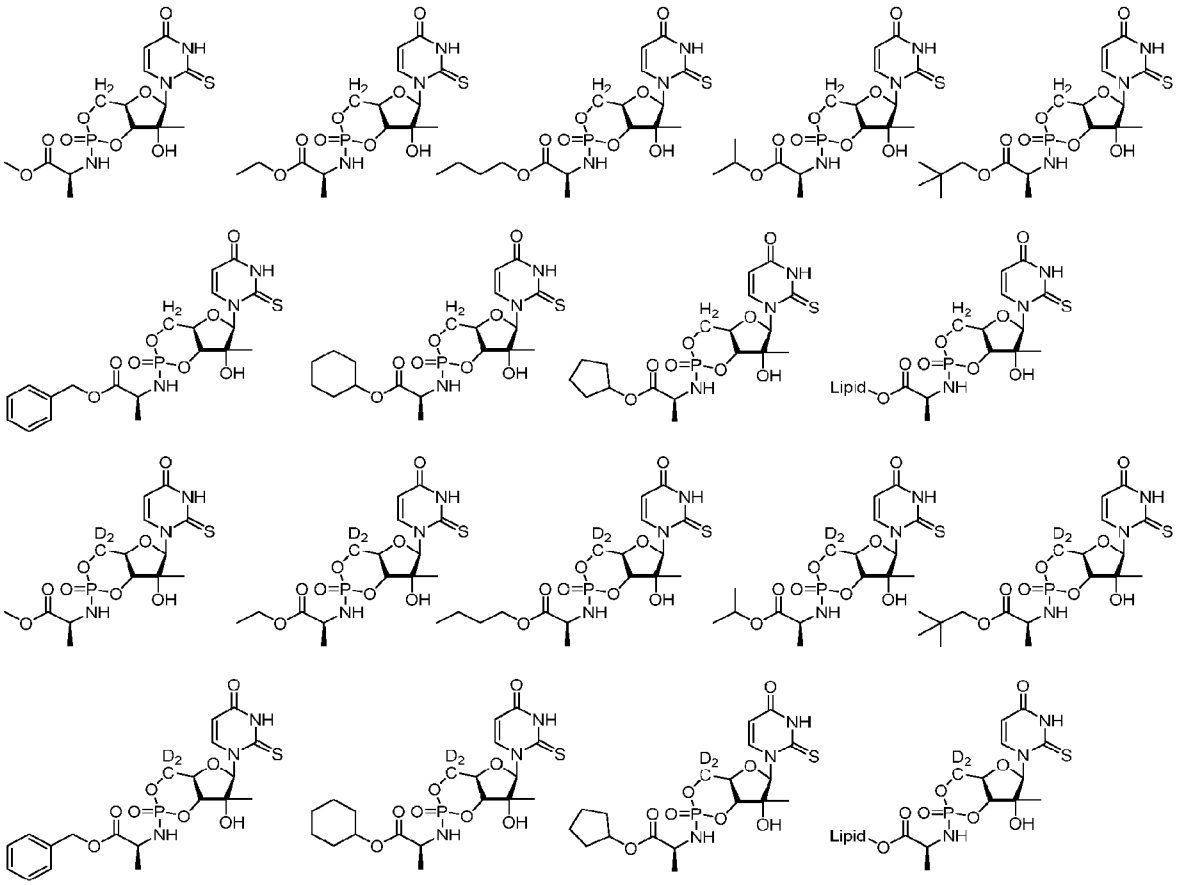
In certain embodiments U is S and W and Z are CH. In other embodiments, U is O and W and Z are CH.

In certain embodiments, R^5 is H. In other embodiments, R^6 is methyl. In still other embodiments, R^7 is hydroxyl. In a preferred embodiment, R^5 is H, R^6 is methyl and R^7 is hydroxyl.

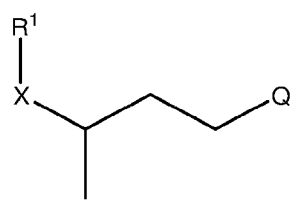
In certain embodiments, R^{50} is alkyl, methyl, ethyl, propyl, n-butyl , branched alkyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or 2-butyl.

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In exemplary embodiments, the compound is selected from:



In certain embodiments, the present disclosure relates to compounds of the following formula:



Formula IV

or a pharmaceutically acceptable salt thereof, wherein

X is O, CH_2 or CD_2;

R^1 is a phosphate, phosphonate, polyphosphate, polyphosphonate substituent wherein the phosphate or a phosphate in the polyphosphate or polyphosphonate is optionally a phosphoroborate, phosphorothioate, or phosphoroamidate, and the substituent is further substituted with an amino acid ester or lipid or derivative optionally substituted with one or more, the same or different, R^6;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

R^6 is the same or different alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^7; and

R^7 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

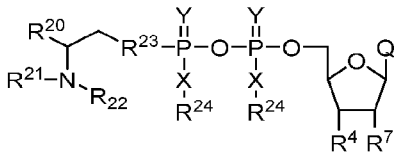
In certain embodiments, the Q heterocyclyl is pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

In certain embodiments, the lipid is a sphingolipid of any of the formula described above or herein.

In certain embodiments, the present disclosure relates to a compound of the following formula

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Formula V

or a pharmaceutically acceptable salt thereof wherein,

each Y is independently O or S;

X is O, S, NH, NR^{24};

R^{23} is O or NH;

R^4 and R^7 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9.

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is an alkyl of 6 to 22 carbons optionally substituted with one or more, the same or different R^{26};

R^{21} and R^{22} are each independently selected from hydrogen, alkyl, or alkanoyl, wherein R^{21} and R^{22} are each optionally substituted with one or more, the same or different R^{26};

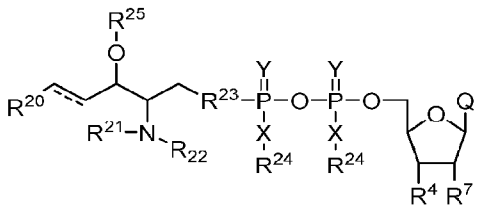
R^{24} and $R^{25}$are each independently selected from hydrogen, alkyl, or aryl, wherein R^{24} and R^{25} are each optionally substituted with one or more, the same or different R^{26};

each R^{26} is independently selected from alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R^4 and R^7 are independently hydrogen, hydroxy, alkoxy, azide, or halogen.

In certain embodiments, the present disclosure relates to compounds of the following formula

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Formula VI

or a pharmaceutically acceptable salt thereof wherein,

the dotted line represents the presence of a single or double bond;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

X is O, S, NH, NR^{24};

R^{23} is O or NH;

R^4 and R^7 are each independently selected from are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{26};

R^{20} is an alkyl of 6 to 22 carbons optionally substituted with one or more, the same or different R^{26};

R^{21}, R^{22}, and R^{25} are independently selected from hydrogen, alkyl, or alkanoyl, wherein R^{21}, R^{22}, and R^{25} are each optionally substituted with one or more, the same or different R^{26};

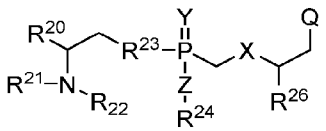
each R^{24} is independently selected from hydrogen, alkyl, or aryl, wherein each R^{24} is optionally substituted with one or more, the same or different R^{26};

each R^{26} is independently selected from alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl

In certain embodiments, the Q heterocyclyl is pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In certain embodiments, the present disclosure relates to a compound having the following formula:

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Formula VII

or a pharmaceutically acceptable salt thereof wherein,

X is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y is O or S;

Z is O, S, NH, NR^{24};

R^{23} is O or NH;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

R^{20} is an alkyl of 6 to 22 carbons optionally substituted with one or more, the same or different R^{37};

R^{21} and R^{22} are each independently selected from hydrogen, alkyl, or alkanoyl, wherein R^{21} and R^{22} are each optionally substituted with one or more, the same or different R^{37};

R^{24} is hydrogen, alkyl, or aryl wherein R^{24} is optionally substituted with one or more, the same or different R^{37};

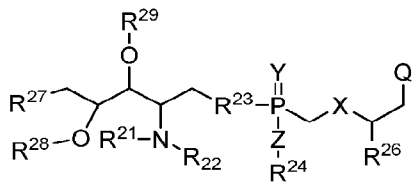
R^{26} is alkyl;

each R^{37} is independently selected from alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the Q heterocyclyl is pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In certain embodiment, the present disclosure relates to compounds having the following formula:

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Formula VIII

or a pharmaceutically acceptable salt thereof wherein,

X is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y is O or S;

Z is O, S, NH, NR^{24};

R^{23} is O or NH;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

R^{27} is an alkyl of 6 to 22 carbons optionally substituted with one or more, the same or different R^{37};

R^{21}, R^{22}, R^{28}, and R^{29} are each independently selected from hydrogen, alkyl, or alkanoyl, wherein R^{21}, R^{22}, R^{28}, and R^{29} are each optionally substituted with one or more, the same or different R^{37};

R^{24} is hydrogen, alkyl, or aryl wherein R^{24} is optionally substituted with one or more, the same or different R^{37};

R^{26} is alkyl;

each R^{37} is independently selected from alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

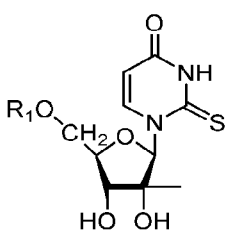
In certain embodiments, the Q heterocyclyl is pyrimidin-2-one-4-thione, pyrimidine-2-thione-4-one, pyrimidine-2,4-dithione, 4-aminopyrimidine-2-thione, 5-fluoropyrimidin-2-one-4-thione, 5-fluoropyrimidine-2-thione-4-one, 5-fluoropyrimidine-2,4-dithione, 4-amino-5-fluoropyrimidine-2-thione, 2-amino-purin-6-thione, 2-amino-7-deaza-purin-6-thione or 2-amino-7-deaza-7-substituted-purin-6-thione.

In preferred embodiments, U is O and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine. In other preferred embodiments, U is S and Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4 position of said pyrimidine.

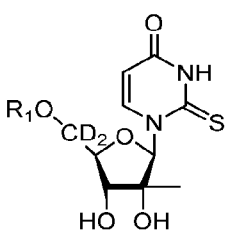
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In certain embodiments, the fragment defined by R^{23}-R^{27} is a sphingolipid. Suitable sphingolipids include, but are not limited to, 2-aminooctadecane-3,5-diol; (2S,3S,5S)-2-aminooctadecane-3,5-diol; (2S,3R,5S)-2-aminooctadecane-3,5-diol; 2-(methylamino)octadecane-3,5-diol; (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 may be optionally substituted with one or more substituents.

In preferred embodiments, the nucleoside conjugate has the following structure:



Formula IXa

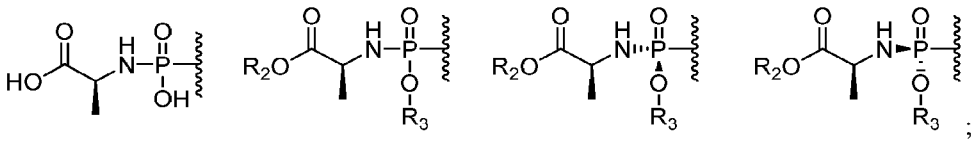


Formula IXb

or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, monophosphate, diphosphate, triphosphate, or selected from one of the following:

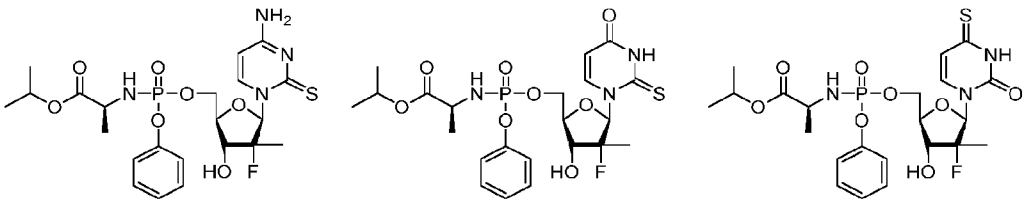
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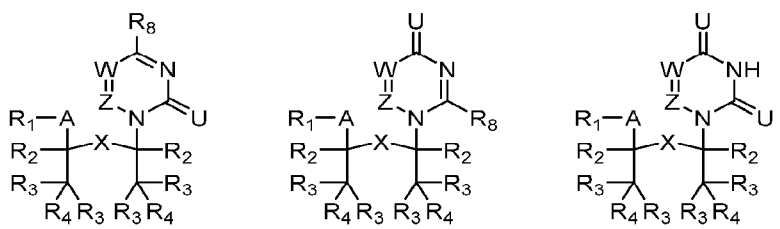
R_2 is alkyl, branched alkyl, or cycloalkyl;

R_3 is aryl, biaryl, or substituted aryl;

In exemplified embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



In certain embodiments, the disclosure relates to a compound of the following formulae:



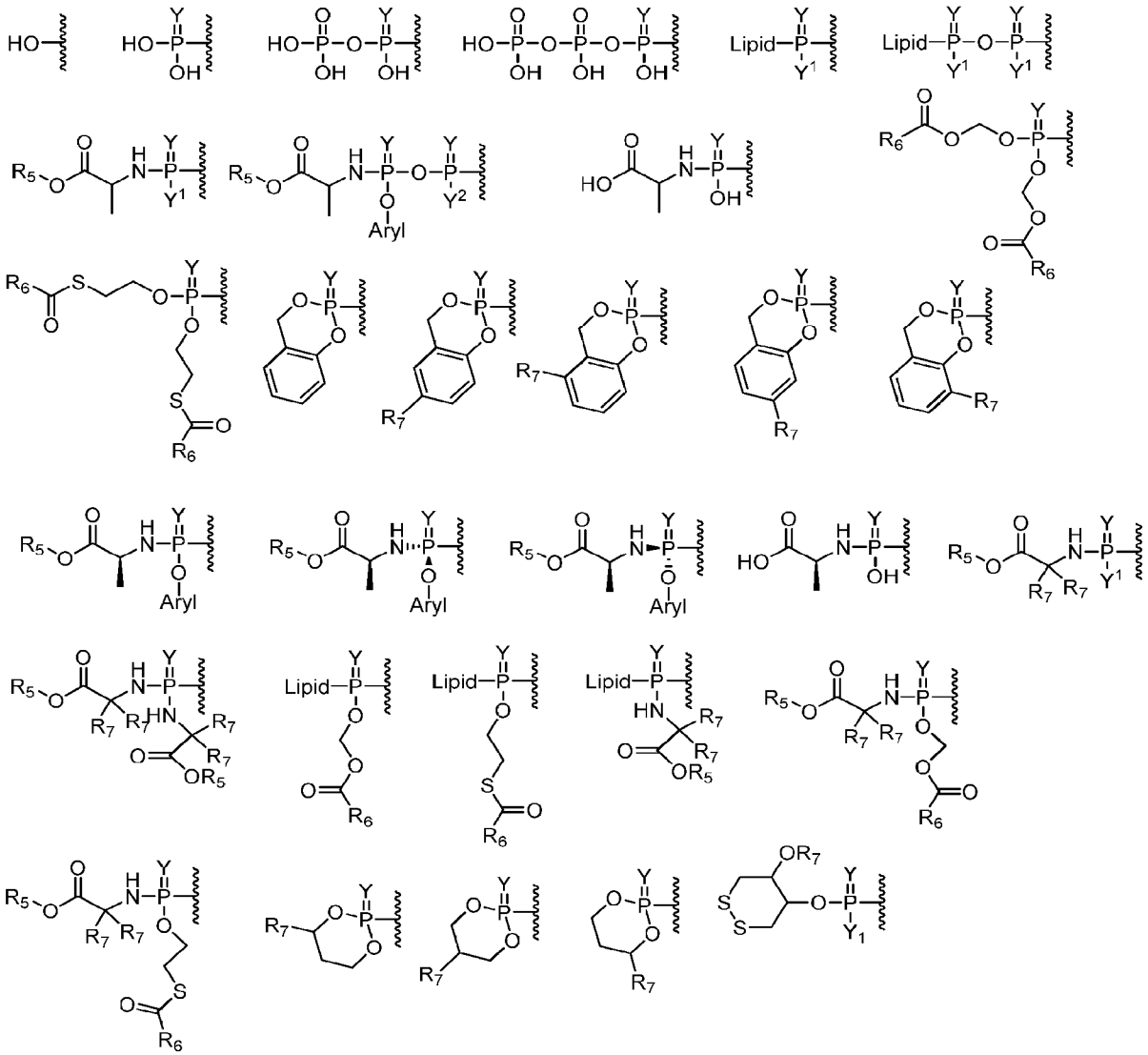
Formula Xa **Formula Xb** **Formula Xc**

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, $C{=}CH_2$, C=CHF, or $C{=}CF_2$;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

each R^8 is independently OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula Xa and Xb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula Xc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R_2 is independently selected from hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, azido, methoxy, or amino;

each R_3 is independently selected from hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, or azido;

each R_4 is independently selected from hydrogen, deuterium, hydroxyl, halogen, fluoro, azido, methoxy, or amino;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_5 is alkyl, branched alkyl, or cycloalkyl;

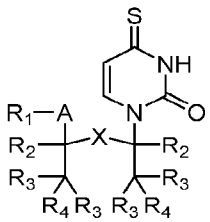
Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

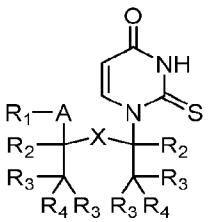
R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In certain embodiments, the disclosure relates to a compound of the following formulae:

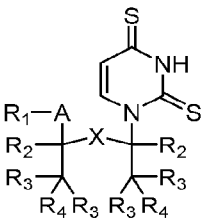
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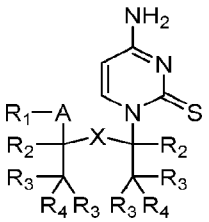
Formula Xd



Formula Xe



Formula Xf

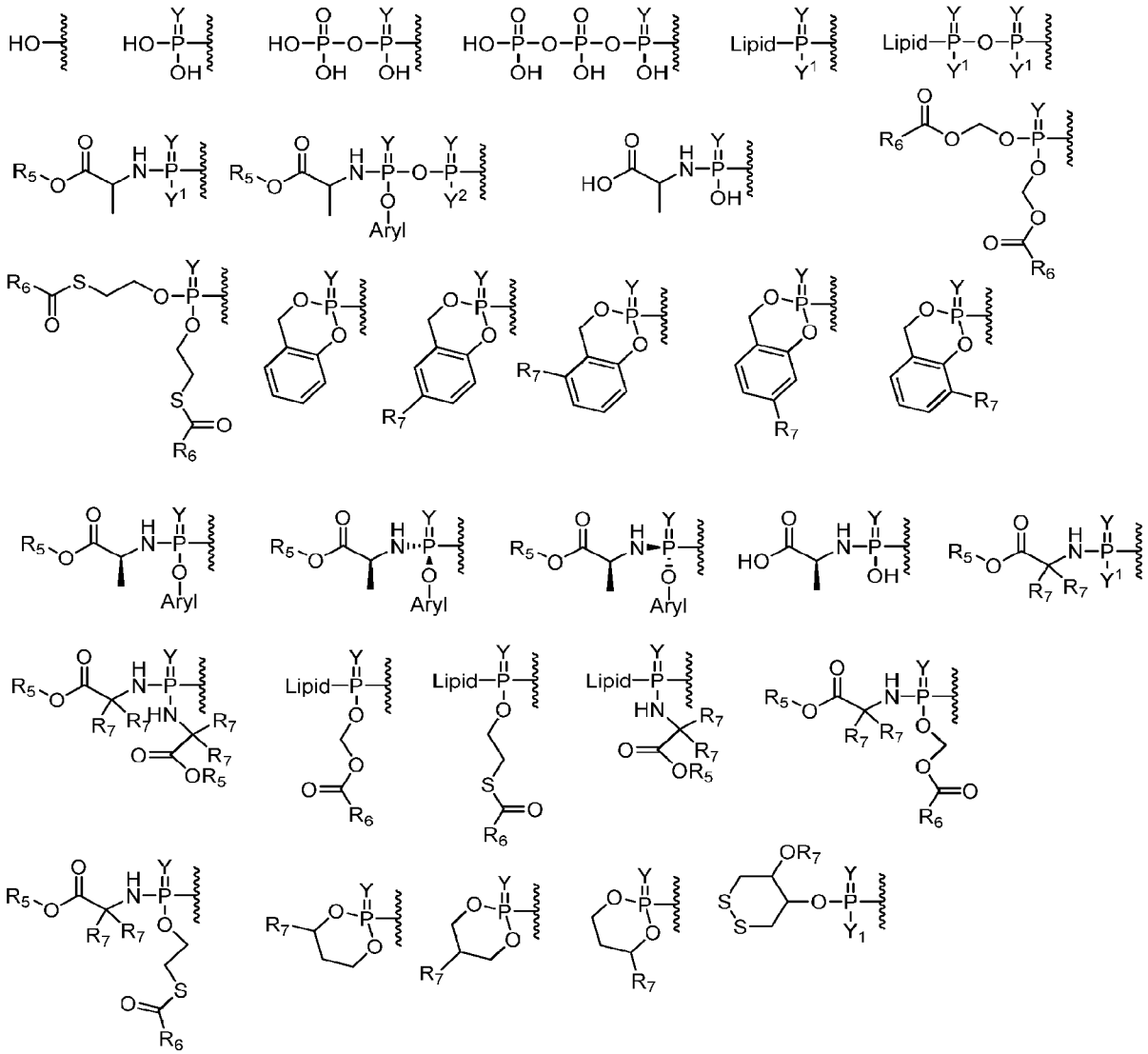


Formula Xg

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:



X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each R_2 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, azido, methoxy, or amino;

each R_3 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, or azido;

each R_4 is independently hydrogen, deuterium, hydroxyl, halogen, fluoro, azido, methoxy, or amino;

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Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

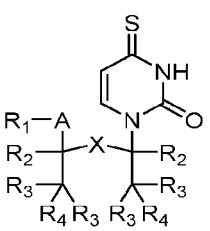
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

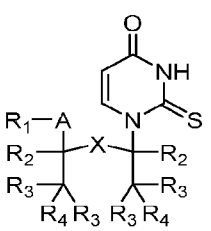
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

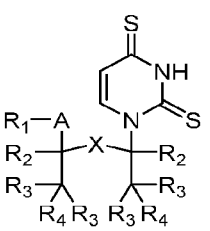
In certain embodiments, the disclosure relates to a compound of the following formulae:



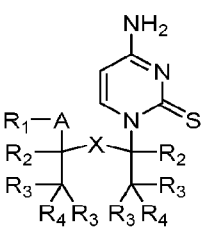
Formula XIa



Formula XIb



Formula XIc



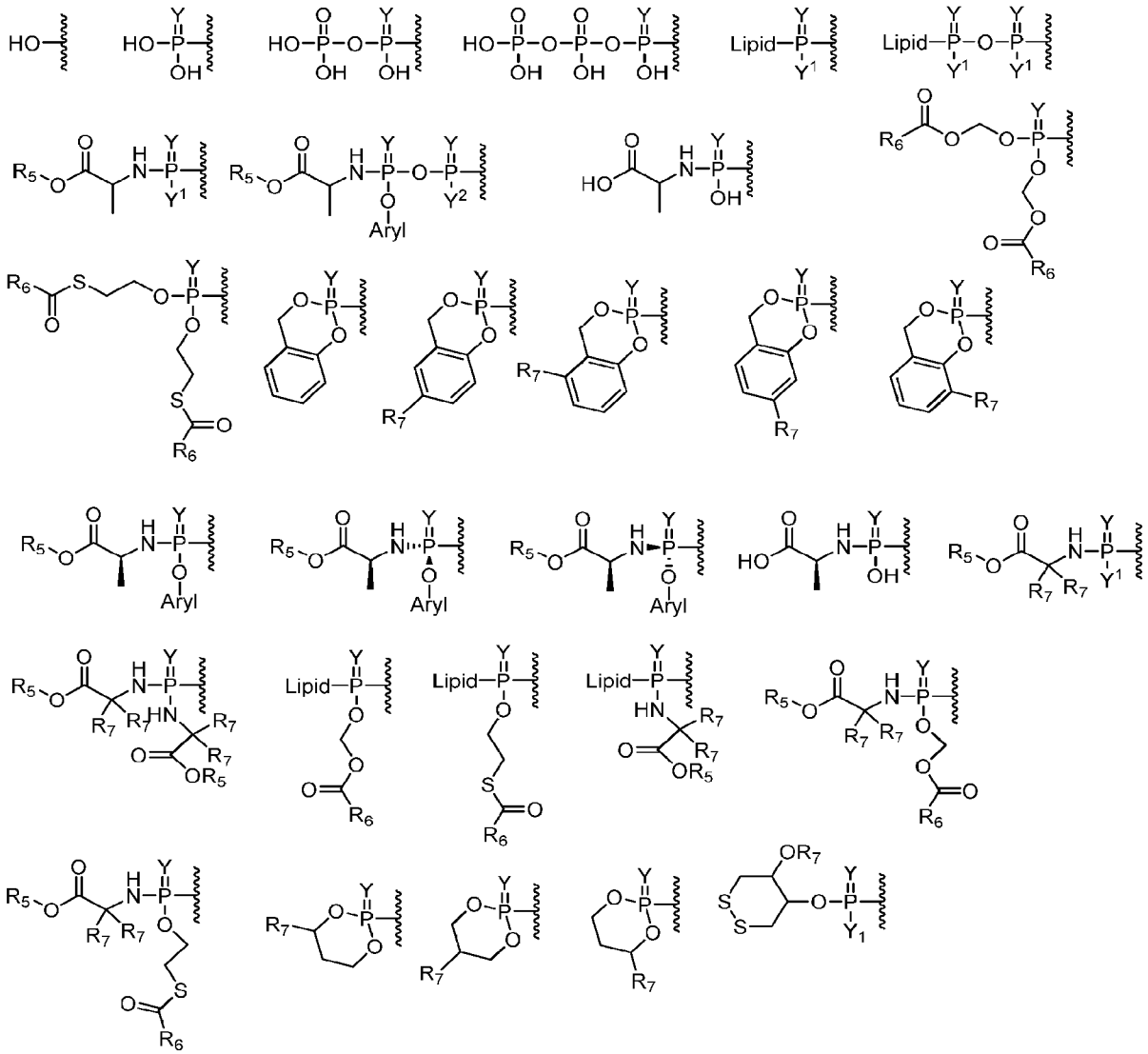
Formula XId

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each R_2 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, azido, methoxy, or amino;

each R_3 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, or azido;

each R_4 is independently hydrogen, deuterium, hydroxyl, halogen, fluoro, azido, methoxy, or amino;

Lipid is as described herein;

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Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

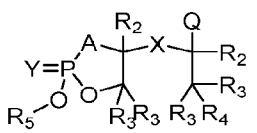
R_5 is alkyl, branched alkyl, or cycloalkyl;

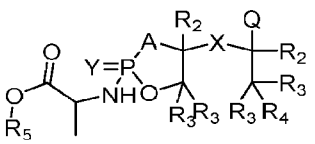
Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In certain embodiments, the disclosure relates to a compound of the following formulae:





Formula XIIa **Formula XIIb**

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

each R_2 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, azido, methoxy, or amino;

each R_3 is independently hydrogen, deuterium, hydroxyl, cyano, halogen, fluoro, methyl, ethynyl, vinyl, allyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trideuteromethyl, or azido;

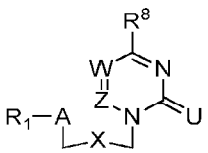
each R_4 is independently hydrogen, deuterium, hydroxyl, halogen, fluoro, azido, methoxy, or amino;

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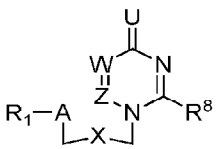
Y is O or S;

R_5 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

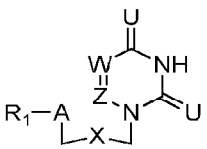
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XIIIa



Formula XIIIb



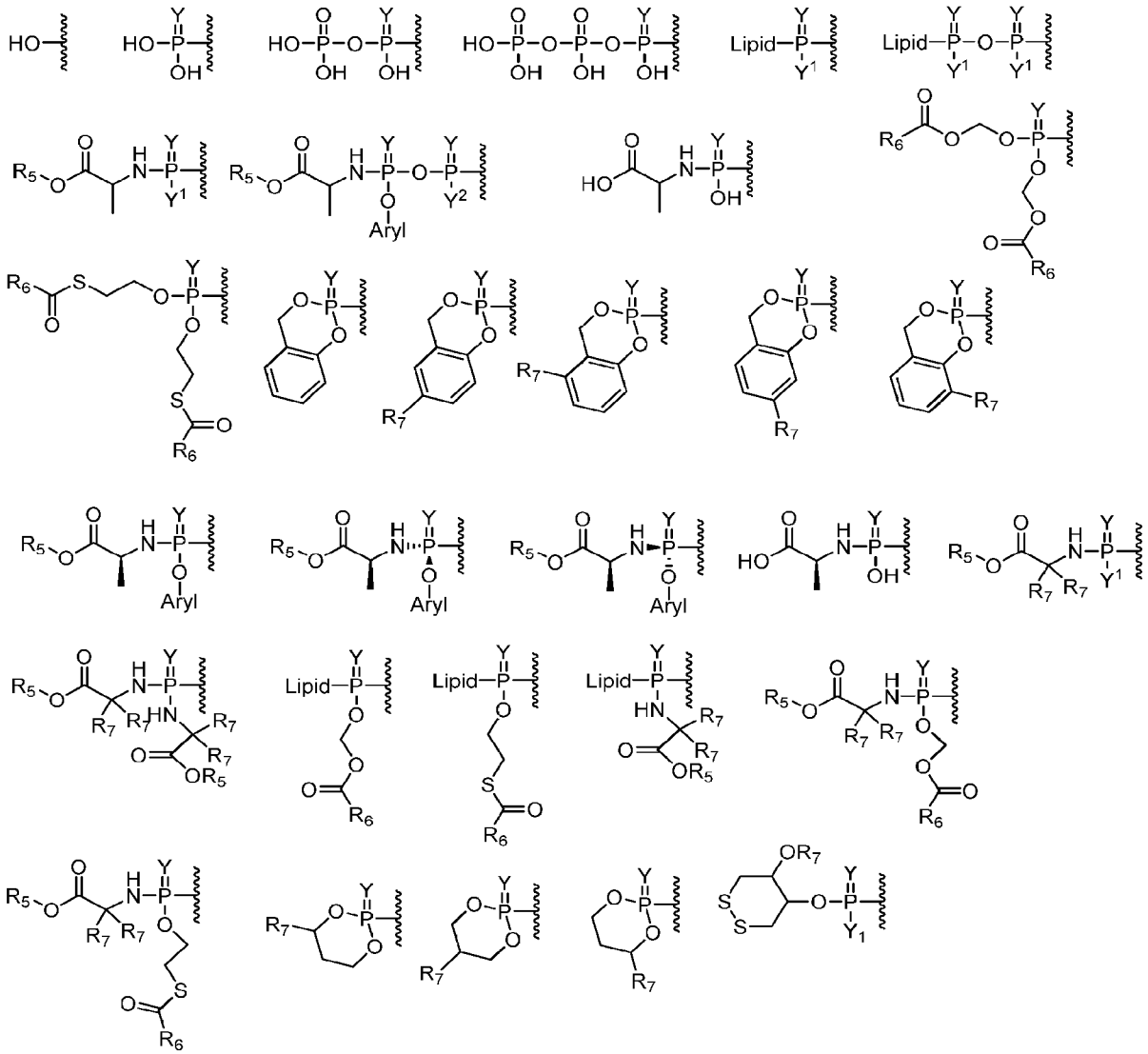
Formula XIIIc

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XIIIa and XIIIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XIIIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

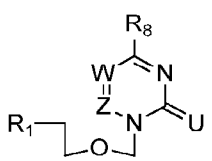
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

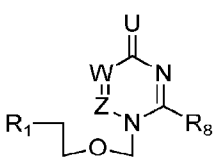
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

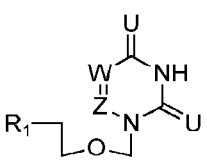
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XIVa



Formula XIVb

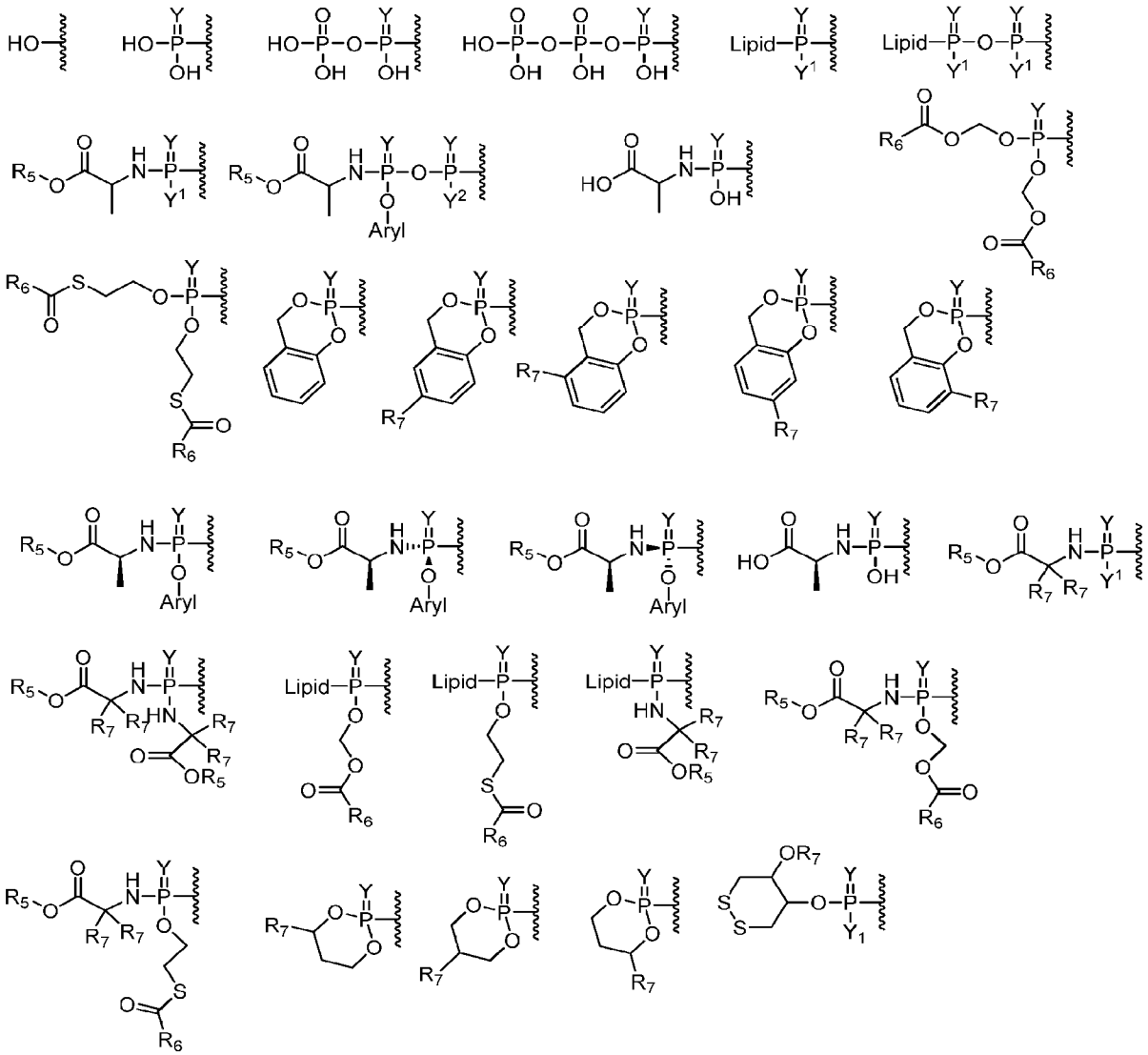


Formula XIVc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XIVa and XIVb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XIVc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

each R^9 is independently methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

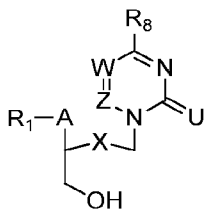
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

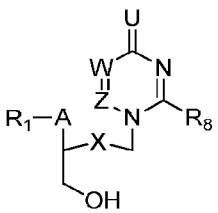
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

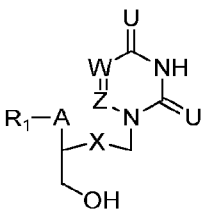
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XVa



Formula XVb



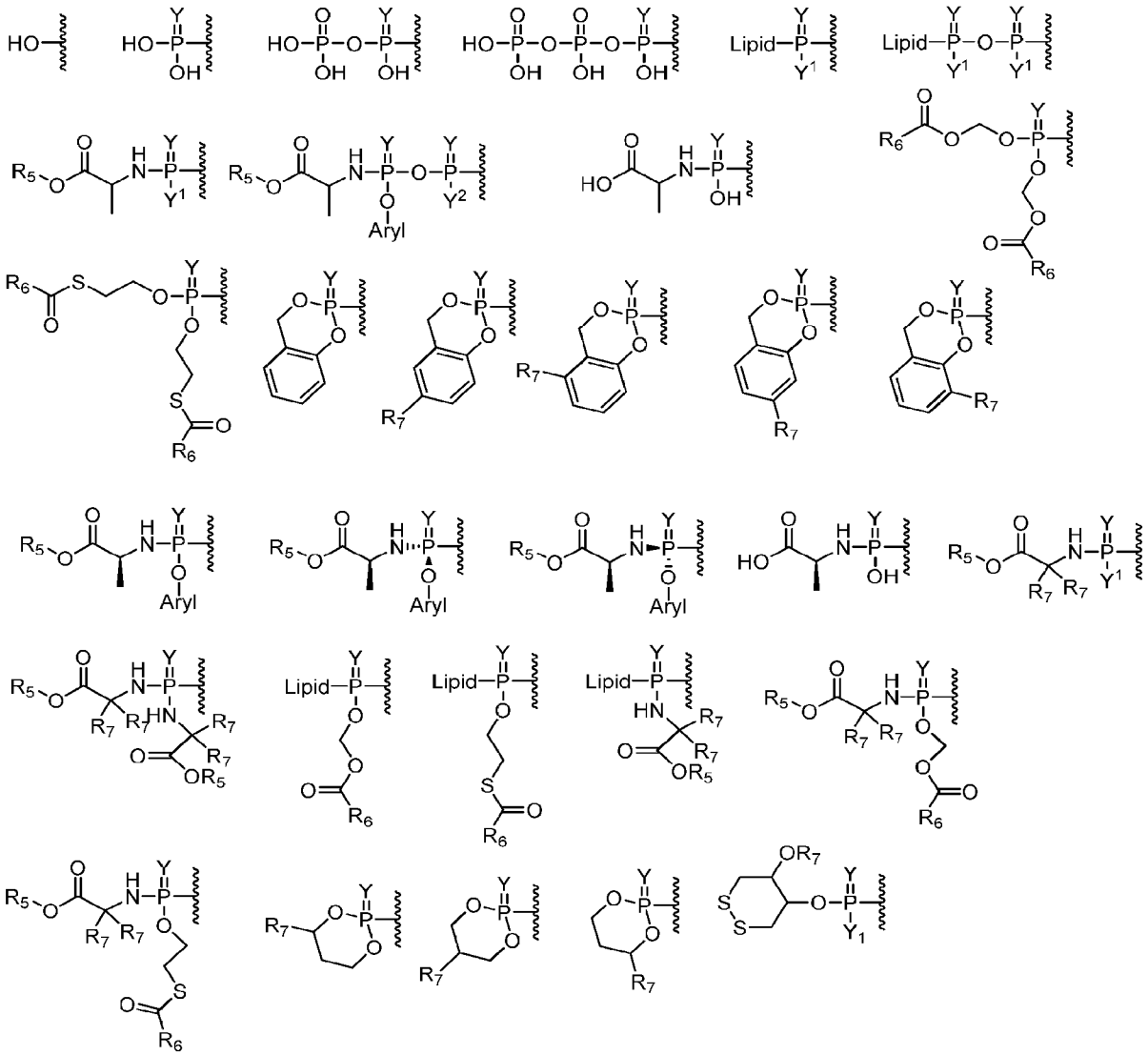
Formula XVc

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XVa and XVb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XVc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

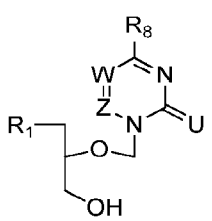
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

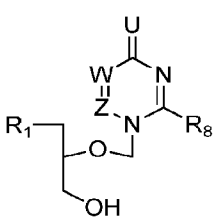
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

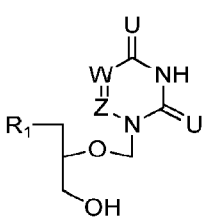
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XVIa



Formula XVIb

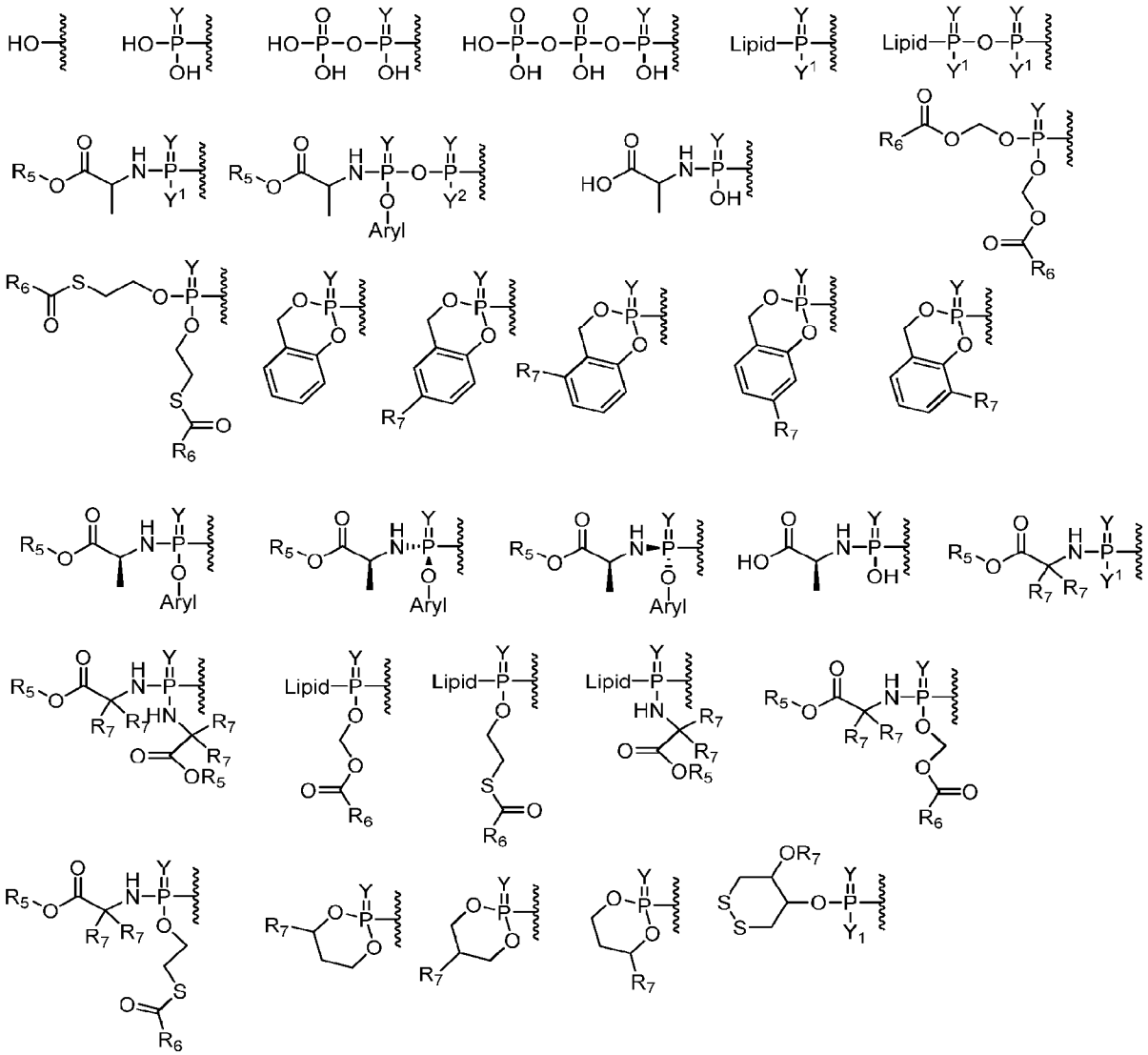


Formula XVIc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XVIa and XVIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XVIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

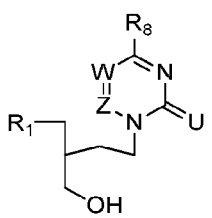
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

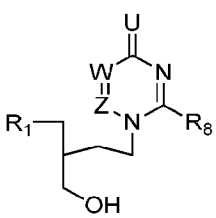
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

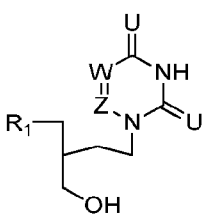
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XVIIa



Formula XVIIb

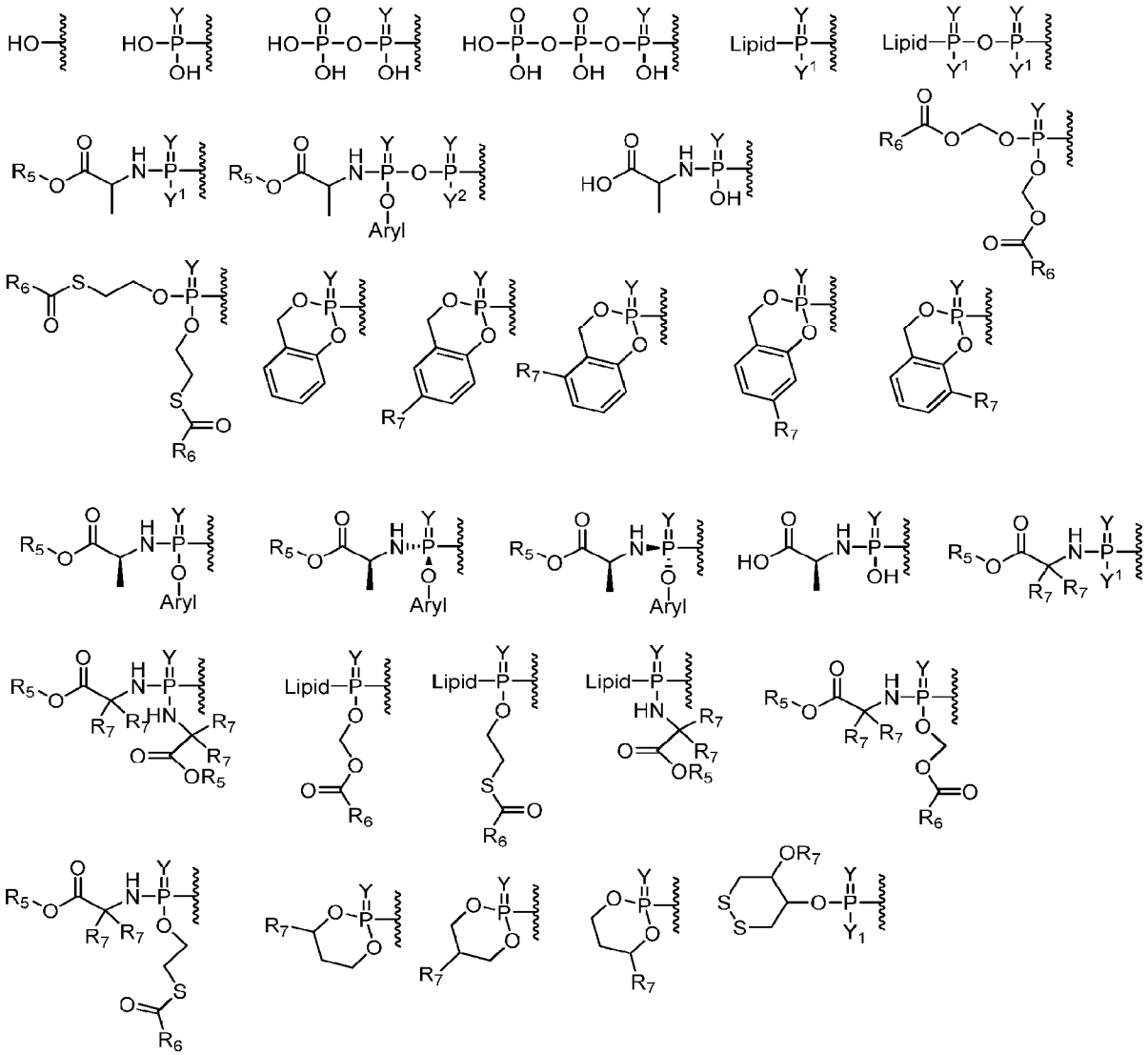


Formula XVIIc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XVIIa and XVIIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XVIIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

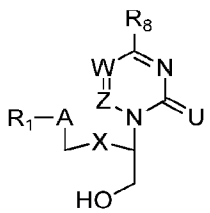
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

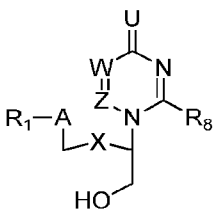
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

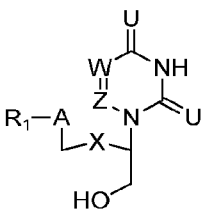
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XVIIIa



Formula XVIIIb



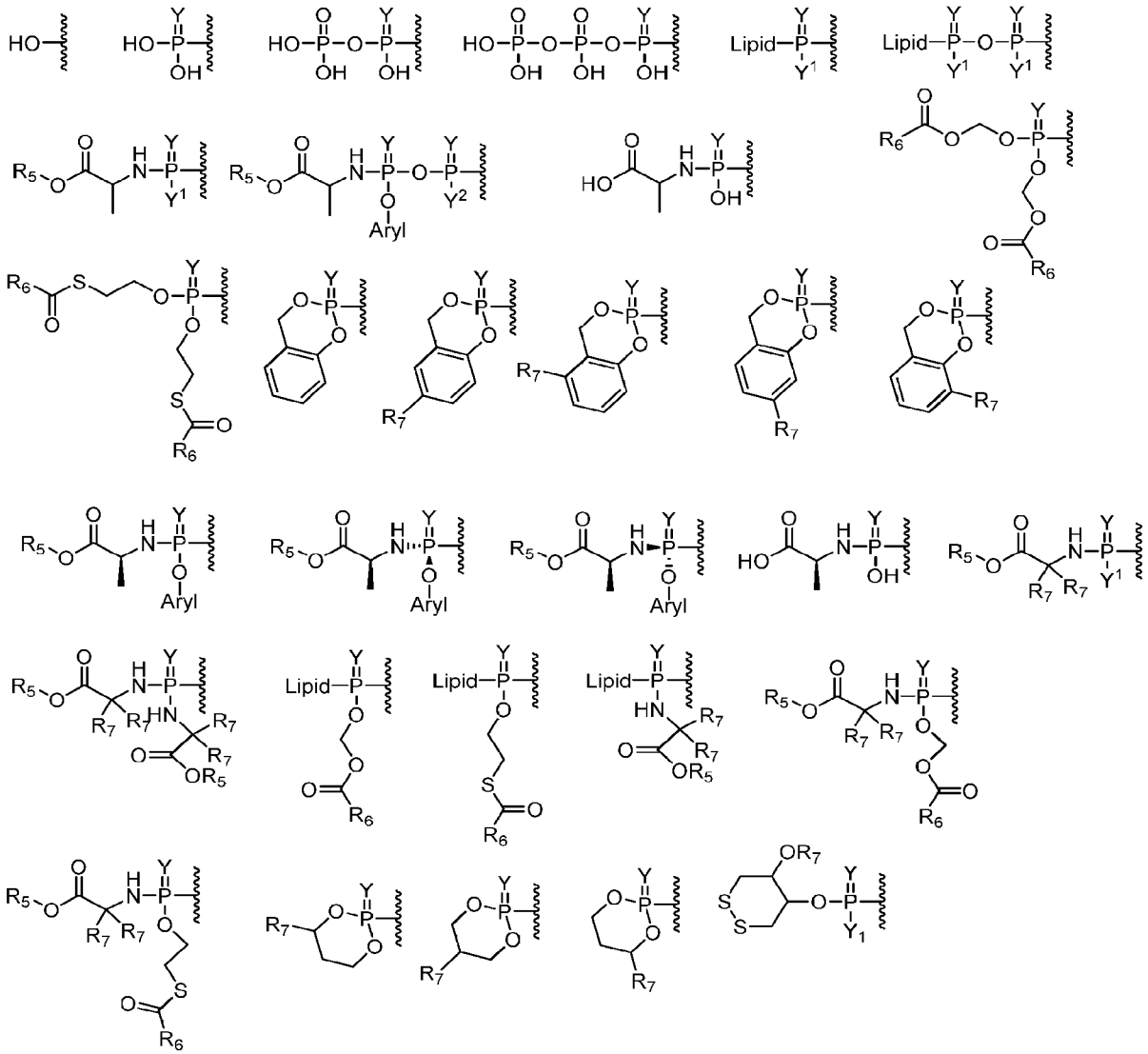
Formula XVIIIc

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XVIIIa and XVIIIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XVIIIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

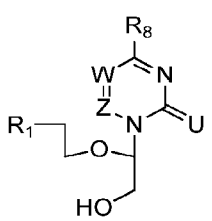
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

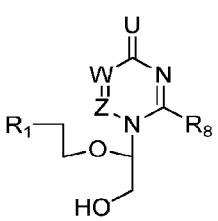
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

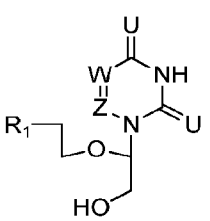
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XIXa



Formula XIXb

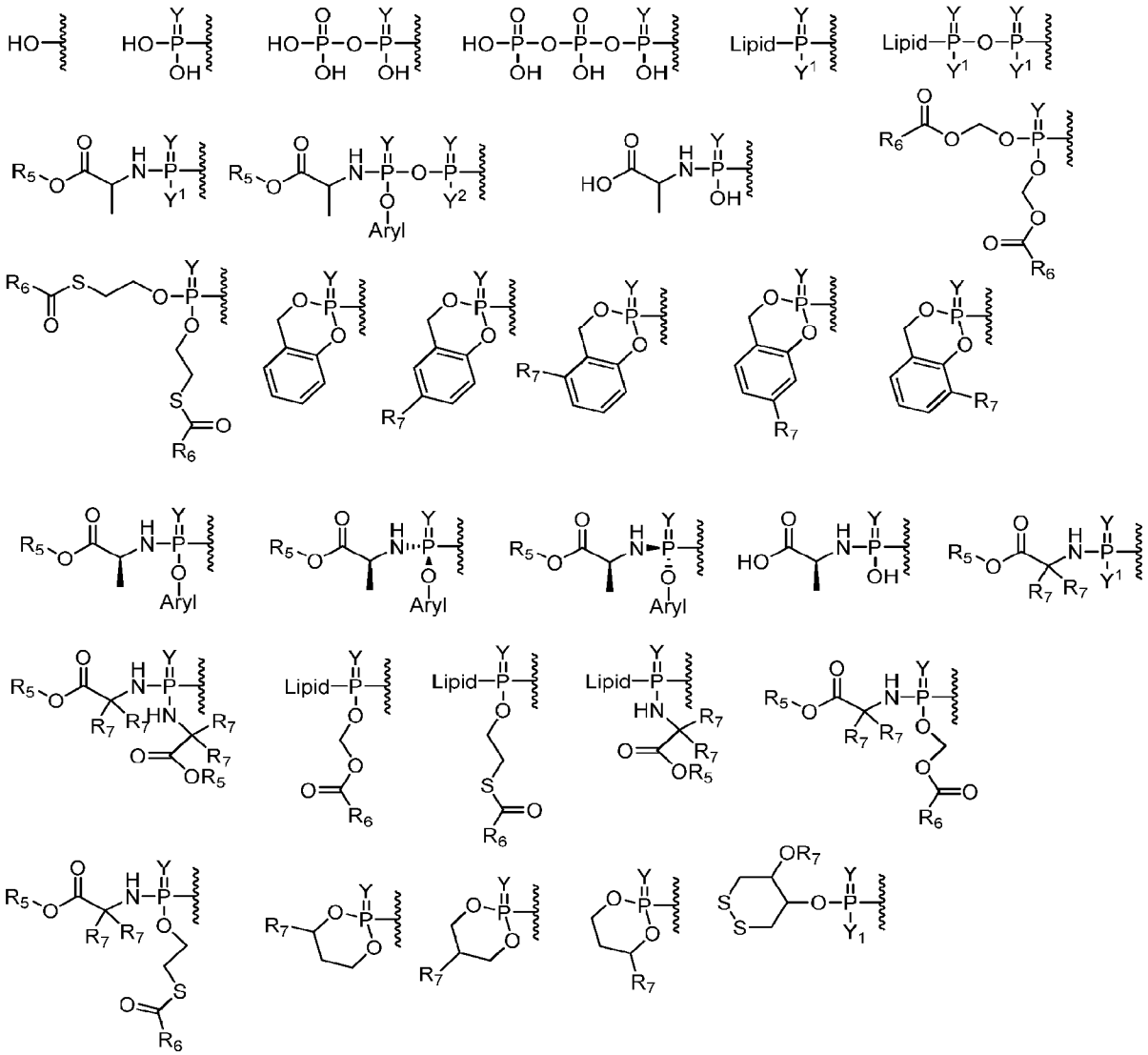


Formula XIXc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XIXa and XIXb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XIXc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

R^9 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

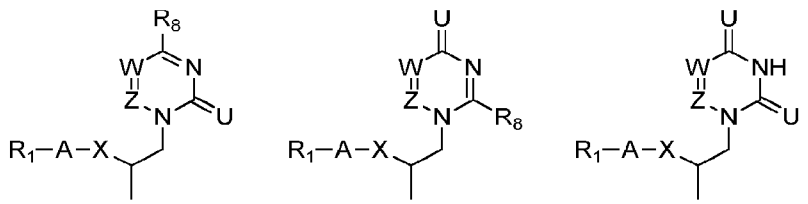
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In certain embodiments, the disclosure relates to a compound of the following formulae:



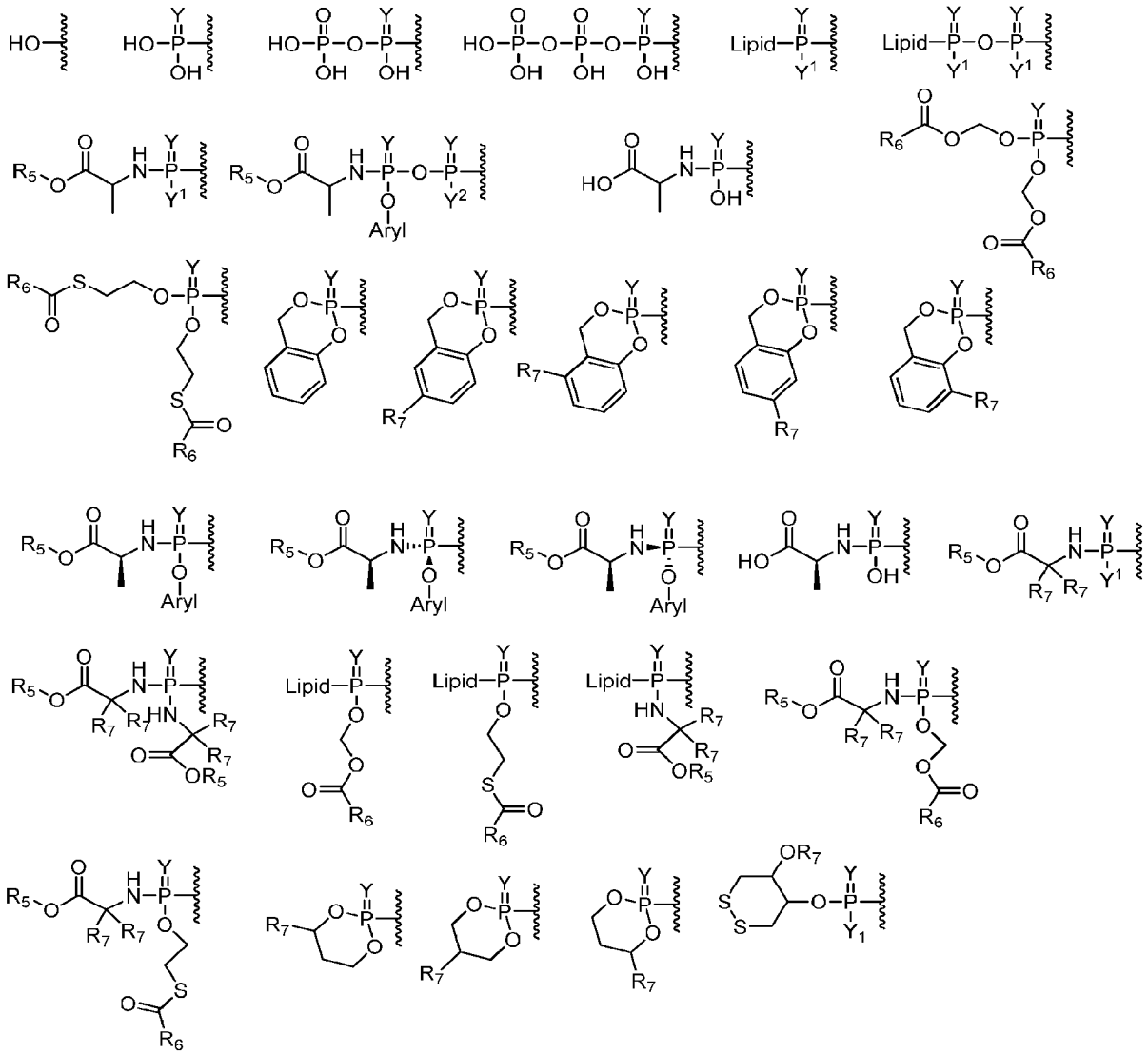
Formula XXa **Formula XXb** **Formula XXc**

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, C=CH_2, C=CHF, or C=CF_2;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XXa and XXb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XXc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

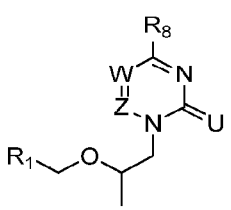
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

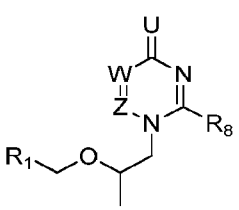
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

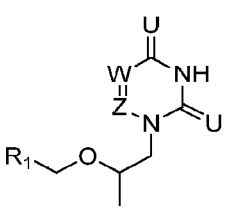
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XXIa



Formula XXIb

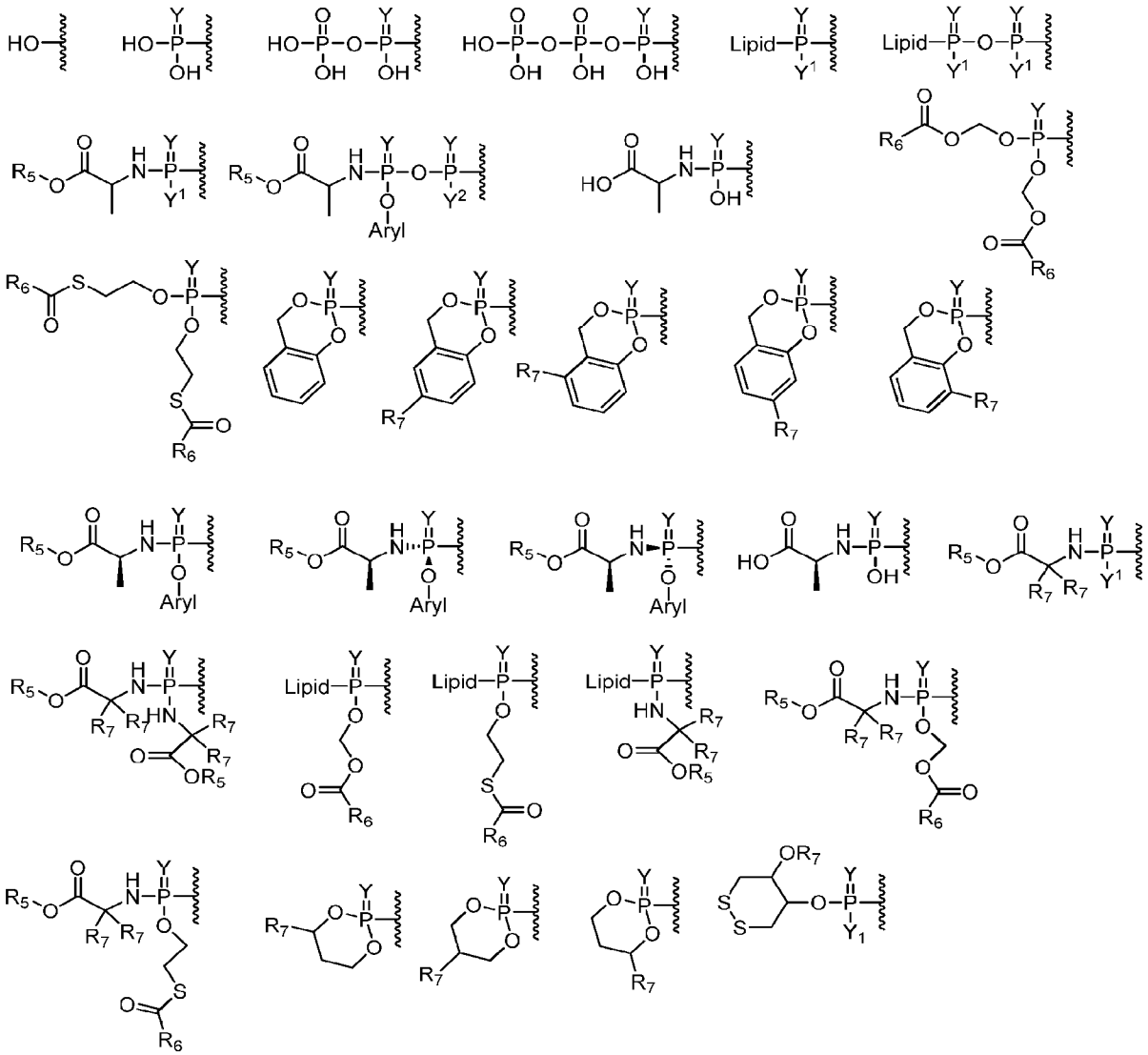


Formula XXIc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XXIa and XXIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XXIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

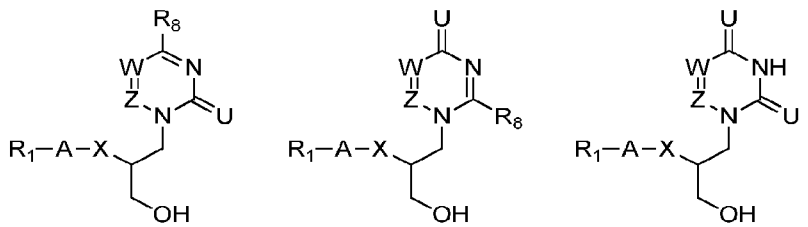
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In certain embodiments, the disclosure relates to a compound of the following formulae:



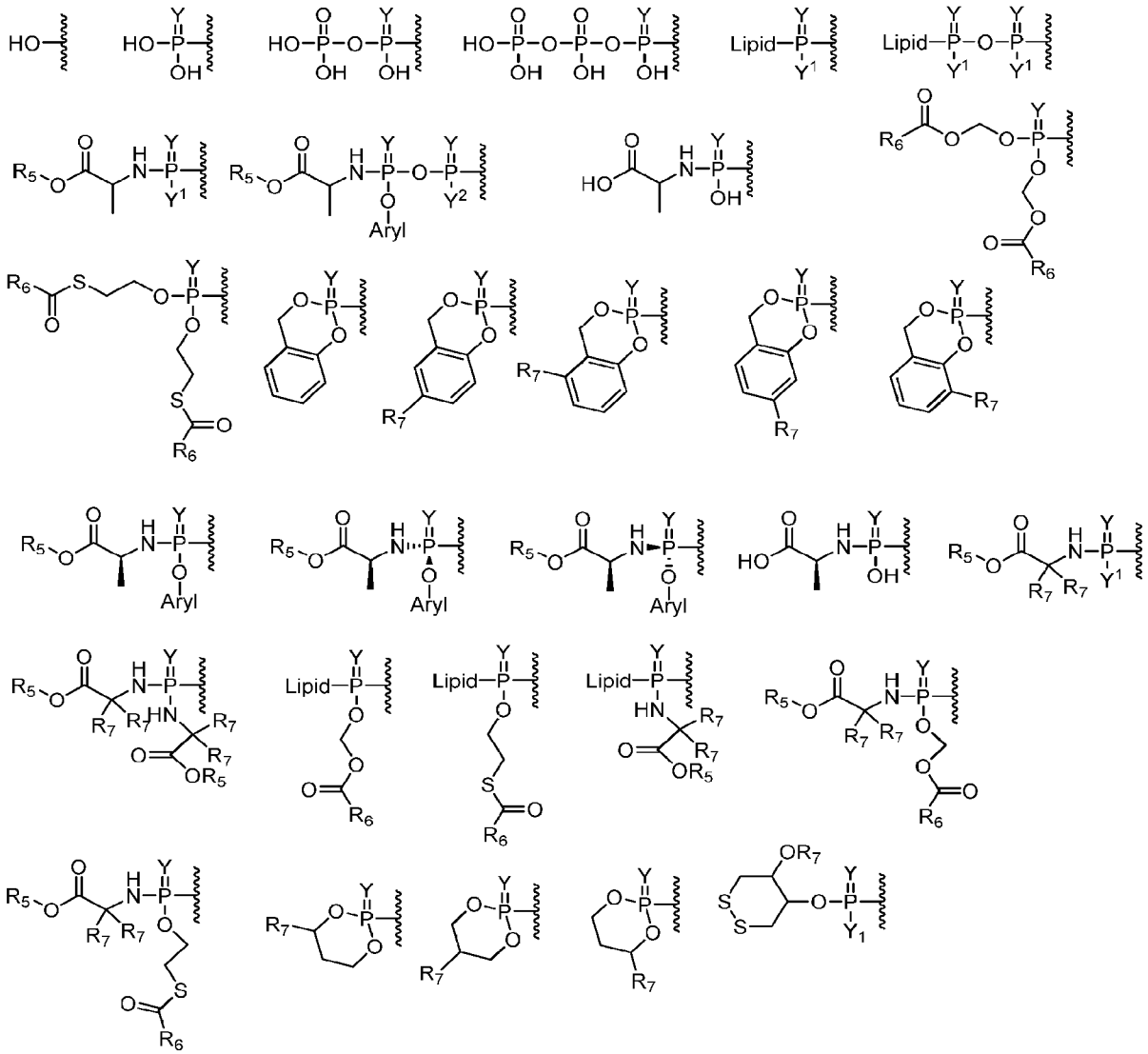
Formula XXIIa **Formula XXIIb** **Formula XXIIc**

or a pharmaceutically acceptable salt thereof, wherein

A is absent or selected from CH_2, CHF, CF_2, CD_2, O, CH_2O, CHFO, CF_2O, CD_2O, OCH_2, OCHF, OCF_2, or OCD_2;

R_1 is selected from one of the following:

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X is O, S, NH, CH_2, CD_2, CHF, CF_2, $C{=}CH_2$, C=CHF, or $C{=}CF_2$;

each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XXIIa and XXIIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XXIIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

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each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

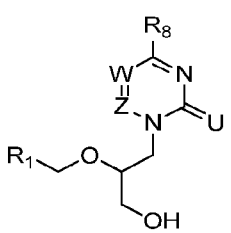
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

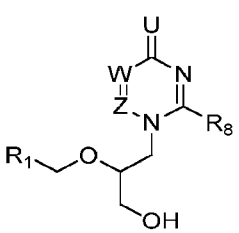
R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

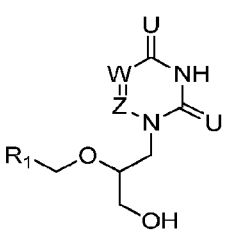
In certain embodiments, the disclosure relates to a compound of the following formulae:



Formula XXIIIa



Formula XXIIIb

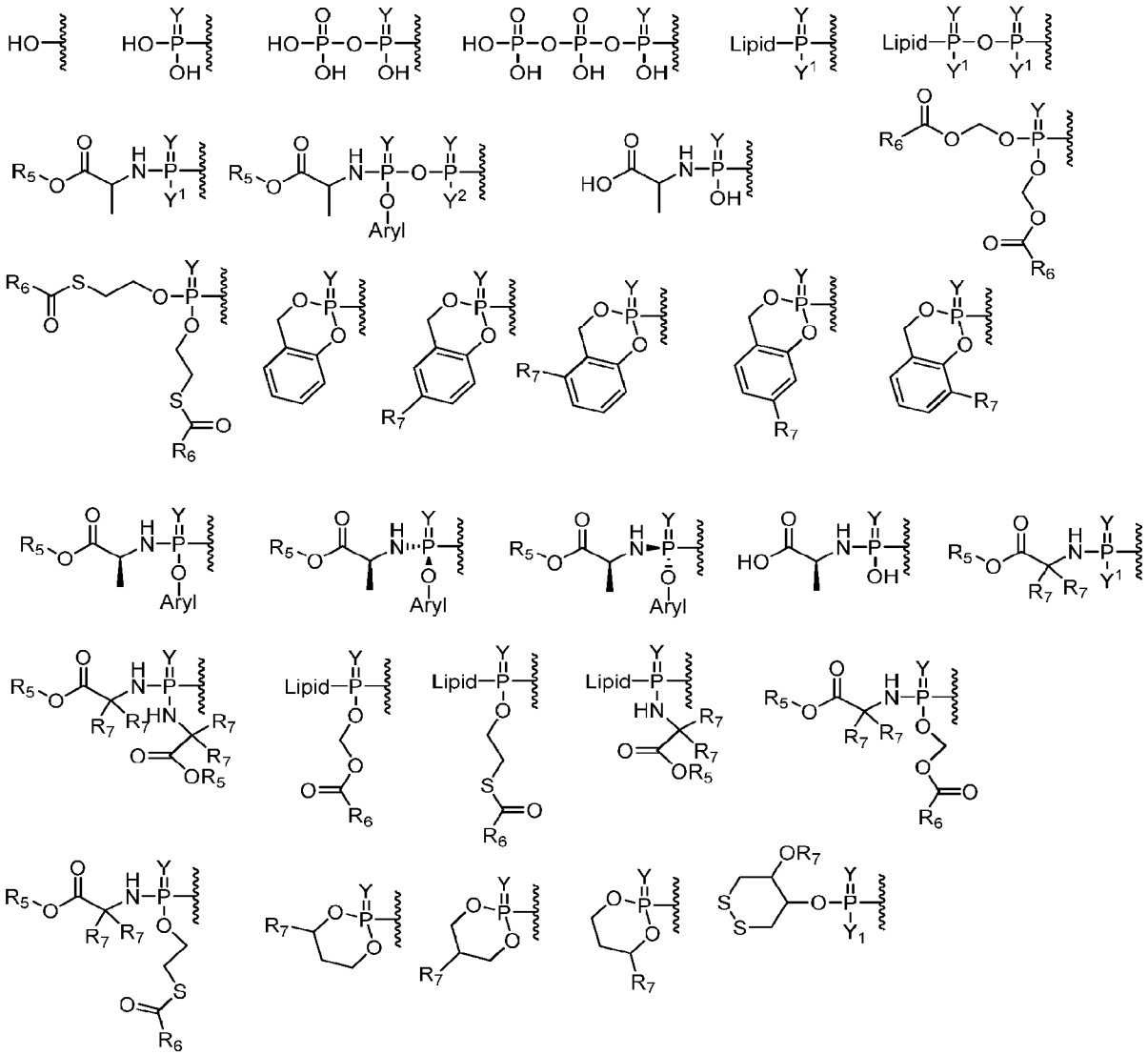


Formula XXIIIc

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from one of the following:

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each U is independently O, S, NH, NR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

R^8 is OH, SH, NH_2, OR^9, SR^9, NHR^9, NHOH, NR^9OH, $NHOR^9$, or NR^9OR^9;

wherein in Formula XXIIIa and XXIIIb, one of U is S or R^8 is SR^9, or both U is S and R^8 is SR^9;

wherein in Formula XXIIIc at least one U is S;

W is CH, N, or CR^9;

Z is CH, N, or CR^9;

each R^9 is independently deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

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each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

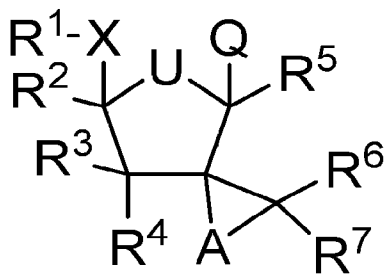
R_5 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_6 is C_{1-22} alkoxy, or C_{1-22} alkyl, alkyl, branched alkyl, cycloalkyl, or alkyoxy;

R_7 is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl.

In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



Formula XXIV

or pharmaceutically acceptable salts thereof wherein,

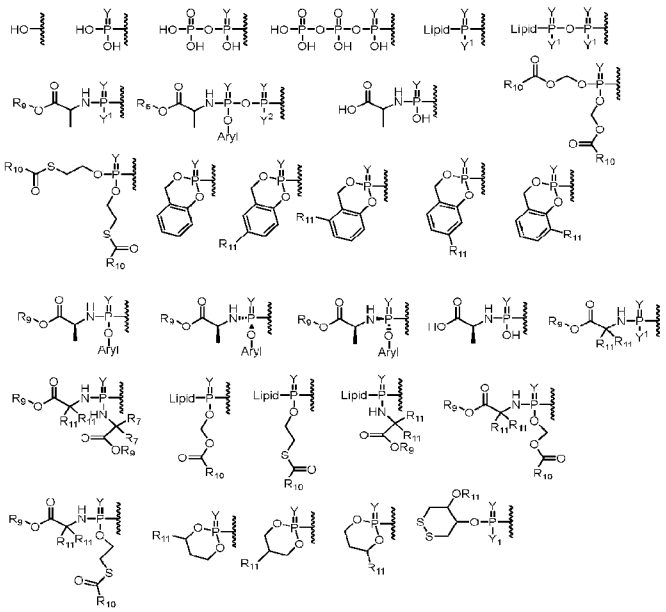
A is S, NH, $NR^{8;}$

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is OCH_2, OCHMe, $OCMe_2$, OCHF, OCF_2, OCD_2, CH_2O, CHFO, CF_2O, CD_2O;

R_1 is selected from one of the following:

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R^2, R^3, R^4, R^6, R^7, and R^8 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{12};

each R^{12} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{12};

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_9 is alkyl, branched alkyl, or cycloalkyl;

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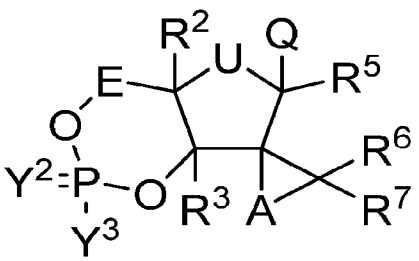
Aryl is as described herein;

R_{10} is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl alkyl, or alkyoxy;

R_{11} is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl; and

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether.

In certain embodiments, the present disclosure relates to a compound of the following formula:



Formula XXV

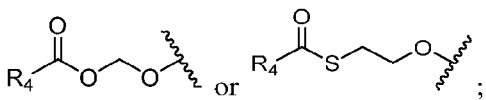
or a pharmaceutically acceptable salt thereof, wherein

A is S, NH, or NR^8;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

Y^2 is O or S;

Y^3 is OH, OR^{10}, SR^{10}, NHR^{10}, $NR^{10}{}_2$, or $BH_3^-M^+$, lipid, or selected from



E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

R^2, R^3, R^6, R^7, and R^8 are independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{11};

R^{10} is C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl, H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Aryl is as described herein;

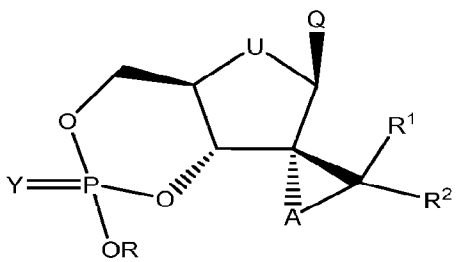
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Lipid is as described herein;

R^4 is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl, alkyl, or alkyoxy; and

each R^{11} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to compounds of the following formula:



Formula XXVa

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

A is S, NH, or NR^3;

wherein R^1, R^2, and R^3 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^4;

each R^4 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

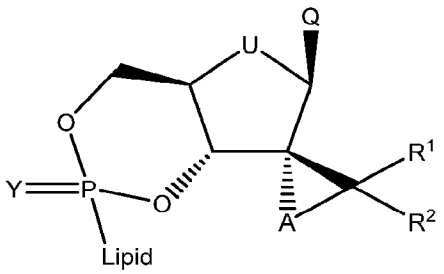
Y is O or S; and

R is straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or benzyl, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, H, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Aryl is as described herein.

In certain embodiments, the disclosure relates to compounds of the formula:

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Formula XXVb

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

A is S, NH, or NR^3;

wherein R^1, R^2, and R^3 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^4;

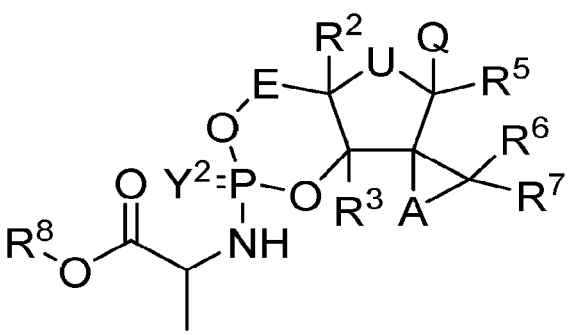
each R^4 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

Y is O or S; and

Lipid is as described herein.

In certain embodiments, the present disclosure relates to a compound of the following formula:



Formula XXVc

or pharmaceutically acceptable salts thereof wherein,

A is S, NH, or NR^9;

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R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

Y^2 is O or S;

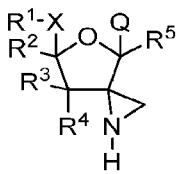
R^2, R^3, R^6, R^7, R^9 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^8 is $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, branched alkyl, or cycloalkyl.

In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



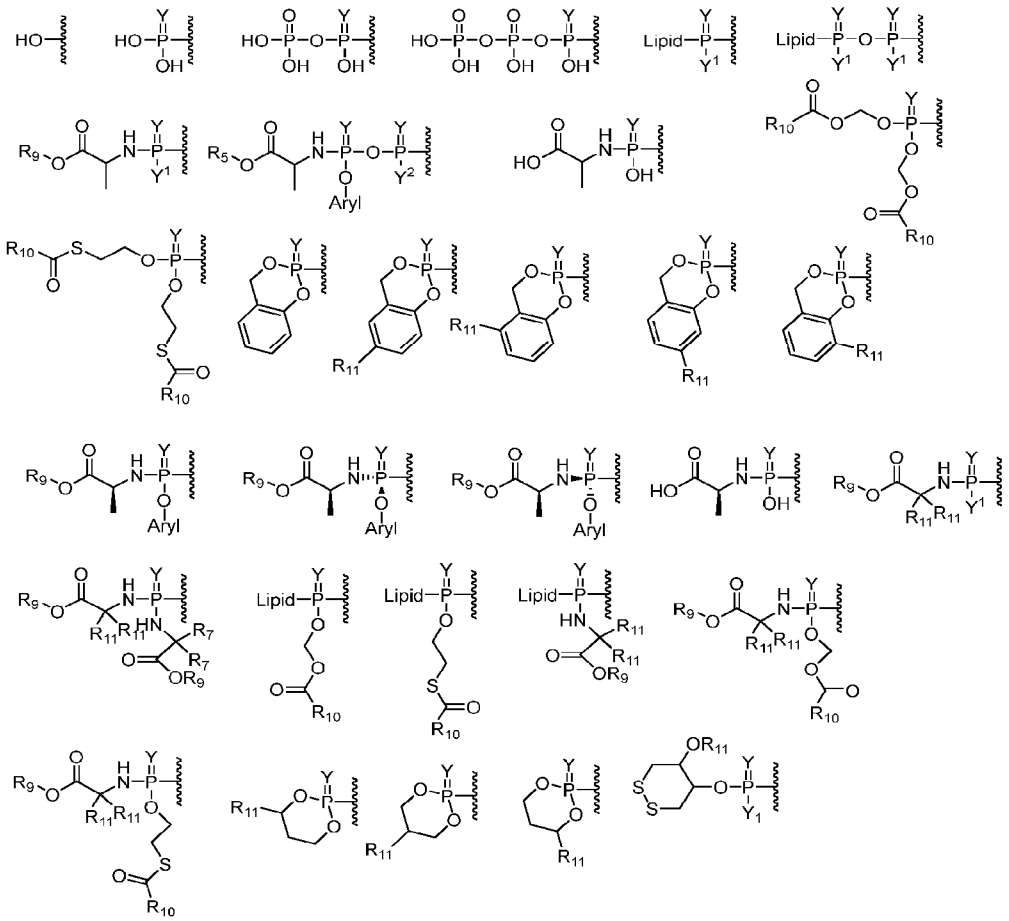
Formula XXVI

or pharmaceutically acceptable salts thereof wherein,

X is OCH_2, OCHMe, $OCMe_2$, OCHF, OCF_2, OCD_2, CH_2O, CHFO, CF_2O, CD_2O;

R_1 is selected from one of the following:

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R^2, R^3, R^4, and R^8 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{12};

each R^{12} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{12};

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

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R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_9 is alkyl, branched alkyl, or cycloalkyl;

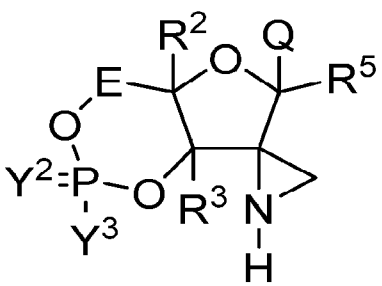
Aryl is as described herein;

R_{10} is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl alkyl, or alkyoxy;

R_{11} is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl; and

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether.

In certain embodiments, the present disclosure relates to a compound of the following formula:

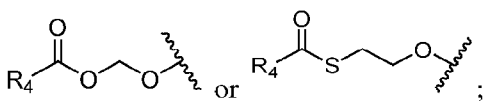


Formula XXVII

or a pharmaceutically acceptable salt thereof, wherein

Y^2 is O or S;

Y^3 is OH, OR^{10}, SR^{10}, NHR^{10}, NR^{10}_2, or $BH_3^-M^+$, lipid, or selected from



;

E is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

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R^2, R^3, and R^8 are independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{11};

R^{10} is C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl, H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

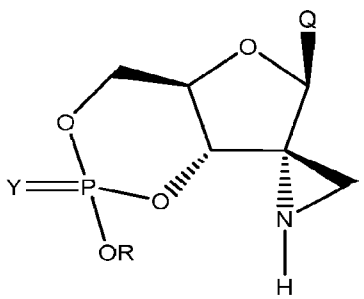
Aryl is as described herein;

Lipid is as described herein;

R^4 is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl, alkyl, or alkyoxy; and

each R^{11} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to compounds of the following formula:



Formula XXVIIa

or a pharmaceutically acceptable salt thereof, wherein

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

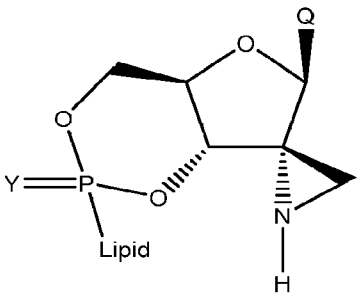
Y is O or S; and

R is straight or branched alkyl, e.g. methyl, ethyl, propyl, n-butyl, isopropyl, 2-butyl, 1-ethylpropyl, 1-propylbutyl, or a C_{12-19} long chain alkyl; cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or benzyl, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, H, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Aryl is as described herein.

In certain embodiments, the disclosure relates to compounds of the formula:

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Formula XXVIIb

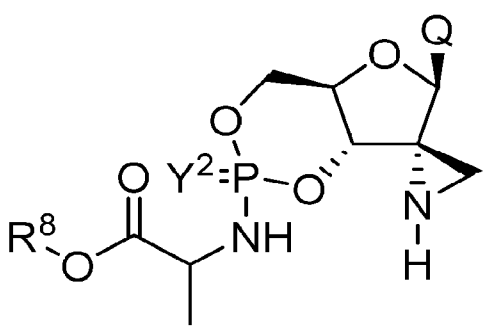
or a pharmaceutically acceptable salt thereof, wherein

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

Y is O or S; and

Lipid is as described herein.

In certain embodiments, the present disclosure relates to a compound of the following formula:



Formula XXVIIc

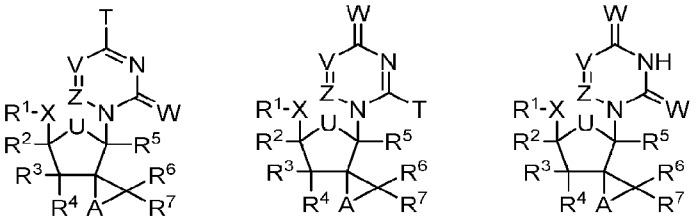
or pharmaceutically acceptable salts thereof wherein,

Y^2 is O or S;

Q is thymine, uracil, cytosine, adenine, guanine or is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether;

R^8 is C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, or cycloalkyl.In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:

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Formula XXVIIIa **Formula XXVIIIb** **Formula XXVIIIc**

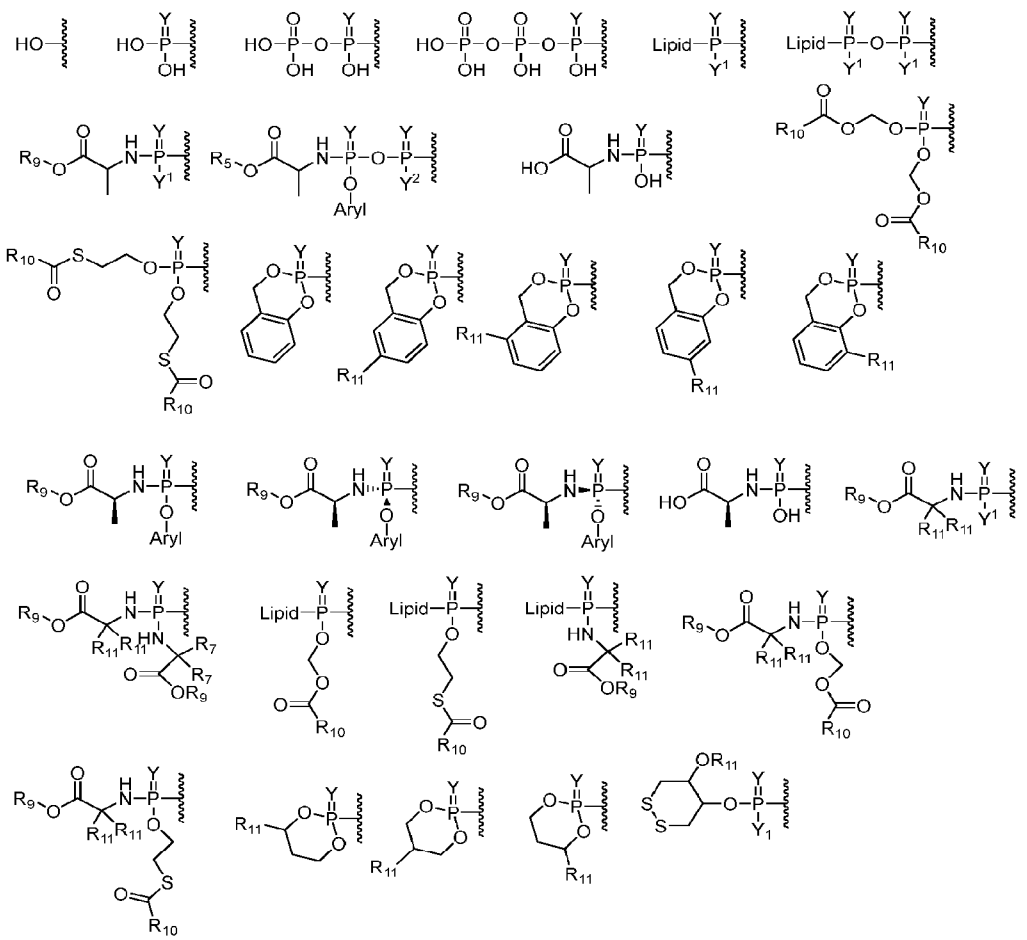
or pharmaceutically acceptable salts thereof wherein,

A is S, NH, $NR^{8;}$

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

X is OCH_2, OCHMe, $OCMe_2$, OCHF, OCF_2, OCD_2, CH_2O, CHFO, CF_2O, CD_2O;

R_1 is selected from one of the following:



R^2, R^3, R^4, R^6, R^7, and R^8 are each independently selected from H, D, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{12};

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each R^{12} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{12};

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_9 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_{10} is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl alkyl, or alkyoxy;

R_{11} is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl;

T is OH, SH, NH_2, OR^{13}, SR^{13}, NHR^{13}, NHOH, $NR^{13}OH$, $NHOR^{13}$, or $NR^{13}OR^{13}$;

W is O or S;

V is CH, N, or CR^{13};

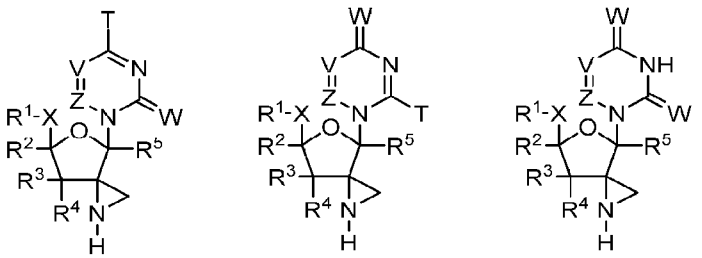
Z is CH, N, or CR^{13};

each R^{13} is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9; and

each R^{14} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

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In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:

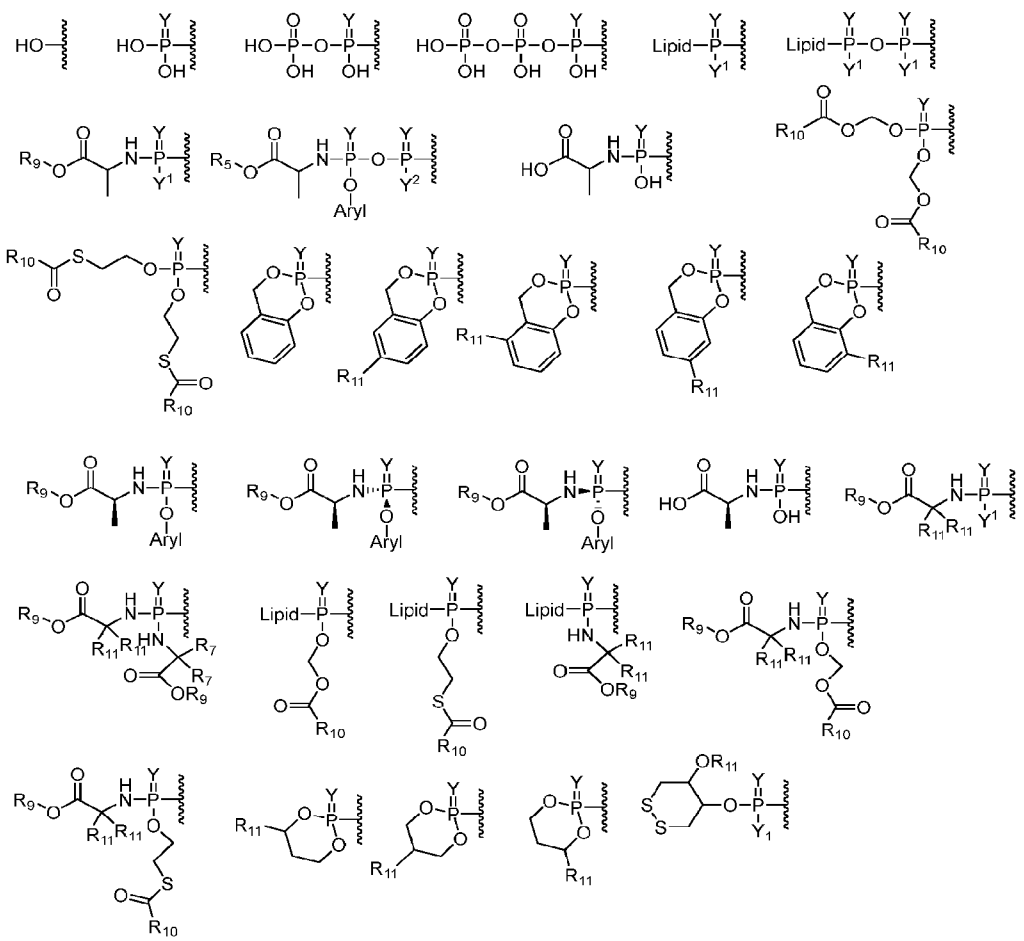


Formula XXIXa **Formula XXIXb** **Formula XXIXc**

or pharmaceutically acceptable salts thereof wherein,

X is OCH_2, OCHMe, $OCMe_2$, OCHF, OCF_2, OCD_2, CH_2O, CHFO, CF_2O, CD_2O;

R_1 is selected from one of the following:



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R^2, R^3, R^4, and R^8 are each independently selected from H, D, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{12};

each R^{12} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{12};

R^5 is H, D, Me, CN, alkyl, alkenyl, alkynyl;

Lipid is as described herein;

Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", $NR"_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_9 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_{10} is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl alkyl, or alkyoxy;

R_{11} is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl;

T is OH, SH, NH_2, OR^{13}, SR^{13}, NHR^{13}, NHOH, $NR^{13}OH$, $NHOR^{13}$, or $NR^{13}OR^{13}$;

W is O or S;

V is CH, N, or CR^{13};

Z is CH, N, or CR^{13};

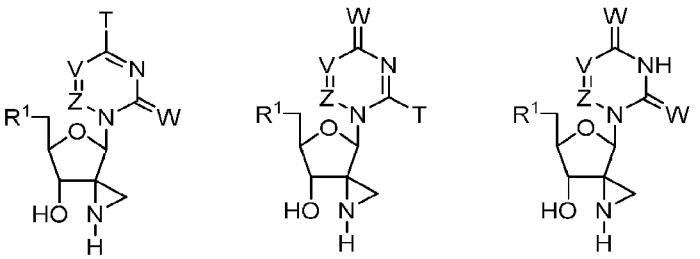
each R^{13} is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9; and

each R^{14} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio,

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alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

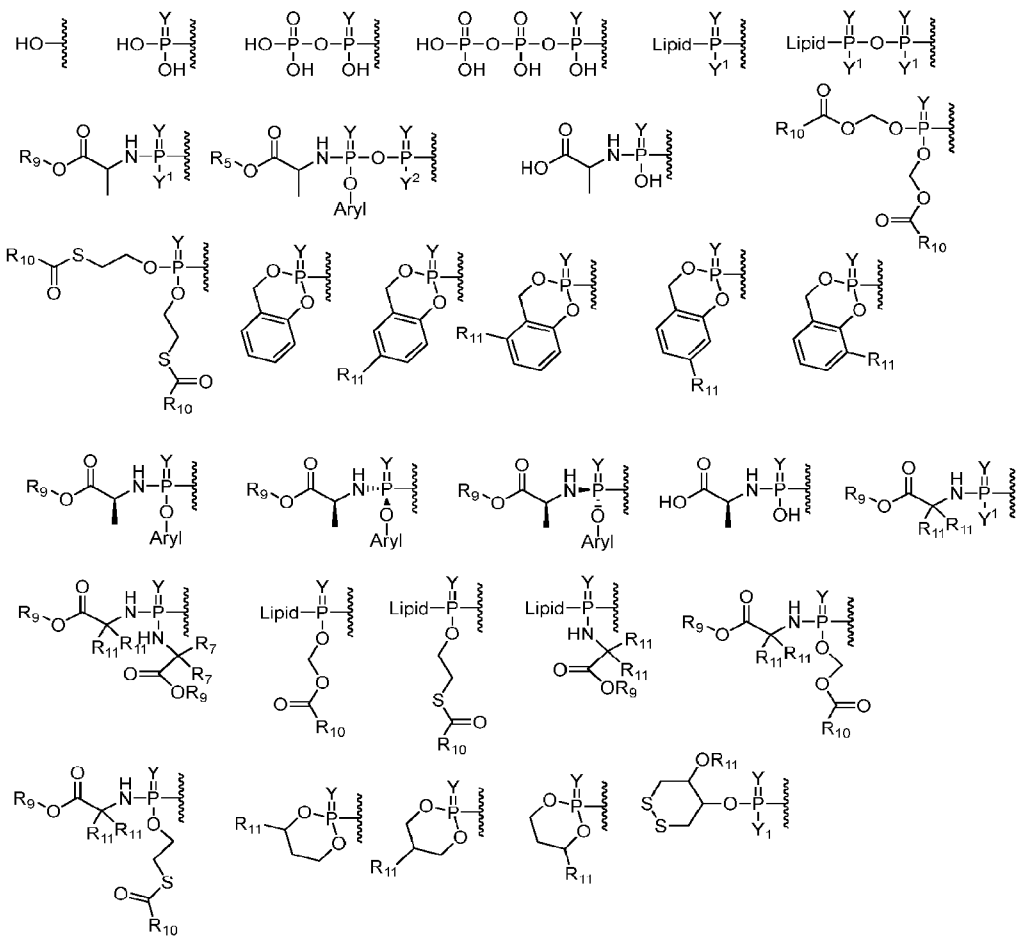
In preferred embodiments, the nucleoside conjugated to a phosphorus moiety or pharmaceutically acceptable salt thereof has the following structure:



Formula XXXa **Formula XXXb** **Formula XXXc**

or pharmaceutically acceptable salts thereof wherein,

R_1 is selected from one of the following:



Lipid is as described herein;

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Y is O or S;

Y^1 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

Y^2 is OH, OAryl, OR", SR", NHR", NR"$_2$, or $BH_3^-M^+$;

R" is H, methyl, ethyl, isopropyl, butyl, alkyl, alkenyl, alkynyl, aryl, heteroaryl, phenyl, benzyl, naphthyl;

R_9 is alkyl, branched alkyl, or cycloalkyl;

Aryl is as described herein;

R_{10} is C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{2-22} alkynyl, branched alkyl, cycloalkyl alkyl, or alkyoxy;

R_{11} is aryl, heteroaryl, substituted aryl, lipid, C_{1-22} alkoxy, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, or substituted heteroaryl;

T is OH, SH, NH_2, OR^{13}, SR^{13}, NHR^{13}, NHOH, $NR^{13}OH$, $NHOR^{13}$, or $NR^{13}OR^{13}$;

W is O or S;

V is CH, N, or CR^{13};

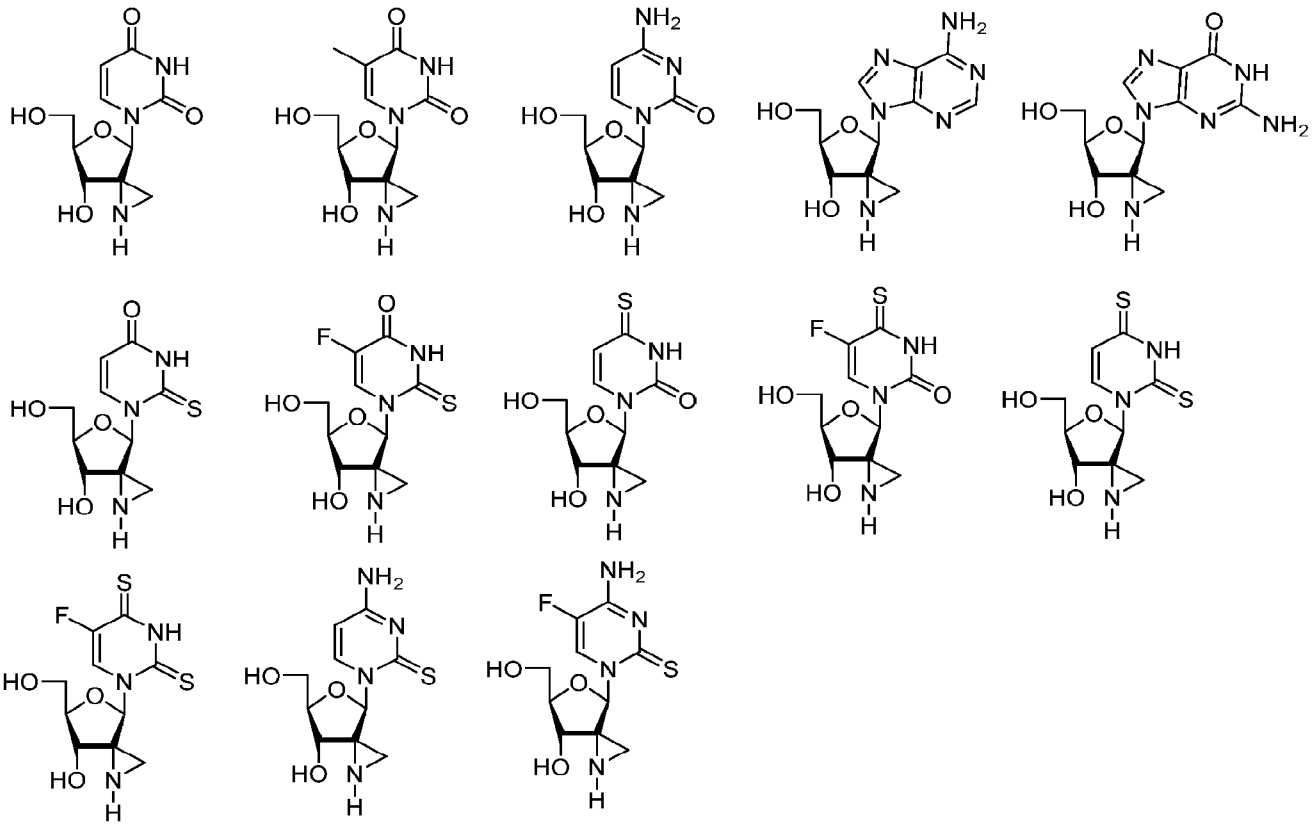
Z is CH, N, or CR^{13};

each R^{13} is independently selected from deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9; and

each R^{14} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

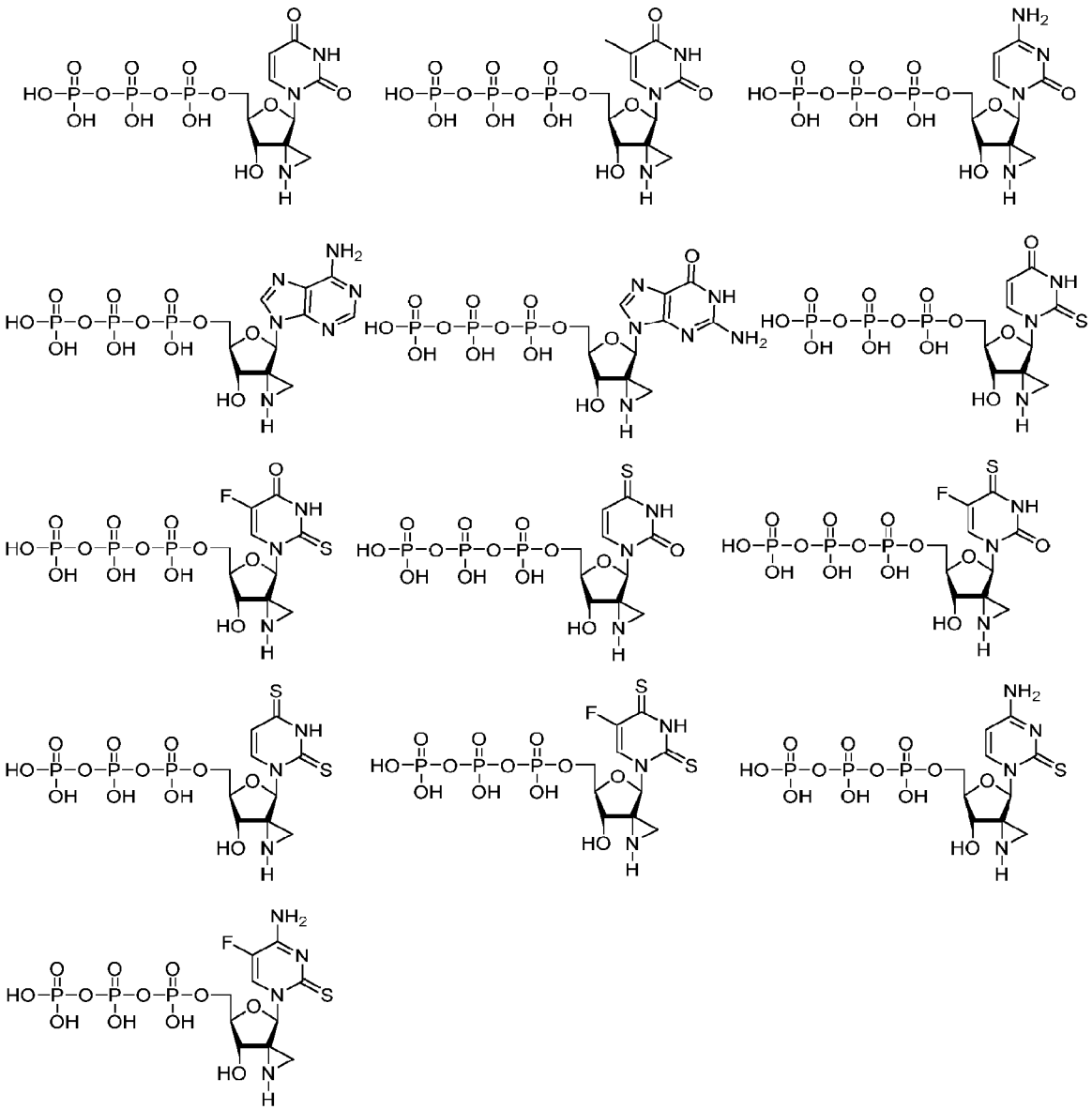
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In exemplary embodiments, the compound is selected from the group consisting of:

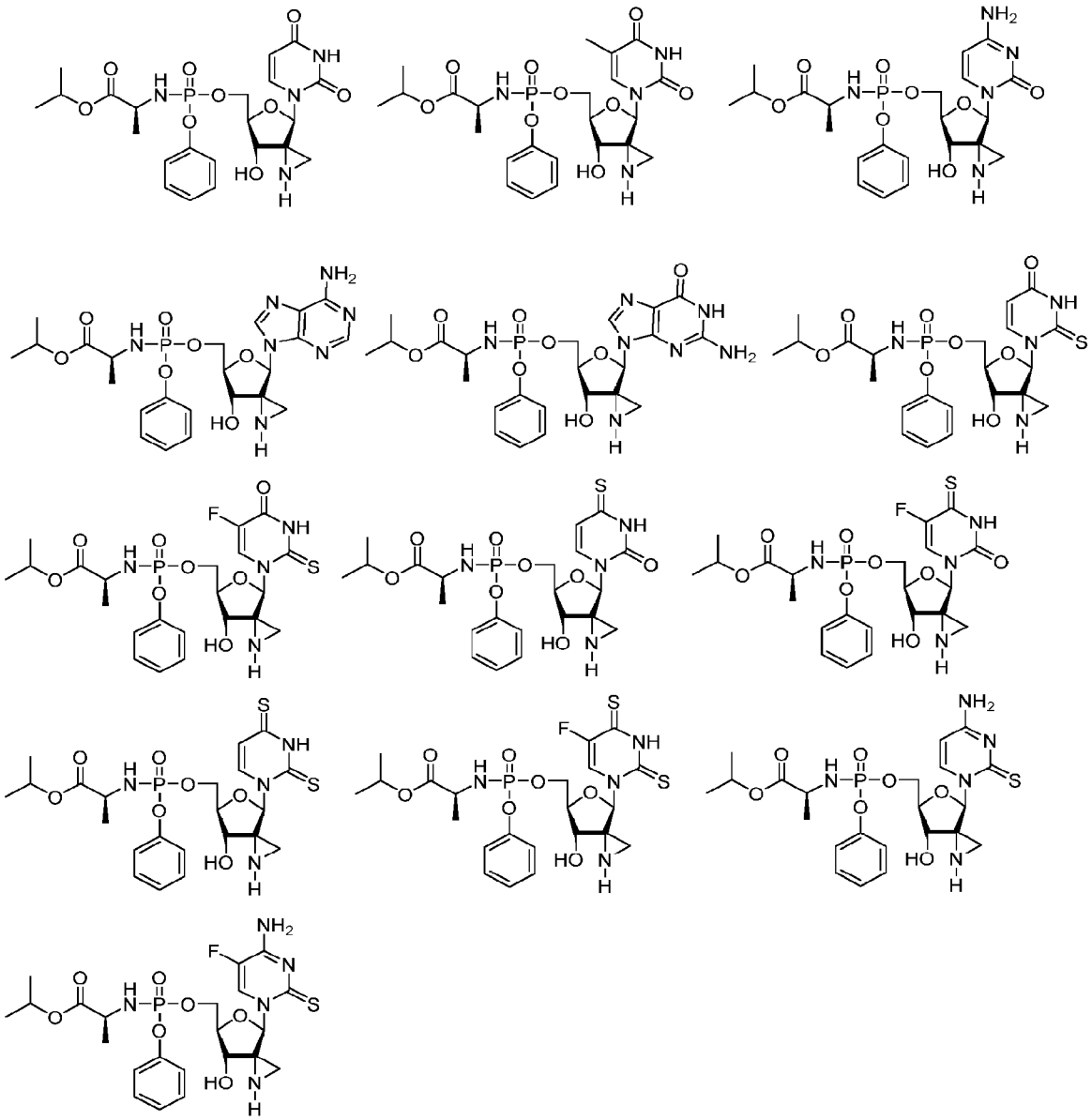


In exemplary embodiments, the compound is selected from the group consisting of:

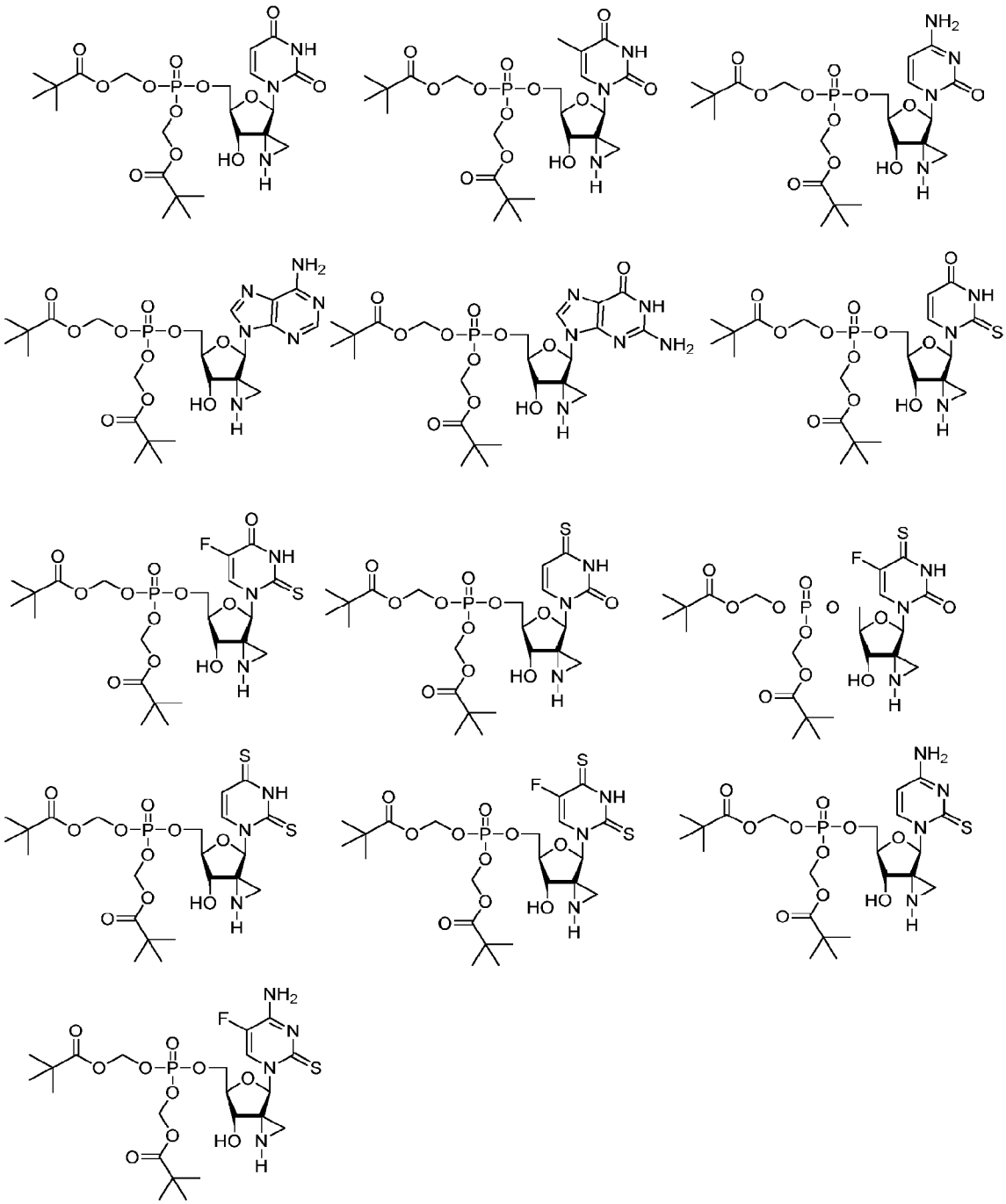
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In exemplary embodiments, the compound is selected from the group consisting of:



In exemplary embodiments, the compound is selected from the group consisting of:



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As provided herein, the nucleotide or nucleoside compounds (comprising a heterocycle comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether) can be formulated in combination with a second antiviral agent. In certain

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embodiments, the second antiviral agent can be selected from 25-hydroxycholesterol, AN-12-H5, disoxaril, , pirodavir, vapendavir and pocapavir, abacavir, acyclovir, acyclovir, adefovir, amantadine, amiloride, amprenavir, ampligen, arbidol, atazanavir, atripla, aurintricarboxilic acid, BF738735, boceprevir, BPR-3P0128, buthionine sulfoxime, cidofovir, cyclosporin A, combivir, darunavir, DAS181, DC07090, delavirdine, dibucaine, didanosine, docosanol, DTrip-22, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, enviroxime, famciclovir, fluoxetine, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, geldanamycin, gemcitabine, gliotoxin, GPC-N114, guanidine hydrochloride, GW5074, HBB, HL05100P2, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, intrazonazole, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, MRL-1237, nelfinavir, nevirapine, nexavir, NIM-811, oseltamivir, OSW-1, peginterferon alfa-2a, penciclovir, peramivir, PIK93, pirlindole, pleconaril (Picovir), podophyllotoxin , raltegravir, ribavirin, rimantadine, ritonavir, rupintrivir, pyramidine, saquinavir, sofosbovir, stavudine, T-00127-HEV1, T-00127-HEV2, TBZE-029, telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, TP-219, TTP-8307, V-7404, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine zalcitabine, zanamivir, zidovudine, or zuclopenthixol and combinations thereof.

In certain examples, the second antiviral compounds used in combination with the above compounds of the subject disclosure include disoxaril, pleconaril, pirodavir, vapendavir and pocapavir. Vapendivir, analogs thereof, and related compounds that can be used in combination with the compounds/compositions/agents of this disclosure are described in US Patent Nos. 8,415,309; 8,501,699; 7,579,465; 7,829,705; 8,217,171; 8,624,025; 8,580,791; 9,447,080; 9,675,694; 9,163,029; 7,504,434; 9,802,926; 9,452,991; 9,974,779; 8,440,833; 9,670,159; and 9,908,858.

Infectious Diseases

The compounds and compositions provided herein can be used to treat viral infectious diseases. Examples of viral infections include but are not limited to, infections caused by RNA viruses (including negative stranded RNA viruses, positive stranded RNA viruses, double stranded RNA viruses and retroviruses) or DNA viruses. All strains, types, and subtypes of RNA viruses and DNA viruses are contemplated herein.

Examples of RNA viruses include, but are not limited to picornaviruses, which include aphthoviruses (for example, foot and mouth disease virus O, A, C, Asia 1, SAT1, SAT2 and SAT3), cardioviruses (for example, encephalomycarditis virus and Theiller's

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murine encephalomyelitis virus), enteroviruses (for example polioviruses 1, 2 and 3, human enteroviruses A-D, bovine enteroviruses 1 and 2, human coxsackieviruses A1-A22 and A24, human coxsackieviruses B1-B5, human echoviruses 1-7, 9, 11-12, 24, 27, 29-33, human enteroviruses 68-71, porcine enteroviruses 8-10 and simian enteroviruses 1-18), erboviruses (for example, equine rhinitis virus), hepatovirus (for example human hepatitis A virus and simian hepatitis A virus), kobuviruses (for example, bovine kobuvirus and Aichi virus), parechoviruses (for example, human parechovirus 1 and human parechovirus 2), rhinovirus (for example, rhinovirus A, rhinovirus B, rhinovirus C, HRV16, HRV16 (VR-11757), HRV14 (VR-284), or HRV1A (VR-1559), human rhinovirus 1-100 and bovine rhinoviruses 1-3) and teschoviruses (for example, porcine teschovirus).

In certain embodiments, the RNA viruses that can be treated by compounds and compositions of this disclosure include enteroviruses. The genus Enterovirus (EV) belonging to the *Picornaviridae* family comprises 13 species, of which seven are human viruses. Four of the species are: (1) EV-A such as coxsackievirus (CV)-A6, CV-A10, CV-A16 and EV-A71, (2) EV-B such as the CV-B viruses, echoviruses (ECHO) and CV-A9, (3) EV-C such as polioviruses (PV) and CV-A21, and (4) EV-D such as EV-D68 and EV-D70. Other species include rhinoviruses RV-A, RV-B and RV-C which are comprised of over 100 different numbered RVs. EV RNA contains a single open reading frame (ORF) flanked by two untranslated regions (UTRs), 5′ UTR and 3′ UTR. The ORF encodes a single polyprotein that is cleaved into P1, P2 and P3 proteins. The P1 protein is proteolytically cleaved to produce capsid proteins VP1–4. P2 and P3 are cleaved to produce non-structural (NS) proteins 2A, 2B, 2C and 3A, 3B, 3C, 3D, respectively. The role of the capsid proteins is to enclose the genetic material and to recognize cellular receptors during viral entry. The NS proteins are crucial for replication, translation and subversion of host cell machinery. The capsid proteins are suitable targets for antiviral development due to their role in cellular entry and uncoating of the genetic material.

The diverse viruses in the genus EV are known to cause a range of diseases such as hand, foot and mouth disease (HFMD), encephalitis, aseptic meningitis, myocarditis and various respiratory diseases. While some EV infections are mild, the symptoms can be severe in the very young and immunodeficient individuals. In recent years, viruses such as EV-A71 and CV-A16 have emerged as serious public health threats, as they have caused major outbreaks of HFMD in China and South East Asia. Additionally, EV-D68 has caused a large outbreak of severe lower respiratory infections in North America in 2014. Therefore, broad-spectrum antiviral drugs that could inhibit multiple EVs across the genus will be instrumental

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to overcome the public health burden caused by these EVs.

The compounds and compositions of this disclosure can be used to treat or prevent diseases caused by enterovirus and to reduce enterovirual burden. In addition, the compounds and compositions of this disclosure can be combined with other drugs to treat enterovirus as provided herein. Anasir et al., J Biomed Sci (2021) 28, 10:5-12 provides a review of enteroviruses and antiviral agents for treating the same, the disclosure of which is incorporated herein by reference in its entirety.

Additional examples of RNA viruses that can be treated or prevented using the composunds and compositions herein include caliciviruses, which include noroviruses (for example, Norwalk virus), sapoviruses (for example, Sapporo virus), lagoviruses (for example, rabbit hemorrhagic disease virus and European brown hare syndrome) and vesiviruses (for example vesicular exanthema of swine virus and feline calicivirus). Other RNA viruses include astroviruses, which include mamastorviruses and avastroviruses. Togaviruses are also RNA viruses. Togaviruses include alphaviruses (for example, Chikungunya virus, Sindbis virus, Semliki Forest virus, Western equine encephalitis virus, Eastern Getah virus, Everglades virus, Venezuelan equine encephalitis virus and Aura virus) and rubella viruses. Additional examples of RNA viruses include the flaviviruses (for example, tick-borne encephalitis virus, Tyuleniy virus, Aroa virus, M virus (types 1 to 4), Kedougou virus, Japanese encephalitis virus (JEV), West Nile virus (WNV), Dengue Virus (including genotypes 1-4), Kokobera virus, Ntaya virus, Spondweni virus, Yellow fever virus, Entebbe bat virus, Modoc virus, Rio Bravo virus, Cell fusing agent virus, pestivirus, GB virus A, GBV-A like viruses, GB virus C, Hepatitis G virus, hepacivirus (hepatitis C virus (HCV)) all six genotypes), bovine viral diarrhea virus (BVDV) types 1 and 2, and GB virus B).

Other examples of RNA viruses are the coronaviruses, which include, human respiratory coronaviruses such as SARS-CoV, HCoV-229E, HCoV-NL63 and HCoV-OC43. Coronaviruses also include bat SARS-like CoV, Middle East Respiratory Syndrome coronavirus (MERS), turkey coronavirus, chicken coronavirus, feline coronavirus and canine coronavirus. Additional RNA viruses include arteriviruses (for example, equine arterivirus, porcine reproductive and respiratory syndrome virus, lactate dehyrogenase elevating virus of mice and simian hemorraghic fever virus). Other RNA viruses include the rhabdoviruses, which include lyssaviruses (for example, rabies, Lagos bat virus, Mokola virus, Duvenhage virus and European bat lyssavirus), vesiculoviruses (for example, VSV-Indiana, VSV-New Jersey, VSV-Alagoas, Piry virus, Cocal virus, Maraba virus, Isfahan virus and Chandipura

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virus), and ephemeroviruses (for example, bovine ephemeral fever virus, Adelaide River virus and Berrimah virus). Additional examples of RNA viruses include the filoviruses. These include the Marburg and Ebola viruses (for example, EBOV-Z, EBOV-S, EBOV-IC and EBOV-R).

The paramyxoviruses are also RNA viruses. Examples of these viruses are the rubulaviruses (for example, mumps, parainfluenza virus 5, human parainfluenza virus type 2, Mapuera virus and porcine rubulavirus), avulaviruses (for example, Newcastle disease virus), respoviruses (for example, Sendai virus, human parainfluenza virus type 1 and type 3, bovine parainfluenza virus type 3), henipaviruses (for example, Hendra virus and Nipah virus), morbilloviruses (for example, measles, Cetacean morvilliirus, Canine distemper virus, Peste des-petits-ruminants virus, Phocine distemper virus and Rinderpest virus), pneumoviruses (for example, human respiratory syncytial virus (RSV) A2, B1 and S2, bovine respiratory syncytial virus and pneumonia virus of mice), metapneumoviruses (for example, human metapneumovirus and avian metapneumovirus). Additional paramyxoviruses include Fer-de-Lance virus, Tupaia paramyxovirus, Menangle virus, Tioman virus, Beilong virus, J virus, Mossman virus, Salem virus and Nariva virus.

Additional RNA viruses include the orthomyxoviruses. These viruses include influenza viruses and strains (e.g., influenza A, influenza A strain A/Victoria/3/75, influenza A strain A/Puerto Rico/8/34, influenza A H1N1 (including but not limited to A/WS/33, A/NWS/33 and A/California/04/2009 strains), influenza B, influenza B strain Lee, and influenza C viruses) H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3 and H10N7), as well as avian influenza (for example, strains H5N1, H5N1 Duck/MN/1525/81, H5N2, H7N1, H7N7 and H9N2) thogotoviruses and isaviruses. Orthobunyaviruses (for example, Akabane virus, California encephalitis, Cache Valley virus, Snowshoe hare virus,) nairoviruses (for example, Nairobi sheep virus, Crimean-Congo hemorrhagic fever virus Group and Hughes virus), phleboviruses (for example, Candiru, Punta Toro, Rift Valley Fever, Sandfly Fever, Naples, Toscana, Sicilian and Chagres), and hantaviruses (for example, Hantaan, Dobrava, Seoul, Puumala, Sin Nombre, Bayou, Black Creek Canal, Andes and Thottapalayam) are also RNA viruses. Arenaviruses such as lymphocytic choriomeningitis virus, Lujo virus, Lassa fever virus, Argentine hemorrhagic fever virus, Bolivian hemorrhagic fever virus, Venezuelan hemorrhagic fever virus, SABV and WWAV are also RNA viruses. Borna disease virus is also an RNA virus. Hepatitis D (Delta) virus and hepatitis E are also RNA viruses.

Additional RNA viruses include reoviruses, rotaviruses, birnaviruses, chrysoviruses,

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cystoviruses, hypoviruses partitiviruses and totoviruses. Orbiviruses such as African horse sickness virus, Blue tongue virus, Changuinola virus, Chenuda virus, Chobar GorgeCorriparta virus, epizootic hemorraghic disease virus, equine encephalosis virus, Eubenangee virus, Ieri virus, Great Island virus, Lebombo virus, Orungo virus, Palyam virus, Peruvian Horse Sickness virus, St. Croix River virus, Umatilla virus, Wad Medani virus, Wallal virus, Warrego virus and Wongorr virus are also RNA viruses. Retroviruses include alpharetroviruses (for example, Rous sarcoma virus and avian leukemia virus), betaretroviruses (for example, mouse mammary tumor virus, Mason-Pfizer monkey virus and Jaagsiekte sheep retrovirus), gammaretroviruses (for example, murine leukemia virus and feline leukemia virus, deltraretroviruses (for example, human T cell leukemia viruses (HTLV-1, HTLV-2), bovine leukemia virus, STLV-1 and STLV-2), epsilonretriviruses (for example, Walleye dermal sarcoma virus and Walleye epidermal hyperplasia virus 1), reticuloendotheliosis virus (for example, chicken syncytial virus, lentiviruses (for example, human immunodeficiency virus (HIV) type 1, human immunodeficiency virus (HIV) type 2, human immunodeficiency virus (HIV) type 3, simian immunodeficiency virus, equine infectious anemia virus, feline immunodeficiency virus, caprine arthritis encephalitis virus and Visna maedi virus) and spumaviruses (for example, human foamy virus and feline syncytia-forming virus).

Examples of DNA viruses include polyomaviruses (for example, simian virus 40, simian agent 12, BK virus, JC virus, Merkel Cell polyoma virus, bovine polyoma virus and lymphotrophic papovavirus), papillomaviruses (for example, human papillomavirus, bovine papillomavirus, adenoviruses (for example, adenoviruses A-F, canine adenovirus type I, canined adeovirus type 2), circoviruses (for example, porcine circovirus and beak and feather disease virus (BFDV)), parvoviruses (for example, canine parvovirus), erythroviruses (for example, adeno-associated virus types 1-8), betaparvoviruses, amdoviruses, densoviruses, iteraviruses, brevidensoviruses, pefudensoviruses, herpes viruses 1,2, 3, 4, 5, 6, 7 and 8 (for example, herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, Kaposi's sarcoma associated herpes virus, human herpes virus-6 variant A, human herpes virus-6 variant B and cercophithecine herpes virus 1 (B virus)), poxviruses (for example, smallpox (variola), cowpox, monkeypox, vaccinia, Uasin Gishu, camelpox, psuedocowpox, pigeonpox, horsepox, fowlpox, turkeypox and swinepox), and hepadnaviruses (for example, hepatitis B and hepatitis B-like viruses). Chimeric viruses comprising portions of more than one viral genome are also contemplated herein.

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In some embodiments, the disclosure relates to treating or preventing an infection by viruses, bacteria, fungi, protozoa, and parasites. In some embodiments, the disclosure relates to methods of treating a viral infection comprising administering a compound herein to a subject that is diagnosed with, suspected of, or exhibiting symptoms of a viral infection.

Viruses are infectious agents that can typically replicate inside the living cells of organisms. Virus particles (virions) usually consist of nucleic acids, a protein coat, and in some cases an envelope of lipids that surrounds the protein coat. The shapes of viruses range from simple helical and icosahedral forms to more complex structures. Virally coded protein subunits will self-assemble to form a capsid, generally requiring the presence of the virus genome. Complex viruses can code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid.

Viruses are transmitted by a variety of methods including direct or bodily fluid contact, e.g., blood, tears, semen, preseminal fluid, saliva, milk, vaginal secretions, lesions; droplet contact, fecal-oral contact, or as a result of an animal bite or birth. A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus respectively. A viral genome is either single-stranded or double-stranded. Some viruses contain a genome that is partially double-stranded and partially single-stranded. For viruses with RNA or single-stranded DNA, the strands are said to be either positive-sense (called the plus-strand) or negative-sense (called the minus-strand), depending on whether it is complementary to the viral messenger RNA (mRNA). Positive-sense viral RNA is identical to viral mRNA and thus can be immediately translated by the host cell. Negative-sense viral RNA is complementary to mRNA and thus must be converted to positive-sense RNA by an RNA polymerase before translation. DNA nomenclature is similar to RNA nomenclature, in that the coding strand for the viral mRNA is complementary to it (negative), and the non-coding strand is a copy of it (positive).

Antigenic shift, or reassortment, can result in novel strains. Viruses undergo genetic change by several mechanisms. These include a process called genetic drift where individual bases in the DNA or RNA mutate to other bases. Antigenic shift occurs when there is a major change in the genome of the virus. This can be a result of recombination or reassortment. RNA viruses often exist as quasispecies or swarms of viruses of the same species but with slightly different genome nucleoside sequences.

The genetic material within viruses, and the method by which the material is replicated, vary between different types of viruses. The genome replication of most DNA

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viruses takes place in the nucleus of the cell. If the cell has the appropriate receptor on its surface, these viruses enter the cell by fusion with the cell membrane or by endocytosis. Most DNA viruses are entirely dependent on the host DNA and RNA synthesizing machinery, and RNA processing machinery. Replication usually takes place in the cytoplasm. RNA viruses typically use their own RNA replicase enzymes to create copies of their genomes.

The Baltimore classification of viruses is based on the mechanism of mRNA production. Viruses must generate mRNAs from their genomes to produce proteins and replicate themselves, but different mechanisms are used to achieve this. Viral genomes may be single-stranded (ss) or double-stranded (ds), RNA or DNA, and may or may not use reverse transcriptase (RT). Additionally, ssRNA viruses may be either sense (plus) or antisense (minus). This classification places viruses into seven groups: I, dsDNA viruses (e.g. adenoviruses, herpesviruses, poxviruses); II, ssDNA viruses (plus)sense DNA (e.g. parvoviruses); III, dsRNA viruses (e.g. reoviruses); IV, (plus)ssRNA viruses (plus)sense RNA (e.g. picornaviruses, togaviruses); V, (minus)ssRNA viruses (minus)sense RNA (e.g. orthomyxoviruses, Rhabdoviruses); VI, ssRNA-RT viruses (plus)sense RNA with DNA intermediate in life-cycle (e.g. retroviruses); and VII, dsDNA-RT viruses (e.g. hepadnaviruses).

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS). Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry of the target cell, the viral RNA genome is converted to double-stranded DNA by a virally encoded reverse transcriptase. This viral DNA is then integrated into the cellular DNA by a virally encoded integrase, along with host cellular co-factors. There are two species of HIV. HIV-1 is sometimes termed LAV or HTLV-III.

HIV infects primarily vital cells in the human immune system such as helper T cells (CD4+ T cells), macrophages, and dendritic cells. HIV infection leads to low levels of CD4+ T cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to other viral or bacterial infections. Subjects with HIV typically develop malignancies associated with the progressive failure of the immune system.

The viral envelope is composed of two layers of phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and a HIV protein known as Env. Env

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contains glycoproteinsgp120, and gp41. The RNA genome consists of at structural landmarks (LTR, TAR, RRE, PE, SLIP, CRS, and INS) and nine genes (gag, pol, and env, tat, rev, nef, vif, vpr, vpu, and sometimes a tenth tev, which is a fusion of tat env and rev) encoding 19 proteins. Three of these genes, gag, pol, and env, contain information needed to make the structural proteins for new virus particles. HIV-1 diagnosis is typically done with antibodies in an ELISA, Western blot, orimmunoaffinity assays or by nucleic acid testing (e.g., viral RNA or DNA amplification).

HIV is typically treated with a combination of antiviral agent, e.g., two nucleoside-analogue reverse transcription inhibitors and one non-nucleoside-analogue reverse transcription inhibitor or protease inhibitor. The three-drug combination is commonly known as a triple cocktail. In certain embodiments, the disclosure relates to treating a subject diagnosed with HIV by administering a pharmaceutical composition disclosed herein in combination with two nucleoside-analogue reverse transcription inhibitors and one non-nucleoside-analogue reverse transcription inhibitor or protease inhibitor.

In certain embodiments, the disclosure relates to treating a subject by administering a compound disclosed herein, emtricitabine, tenofovir, and efavirenz. In certain embodiments, the disclosure relates to treating a subject by administering a compound disclosed herein, emtricitabine, tenofovir and raltegravir. In certain embodiments, the disclosure relates to treating a subject by administering a compound disclosed herein, emtricitabine, tenofovir, ritonavir and darunavir. In certain embodiments, the disclosure relates to treating a subject by administering a compound disclosed herein, emtricitabine, tenofovir, ritonavir and atazanavir.

Banana lectin (BanLec or BanLec-1) is one of the predominant proteins in the pulp of ripe bananasand has binding specificity for mannose and mannose-containing oligosaccharides. BanLec binds to the HIV-1 envelope protein gp120. In certain embodiments, the disclosure relates to treating viral infections, such as HIV, by administering a compound disclosed herein in combination with a banana lectin.

The hepatitis C virus is a single-stranded, positive sense RNA virus. It is the only known member of the hepacivirus genus in the family Flaviviridae. There are six major genotypes of the hepatitis C virus, which are indicated numerically. The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell, and further encased in a lipid envelope. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope. The genome consists of a single open reading frame translated to produce a single protein. This large pre-protein is later cut by cellular and viral

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proteases into smaller proteins that allow viral replication within the host cell, or assemble into the mature viral particles, e.g., E1, E2, NS2, NS3, NS4, NS4A, NS4B, NS5, NS5A, and NS5B.

HCV leads to inflammation of the liver, and chronic infection leads to cirrhosis. Most people with hepatitis C infection have the chronic form. Diagnosis of HCV can occur via nucleic acid analysis of the 5′-noncoding region. ELISA assay may be performed to detect hepatitis C antibodies and RNA assays to determine viral load. Subjects infected with HCV may exhibit symptoms of abdominal pain, ascites, dark urine, fatigue, generalized itching, jaundice, fever, nausea, pale or clay-colored stools and vomiting.

Therapeutic agents in some cases may suppress the virus for a long period of time. Typical medications are a combination of interferon alpha and ribavirin. Subjects may receive injections of pegylated interferon alpha. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6). In certain embodiments, the disclosure relates to treating a subject with HCV by administering a compound disclosed herein to a subject exhibiting symptoms or diagnosed with HCV. In certain embodiments, the compound is administered in combination with interferon alpha and another antiviral agent such as ribavirin, and/or a protease inhibitor such as telaprevir or boceprevir. In certain embodiments, the subject is diagnosed with genotype 2, 3, 5, or 6. In other embodiments, the subject is diagnosed with genotype 1 or 4.

In certain embodiments, the subject is diagnosed to have a virus by nucleic acid detection or viral antigen detection. Cytomegalovirus (CMV) belongs to the Betaherpesvirinae subfamily of Herpesviridae. In humans it is commonly known as HCMV or Human Herpesvirus 5 (HHV-5). Herpesviruses typically share a characteristic ability to remain latent within the body over long periods. HCMV infection may be life threatening for patients who are immunocompromised. In certain embodiments, the disclosure relates to methods of treating a subject diagnosed with cytomegalovirus or preventing a cytomegalovirus infection by administration of a compound disclosed herein. In certain embodiments, the subject is immunocompromised. In typical embodiments, the subject is an organ transplant recipient, undergoing hemodialysis, diagnosed with cancer, receiving an immunosuppressive drug, and/or diagnosed with an HIV-infection. In certain embodiments, the subject may be diagnosed with cytomegalovirus hepatitis, the cause of fulminant liver failure, cytomegalovirus retinitis (inflammation of the retina, may be detected by ophthalmoscopy), cytomegalovirus colitis (inflammation of the large bowel), cytomegalovirus pneumonitis, cytomegalovirus esophagitis, cytomegalovirus mononucleosis,

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polyradiculopathy, transverse myelitis, and subacute encephalitis. In certain embodiments, a compound disclosed herein is administered in combination with an antiviral agent such as valganciclovir or ganciclovir. In certain embodiments, the subject undergoes regular serological monitoring.

HCMV infections of a pregnant subject may lead to congenital abnormalities. Congenital HCMV infection occurs when the mother suffers a primary infection (or reactivation) during pregnancy. In certain embodiments, the disclosure relates to methods of treating a pregnant subject diagnosed with cytomegalovirus or preventing a cytomegalovirus infection in a subject at risk for, attempting to become, or currently pregnant by administering compound disclosed herein.

Subjects who have been infected with CMV typically develop antibodies to the virus. A number of laboratory tests that detect these antibodies to CMV have been developed. The virus may be cultured from specimens obtained from urine, throat swabs, bronchial lavages and tissue samples to detect active infection. One may monitor the viral load of CMV-infected subjects using PCR. CMV pp65 antigenemia test is an immunoaffinity based assay for identifying the pp65 protein of cytomegalovirus in peripheral blood leukocytes. CMV should be suspected if a patient has symptoms of infectious mononucleosis but has negative test results for mononucleosis and Epstein-Barr virus, or if they show signs of hepatitis, but have negative test results for hepatitis A, B, and C. A virus culture can be performed at any time the subject is symptomatic. Laboratory testing for antibody to CMV can be performed to determine if a subject has already had a CMV infection.

The enzyme-linked immunosorbent assay (or ELISA) is the most commonly available serologic test for measuring antibody to CMV. The result can be used to determine if acute infection, prior infection, or passively acquired maternal antibody in an infant is present. Other tests include various fluorescence assays, indirect hemagglutination, (PCR), and latex agglutination. An ELISA technique for CMV-specific IgM is available.

Hepatitis B virus is a hepadnavirus. The virus particle, (virion) consists of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein. The genome of HBV is made of circular DNA, but the DNA is not fully double-stranded. One end of the strand is linked to the viral DNA polymerase. The virus replicates through an RNA intermediate form by reverse transcription. Replication typically takes place in the liver where it causes inflammation (hepatitis). The virus spreads to the blood where virus-specific proteins and their corresponding antibodies are found in infected people. Blood tests for these proteins and antibodies are used to diagnose the infection.

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Hepatitis B virus gains entry into the cell by endocytosis. Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host chaperones. The partially double stranded viral DNA is then made fully double stranded and transformed into covalently closed circular DNA (cccDNA) that serves as a template for transcription of viral mRNAs. The virus is divided into four major serotypes (adr, adw, ayr, ayw) based on antigenic epitopes presented on its envelope proteins, and into eight genotypes (A-H) according to overall nucleotide sequence variation of the genome.

The hepatitis B surface antigen (HBsAg) is typically used to screen for the presence of this infection. It is the first detectable viral antigen to appear during infection. However, early in an infection, this antigen may not be present and it may be undetectable later in the infection if it is being cleared by the host. The infectious virion contains an inner "core particle" enclosing viral genome. The icosahedral core particle is made of core protein, alternatively known as hepatitis B core antigen, or HBcAg. IgM antibodies to the hepatitis B core antigen (anti-HBc IgM) may be used as a serological marker. Hepatitis B e antigen (HBeAg) may appear. The presence of HBeAg in the serum of the host is associated with high rates of viral replication. Certain variants of the hepatitis B virus do not produce the 'e' antigen,

If the host is able to clear the infection, typically the HBsAg will become undetectable and will be followed by IgG antibodies to the hepatitis B surface antigen and core antigen, (anti-HBs and anti HBc IgG). The time between the removal of the HBsAg and the appearance of anti-HBs is called the window period. A person negative for HBsAg but positive for anti-HBs has either cleared an infection or has been vaccinated previously. Individuals who remain HBsAg positive for at least six months are considered to be hepatitis B carriers. Carriers of the virus may have chronic hepatitis B, which would be reflected by elevated serum alanine aminotransferase levels and inflammation of the liver that may be identified by biopsy. Nucleic acid (PCR) tests have been developed to detect and measure the amount of HBV DNA in clinical specimens.

Acute infection with hepatitis B virus is associated with acute viral hepatitis. Acute viral hepatitis typically begins with symptoms of general ill health, loss of appetite, nausea, vomiting, body aches, mild fever, dark urine, and then progresses to development of jaundice. Chronic infection with hepatitis B virus may be either asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), possibly leading to cirrhosis. Having chronic hepatitis B infection increases the incidence of hepatocellular carcinoma (liver cancer).

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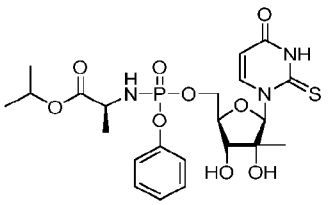
During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. The adaptive immune response, particularly virus-specific cytotoxic T lymphocytes (CTLs), contributes to most of the liver injury associated with HBV infection. By killing infected cells and by producing antiviral cytokines capable of purging HBV from viable hepatocytes, CTLs eliminate the virus. Although liver damage is initiated and mediated by the CTLs, antigen-nonspecific inflammatory cells can worsen CTL-induced immunopathology, and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver.

Therapeutic agents can stop the virus from replicating, thus minimizing liver damage. In certain embodiments, the disclosure relates to methods of treating a subject diagnosed with HBV by administering a compound disclosed herein disclosed herein. In certain embodiments, the subject is immunocompromised. In certain embodiments, the compound is administered in combination with another antiviral agent such as lamivudine, adefovir, tenofovir, telbivudine, and entecavir, and/or immune system modulators interferon alpha-2a and pegylated interferon alpha-2a (Pegasys). In certain embodiments, the disclosure relates to preventing an HBV infection in an immunocompromised subject at risk of infection by administering a pharmaceutical composition disclosed herein and optionally one or more antiviral agents. In certain embodiments, the subject is at risk of an infection because the sexual partner of the subject is diagnosed with HBV.

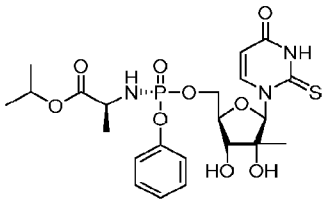
Compounds of the present disclosure can be administered in combination with a second antiviral agent such as disoxaril, pleconaril, pirodavir, vapendavir, pocapavir, abacavir, acyclovir, acyclovir, adefovir, amantadine, amprenavir, ampligen, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, imunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, lamivudine, lopinavir, loviride, maraviroc, moroxydine, methisazone, nelfinavir, nevirapine, nexavir, oseltamivir, peginterferon alfa-2a, penciclovir, peramivir, pleconaril, podophyllotoxin , raltegravir, ribavirin, rimantadine, ritonavir, pyramidine, saquinavir, sofosbovir, stavudine, telaprevir, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine zalcitabine, zanamivir, or zidovudine and combinations thereof.

In a particular embodiment, one of the following compounds is administered together with a second antiviral agent mentioned above:

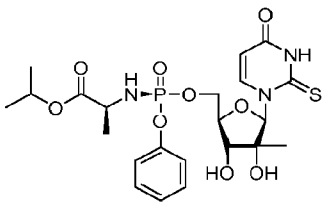
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Methods for treating enterovirus and HCV infection in a subject are also provided. The methods comprise administering the compounds of this disclosure to provide at least two direct acting antiviral agents (DAAs) with or without ribavirin for a duration of no more than twelve weeks, or for another duration as set forth herein. In one embodiment, the duration of the treatment is no more than twelve weeks. In another embodiment, the duration of the treatment is no more than eight weeks. Preferably, the two or more direct acting antiviral agents (DAAs), with or without ribavirin, are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in a subject. The subject is not administered interferon during the treatment regimen. Put another way, in one embodiment, the methods exclude the administration of interferon to the subject, thereby avoiding the side effects associated with interferon. In some embodiments, the methods further comprise administering an inhibitor of cytochrome P-450 (such as ritonavir) to the subject to improve the pharmacokinetics or bioavailability of one or more of the DAAs.

As another aspect, methods for treating enterovirus and HCV infection in a subject are provided. The methods comprise administering (a) protease inhibitor, (b) at least one polymerase inhibitor, wherein at least one is a polymerase of this disclosure and combinations thereof, with or without (c) ribavirin and/or (d) an inhibitor or cytochrome P-450 to the subject for a duration of no more than twelve weeks, or for another duration as set forth herein (e.g., the treatment regimen can last a duration of for no more than 8 weeks). Preferably, the compounds are administered in amounts effective to provide high rates of SVR or another measure of effectiveness in the subject. As non-limiting examples, the compounds can be co-formulated and administered once daily, and the treatment regimen preferably lasts for eight weeks or six weeks.

As still another aspect, methods for treating a population of subjects having enterovirus or HCV infection are provided. The methods comprise administering at least two DAAs, wherein one of the DAAs is a compound of this disclosure, with or without ribavirin, to the subjects for a duration of no more than 12 or 8 or 6 weeks. Preferably, the at least two DAAs are administered to the subjects in amounts effective to result in SVR or another

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measure of effectiveness in at least about 70% of the population, preferably at least 90% of the population.

In the foregoing methods as well as methods described herein below, the DAAs can be selected from the group consisting of protease inhibitors, nucleoside or nucleotide polymerase inhibitors (one of which is provided herein), non-nucleoside polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, and combinations of any of the foregoing. For example, in some embodiments, the DAAs used in the present methods comprise or consist of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor provided herein.

At least one of the enterovirus and/or HCV polymerase inhibitors is one of the compounds of this disclosure (described herein). By way of example, compounds of this disclosure can be administered a total daily dose of from about 100 mg to about 250 mg, or administered once daily at a dose of from about 150 mg to about 250 mg.

In some embodiments, the at least two DAAs comprise at least one enterovirus and/or HCV polymerase inhibitors of this disclosure and at least one NS5A inhibitor. By way of example, the polymerase inhibitor of this disclosure can be administered at a total daily dosage from about 100 mg to about 250 mg, and the NS5A inhibitor can be administered in a total daily dose from about 25 mg to about 200 mg. Ritonavir (or another cytochrome P-450 3A4 inhibitor) can be co-administered with to improve the pharmacokinetics and bioavailability of the compounds.

In the foregoing methods as well as methods described herein, the DAAs with or without ribavirin can be administered in any effective dosing schemes and/or frequencies, for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered at lease once a day, at least twice a day, or at least three times a day. Likewise, the ribavirin can be administered at least once a day, at least twice a day, or at least three times a day, either separately or in combination with one of more of the DAAs. In some preferred embodiments, the compounds are administered once daily.

In some aspects, the present technology provides a method for treating enterovirus and/or HCV infection comprising administering to a subject in need thereof at least two DAAs with or without ribavirin for a duration of no more than twelve or eight or six weeks, wherein the subject is not administered with interferon during said duration. In some aspects, the at least two DAAs with or without ribavirin are administered in an amount effective to

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result in SVR. Some methods further comprise administering an inhibitor of cytochrome P450 to the subject. In some aspects, the duration is no more than eight weeks.

In yet another aspect, the at least two direct acting antiviral agents comprises a drug combination selected from the group consisting of: a compound of this disclosure, with one or more of disoxaril, pleconaril, pirodavir, vapendavir, pocapavir, ABT-450 and/or ABT-267, and/or ABT-333; a novel compound of this disclosure with a compound disclosed in any of US 2010/0144608; US 61/339,964; US 2011/0312973; WO 2009/039127; US 2010/0317568; 2012/151158; US 2012/0172290; WO 2012/092411; WO 2012/087833; WO 2012/083170; WO 2009/039135; US 2012/0115918; WO 2012/051361; WO 2012/009699; WO 2011/156337; US 2011/0207699; WO 2010/075376; US 7,9105,95; WO 2010/120935; WO 2010/111437; WO 2010/111436; US 2010/0168384 or US 2004/0167123; a compound of this disclosure with one or more of Simeprevir, and/or GSK805; a compound of this disclosure with one or more of Asunaprevir, and/or Daclastavir, and/or BMS-325; a compound of this disclosure with one or more of GS-9451, and/or Ledisasvir and/or Sofosbuvir, and/or GS-9669; a compound of this disclosure with one or more of ACH-2684, and/or ACH-3102, and/or ACH-3422; a compound of this disclosure with one or more of Boceprevir, and/or MK-8742; a compound of this disclosure with one or more of Faldaprevir and/or Deleobuvir; a compound of this disclosure with PPI-668; a compound of this disclosure with one or more of telaprevir and/or VX-135; a compound of this disclosure with one or more of Samatasvir and/or IDX-437; a compound of this disclosure with PSI-7977 and/or PSI-938, a compound of this disclosure with BMS-790052 and/or BMS-650032; a compound of this disclosure with GS-5885 and/or GS-9451; a compound of this disclosure with GS-5885, GS-9190 and/or GS-9451; a compound of this disclosure in combination with BI-201335 and/or BI-27127; a compound of this disclosure in combination with telaprevir and/or VX-222; a compound of this disclosure combination with PSI-7977 and/or TMC-435; and a compound of this disclosure in combination with danoprevir and/or R7128.

In yet another aspect, the at least two direct acting antiviral agents comprises a compound of this disclosure in a combination of PSI-7977 and/or BMS-790052 (daclatasvir). In yet another aspect, the at least two direct acting antiviral agents comprises a compound of this disclosure in a combination of PSI-7977 and/or BMS-650032 (asunaprevir). In still another aspect, the at least direct acting antiviral agents comprise a compound of this disclosure in combination with PSI-7977, BMS-650032 (asunaprevir) and/or BMS-790052 (daclatasvir). The compounds of this disclosure can be either added to these combinations or used to replace the listed polymerase.

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In another aspect, the present technology features a combination of at least two DAAs for use in treating enterovirus and/or HCV infection, wherein the duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5. 4, or 3 weeks). The treatment comprises administering the at least two DAAs to a subject infected with HCV. The duration of the treatment can be 12 weeks and also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment can include administering ribavirin but does not include administering interferon. The treatment may also include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The at least two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and another DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype la or lb. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder, a partial responder or a relapser), or not a candidate for interferon treatment.

In another aspect, the present technology features a combination of at least two DAAs for use in treating enterovirus and/or HCV infection, wherein said combination comprises a compound of this disclosure, and in particular EIDD-2023 and prodrugs thereof, in combination with compounds selected from:

a combination of PSI-7977 and/or PSI-938;

a combination of BMS-790052 and/or BMS-650032;

a combination of GS-5885 and/or GS-9451;

a combination of GS-5885, GS-9190 and/or GS-9451;

a combination of BI-201335 and/or BI-27127;

at combination of telaprevir and/or VX-222;

combination of PSI-7977 and/or TMC -435;

a combination of danoprevir and/or R7128;

a combination of ABT-450 and/or ABT-267 and/or ABT-333;

a combination of vapendavir and/or disoxaril;

a combination of vapendavir and/or pleconaril;

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a combination of vapendavir and/or pirodavir;
a combination of vapendavir/or and pocapavir;
a combination of vapendatir/and or one or more of the following: disoxaril, pleconaril, pirodavir, and pirodavir;
one or more of the following protease inhibitors: ABT450, Simeprevir, Asunaprevir, GS-9451, ACH-2684, Boceprevir, MK-5172, Faldaprevir, and Telaprevir;
one or more of the following NS5A inhibitors: ABT-267, GSK805, Daclastavir, Dedipasvir, GS-5816, ACH-3102, MK-8742, PPI-668, and Samatasvir;
one or more of the following Non-nuc NS5B Inhibitors: ABT-333, TMC055, BMS-325, GS-9669, and Deleobuvir.

In one embodiment, the compound of the present disclosure used in the combination therapies above is EIDD-1911, EIDD-2023, or EIDD-2024. In a currently preferred embodiment, the compound of the present disclosure used in the combination therapies above is EIDD-2023. One or more of EIDD-1911, EIDD-2023 and EIDD-2024 can be combined with one or more of disoxaril, pleconaril, pirodavir, vapendavir, pocapavir, ABT-450, ABT-267 and/or ABT-333 and/or a compound disclosed in US 2010/0144608; US 61/339,964; US 2011/0312973; WO 2009/039127; US 2010/0317568; 2012/151158; US 2012/0172290; WO 2012/092411; WO 2012/087833; WO 2012/083170; WO 2009/039135; US 2012/0115918; WO 2012/051361; WO 2012/009699; WO 2011/156337; US 2011/0207699; WO 2010/075376; US 7,9105,95; WO 2010/120935; WO 2010/111437; WO 2010/111436; US 2010/0168384 or US 2004/0167123.

In yet another aspect, the present technology features a combination of at least two DAAs for use in treating enterovirus or HCV infection, wherein said combination comprises a compound of this disclosure in a combination selected from:
ABT-450, and/or ABT-267 and/or ABT-333 and/or a compound disclosed in US 2010/0144608; US 61/339,964; US 2011/0312973; WO 2009/039127; US 2010/0317568; 2012/151158; US 2012/0172290; WO 2012/092411; WO 2012/087833; WO 2012/083170; WO 2009/039135; US 2012/0115918; WO 2012/051361; WO 2012/009699; WO 2011/156337; US 2011/0207699; WO 2010/075376; US 7,9105,95; WO 2010/120935; WO 2010/111437; WO 2010/111436; US 2010/0168384 or US 2004/0167123;
a combination of PSI-797 and/or BMS-790052;
a combination of PSI-7977 and/or BMS-650032;
a combination of PSI-7977, BMS-790052 and/or BMS-650032;
a combination of INX-189 and/or BMS-790052;

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combination of INX-189 and/or BMS-650032; or

a combination of INX-189, BMS-790052 and/or BMS-650032.

In still another aspect, the present technology features PSI-7977, or a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination of a compound of this disclosure and a compound selected from:

a combination of mericitabine and/or danoprevir;

a combination of daclatasvir and/or BMS-791325; and

a combination of PSI-7977 and/or GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV or enterovirus.

In still another aspect, the present technology features a compound of this disclosure with PSI-7977, or a combination of at least two DAAs, for use in treating HCV or enterovirus infection, wherein said combination comprises a combination selected from:

a combination of mericitabine and/or danoprevir;

combination of INX-189, daclatasvir and/or BMS-791325; and

a combination of PSI-7977 and/or GS-5885.

The treatment comprises administering PSI-7977 or the DAA combination to a subject infected with HCV.

In still another aspect, the present technology features a combination of at least two DAAs, for use in treating HCV infection, wherein said combination comprises a combination selected from a compound of this disclosure and:

a combination of tegobuvir and/or GS-9256;

a combination of BMS-791325, asunaprevir and/or daclatasvir; and

a combination of TMC-435 and/or daclatasvir.

The treatment comprises administering the DAA combination to a subject infected with HCV.

In yet another aspect, the present technology features a combination of a compound of this disclosure with PSI-7977 and/or BMS-790052 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV or enterovirus.

In yet another aspect, the present technology features a combination of a compound of this disclosure with PSI-7977 and/or TMC-435 for use in treating HCV infection or enterovirus.

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In yet another aspect, the present technology features a combination of a compound of this disclosure with danoprevir and/or mercitabine for use in treating HCV infection enterovirus.

In yet another aspect, the present technology features a combination of a compound of this disclosure with daclatasvir and/or BMS-791325 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV or enterovirus.

In yet another aspect, the present technology features a combination of a compound of this disclosure with PSI-7977 and/or GS-5885 for use in treating HCV infection. The treatment comprises administering the DAA combination to a subject infected with HCV or enterovirus.

The duration of the treatment regimens in some aspects is no more than sixteen weeks (e.g., the duration being 16 weeks; or the duration being 14, 12 or 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 weeks). The treatment includes administering ribavirin but does not include administering interferon. The treatment may include administering ritonavir or another CYP3A4 inhibitor (e.g., cobicistat) if one of the DAAs requires pharmacokinetic enhancement. The two DAAs can be administered concurrently or sequentially. For example, one DAA can be administered once daily, and the other DAA can be administered twice daily. For another example, the two DAAs are administered once daily. For yet another example, the two DAAs are co-formulated in a single composition and administered concurrently (e.g., once daily). As a non-limiting example, the patient being treated can be infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient can be infected with HCV genotype 2 or 3. As yet another non-limiting example, the patient can be a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responded (e.g., a null responder), or not a candidate for interferon treatment.

In yet another embodiment of this aspect of the disclosure, the at least two DAAs comprise a HCV or enterovirus protease inhibitor and a HCV polymerase inhibitor of this disclosure. The treatment can last, for example and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11, or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype 1a. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

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In yet another embodiment of this aspect of the disclosure, the at least two DAAs comprise a compound of this disclosure with an HCV or enterovirus protease inhibitor and a non-nucleoside or non-nucleotide HCV polymerase inhibitor. The treatment can last, for example, and without limitation, for no more than 12 weeks, such as 8, 9, 10, 11 or 12 weeks. Preferably, the treatment lasts for 12 weeks. The treatment can also last for 8 weeks. The subject being treated can be, for example, a treatment-naïve patient. The subject can also be a treatment-experienced patient, or an interferon non-responder (e.g., a null responder). Preferably, the subject being treated is infected with HCV genotype 1, e.g., HCV genotype la. As another non-limiting example, the subject being treatment is infected with HCV genotype 3.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure with an enterovirus or HCV protease inhibitor and a HCV NS5A inhibitor.

In yet another embodiment of this aspect of the disclosure, the at least two DAAs comprise a HCV polymerase inhibitor of this disclosure and a HCV NS5A inhibitor.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure and a HCV non-nucleoside or non-nucleotide polymerase inhibitor and a HCV NS5A inhibitor.

In yet another embodiment of this aspect of the disclosure, the DAAs can comprise a HCV nucleoside or nucleotide polymerase inhibitor of this disclosure and a HCV NS5A inhibitor.

In yet another embodiment of this aspect of the disclosure, the at least two DAAs comprise a compound of this disclosure with PSI-7977 and/or TMC-435.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure with PSI-7977 and/or daclatasvir.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure with PSI-7977 and/or GS-5885.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure with mericitabine and/or danoprevir.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure with BMS-790052 and/or BMS-650032.

In yet another embodiment of this aspect of the disclosure, the DAAs comprise a compound of this disclosure and INX-189, daclatasvir and/or BMS-791325.

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A treatment regimen of the present technology generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described herein generally does not include any subsequent interferon-containing treatment.

As a further aspect, methods for treating enterovirus in a subject are provided. The methods comprise administering nucleoside or nucleotide compounds of this disclosure. In addition, the methods comprise administering nucleoside or nucleotide compounds of this disclosure in combination with a second antiviral agent active against enteroviruses. In certain embodiments, the disclosure relates to methods of treating a subject diagnosed with an infection caused by enterovirus or preventing an enterovirus infection by administration of a compound or composition disclosed herein. In certain embodiments, the subject is immune-compromised, immune-deficient or immune-suppressed (i.e. a subject in whom any part of the immune system is not working normally, or is working sub-normally, in other words in whom any part of the immune response, or an immune activity is reduced or impaired, whether due to disease or clinical intervention or other treatment, or in any way). In certain embodiments, the nucleoside or nucleotide compounds of this disclosure can be combined with a second antiviral agent as provided in Anasir et al., J Biomed Sci (2021) 28, 10:5-12. Anasir et al. provide a review of antiviral agents for treating enteroviruses, the disclosure of which is incorporated herein by reference in its entirety.

For example, the nucleoside or nucleotide compounds of this disclosure can be combined with a drug that hinder EV infections by targeting their capsids. There are three regions on the EV capsid that have been identified to be viable targets. The first is the VP1 hydrophobic pocket occupied by the pocket factor. Many direct-acting antivirals targeting this pocket have been identified. These compounds dislodge the pocket factor and bind to the hydrophobic pocket to stabilize the capsid in a rigid and compressed form. This prevents the formation of expanded A particles that is required for genome uncoating. Additionally, there are evidence that demonstrated the binding of compounds to this pocket hindered EV attachment to host cells. Five compounds that have been evaluated in phase I and II clinical trials were disoxaril, pleconaril, pirodavir, vapendavir and pocapavir. Despite their promising in vitro potencies, the majority of these inhibitors demonstrated insufficient efficacy and unwanted side effects at doses tested in clinical trials. The unwanted side effects include asymptomatic crystalluria seen in patients receiving disoxaril and the induction of cytochrome P-450 3A (CYP3A4) enzymes by pleconaril that led to menstrual irregularities in pleconaril-treated women taking oral contraceptives. In specific examples, the nucleoside or

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nucleotide compounds of this disclosure can be combined with a second antiviral agent selected from disoxaril, pleconaril, pirodavir, vapendavir and pocapavir for treating infections caused by enteroviruses.

In addition to the capsid binders, the nucleoside or nucleotide compounds of this disclosure can be combined with 3C protease inhibitors such as rupintrivir and its analog AG7404 for treating infections caused by enteroviruses. The 3C proteases are essential for cleaving the polyprotein precursor into structural proteins and non-structural proteins responsible for viral replication. However, when administered alone, these inhibitors failed to show significant beneficial effects in clinical trials involving RV. Enviroxime is another compound that has been shown to inhibit EV infections by targeting the viral proteins 3A and/or 3AB to prevent the formation of the replication complex. Despite showing potent EV replication inhibition in vitro, its clinical development was halted due to gastrointestinal side effects and the lack of therapeutic effect when administered alone at the doses tested. In specific examples, the nucleoside or nucleotide compounds of this disclosure can be combined with a second antiviral agent selected from rupintrivir, its analog AG7404, or enviroxime for treating infections caused by enteroviruses.

In further embodiments, the nucleoside or nucleotide compounds of this disclosure can be combined with compounds that target the VP1 hydrophobic pocket of enteroviruses. For instance, Kim et al. (J. Med. Chem. 2017, 60, 13, 5472–5492) identified a series of benzothiophene derivatives and analogues with potent antiviral activities against RV-A and RV-B strains. In particular, compound 6g inhibited RV-A21, RV-A71, RV-B14, and PV3. In addition, PR66 which is an imidazolidinone derivative was found to inhibit the uncoating process of EV-A71 by interacting with the VP1 hydrophobic pocket. Compounds ALD and NLD have also been shown to inhibit a wide range of other EVs including CV-A9, CV-A16, CV-A21, CV-B3, PV1-3, RV-2 and RV-14, acting as VP1 hydrophobic pocket binders. In specific examples, the nucleoside or nucleotide compounds of this disclosure can be combined with a second antiviral agent selected from benzothiophene derivatives, PR66, or compounds ALD or NLD for treating infections caused by enteroviruses.

In certain embodiments, the nucleoside or nucleotide compounds of this disclosure can be combined with a drug that target the fivefold axis of the capsid in enteroviruses. Many of the EV-A members such as CV-A6, CV-A16 and EV-A71 and EV-B members like CV-A9 and ECHO5 possess the positively charged fivefold axis that is responsible for viral attachment to host cell receptors including PSGL1 and heparan sulfate. SCARB2 was demonstrated to be the main attachment and uncoating receptor for EV-A viruses, thus, the

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compounds and compositions of this disclosure can be combined with an antiviral agent capable of inhibiting the binding of EVs to SCARB2.

Various compound series have been identified to target the fivefold axis. One of the compounds, suramin, has been shown to inhibit several EV-A viruses including CV-A2, 3, 10, 12, and 16, and some EV-B viruses such as CV-A9, ECHO20 and ECHO25. Suramin and its derivatives such as NF449 were proposed to interact with the fivefold axis of the capsid to prevent EV association with PSGL1 and heparan sulfate. In vivo studies revealed that suramin significantly reduced mortality in mice challenged with a lethal dose of EV-A71 and decreased the peak viral load in adult rhesus monkeys. Screening of sulfonated azo dyes against EVs has shown that the majority of the dyes exhibited in vitro inhibitory effects on the infectivity of EV-A71. In particular, brilliant black BN (E151) inhibited three EVs which are EV-A71, CV-A6 and CV-A16. It had the highest efficacy in blocking virus entry and it protected AG129 mice against EV-A71 lethal challenge. However, the in vitro potency of E151 is low with IC_{50} values ranging from 2.39 to 28.12 μM for various EV-A71 strains. E151 was identified to interact with the fivefold axis of the capsid and inhibited PSGL1 and cyclophilin A (CyP-A)-mediated EV-A71 entry into host cells. Furthermore, the attachment of EV-A71 to host cells via PSGL1 and heparan sulfate was reported to be inhibited by a series of tryptophan dendrimers that target the fivefold axis of EV capsid. These dendrimers contain different central scaffolds and multiple tryptophan groups that are linked to the dendrimer branches through an amino group. A consensus compound named dendrimer 12 that was synthesized according to the structure–activity relationship analysis of the series was found to inhibit a large panel of EV-A71 clinical isolates with high potency in the nM to pM range. The anti-EV activities of heparan sulfate mimetics have also been evaluated since a number of in vivo studies in mice and monkeys have demonstrated heparan sulfate could specifically interact with the key residue VP1-145G in EV-A71 to inhibit the virus. The mimetics including heparin, heparan sulfate and pentosan polysulfate were shown to exhibit antiviral actions against EV-A71 with low potency in the μM range. In addition, shorter heparan sulfate-based fragments exhibited inhibitory actions against EV-A71 infection. Rosmarinic acid (RA) which is a compound from herbal medicine *Salvia miltiorrhiza* (Danshen) was found to target this region as well. Similar to most of the compounds targeting this region, RA inhibited various EV-A71 genotypes with IC_{50} values in the μM range. In specific examples, the nucleoside or nucleotide compounds of this disclosure can be combined with a second antiviral agent selected from suramin and its derivatives such as NF449, sulfonated azo dyes such as brilliant black BN (E151), tryptophan

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dendrimers, heparan sulfate mimetics including heparin, heparan sulfate and pentosan polysulfate, rosmarinic acid (RA), or combinations thereof for treating infections caused by enteroviruses.

In certain embodiments, the nucleoside or nucleotide compounds of this disclosure can be combined with a drug that target the VP1–VP3 interprotomer binding pocket of enteroviruses. A druggable pocket within the conserved VP1–VP3 interprotomer interface of the viral capsid has been identified. 4-Dimethylamino benzoic acid (compound 12) displayed weak potency with an EC_{50} value of 9 μM while its analogue compound 1 displayed antiviral activity with an EC_{50} of 2.6 μM against CV-B3. These compounds were identified to be highly specific against CV-B viruses. A benzenesulfonamide derivative, compound 17, was also identified as an inhibitor of CV-B3, CV-B1, CV-B6, CV-B4, CV-B5 and CV-A9. Structural study of compound 17 interaction with the viral capsid revealed that the compound binds to a pocket formed by two VP1 units (amino acids 73, 75–78, 155–157,159–160, 219, and 234) and one VP3 unit (amino acids 233–236) at the interface of an interprotomer. Sequence analysis revealed that the pocket is reasonably conserved across the EV-B group, with 7 of 16 amino acids being identical across the eight CV-B viruses including CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6, CV-A9 and ECHO11. Furthermore, the binding site is also conserved across a panel of EVs, in particular the amino acids Arg219 and Arg234 of CV-B3.

As described herein, the nucleoside or nucleotide compounds of this disclosure can be used in combination with a second antiviral agent described herein. Of particular importance is the combination of the nucleoside or nucleotide compounds compounds herein with failed clinical compounds including disoxaril, pleconaril, pirodavir, vapendavir and pocapavir. More specifically the compounds of the subject disclosure can be combined with vapendavir. In one perfered embodiment EIDD-2023, or an alternate prodrug thereof, is combined with vapendavir. These combinations can be co-formulated or administered separately as provided herein.

Particular advantage in combination therapy is that the compounds, compositions, combinations of this disclosure are viral polymerase inhibitors, including nucleoside and nucleotide viral polymerase inhibitors which have a high barrier to viral resistance. Compounds that target the viral capsid, such as vapendivir, typically have a low barrier to viral resistance. Thus, the combination of the nucleoside/tide inhibitors, including EIDD-2023, EIDD-2024, EIDD-1911, and related prodrugs, with capsid inhibitors, such as vapendavir are particularly advantageous in treating enterovirus, as well as other viral familes

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that overlap between the compounds provided herein, such as EIDD-2023, EIDD-2024, EIDD-1911, and related prodrugs, and capsid inhibitors, such as vapendavir and other compounds.

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

Formulations

Pharmaceutical compositions disclosed herein may be in the form of pharmaceutically acceptable salts, 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 compounds of the disclosure contain an acidic group as well as a basic group, the compounds of the disclosure may also form internal salts, and such compounds are within the scope of the disclosure. When a compound of the disclosure contains a hydrogen-donating heteroatom (e.g., NH), the disclosure also covers salts and/or isomers formed by the transfer of the hydrogen atom to a basic group or atom within the molecule.

Pharmaceutically acceptable salts of the 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

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phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases that 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 may 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.

The compounds described herein may be administered in the form of prodrugs. A prodrug can include a covalently bonded carrier that 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 mammalian 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 a prodrug are known, for example, in 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. It has been shown that ester prodrugs are readily degraded in the body to release the corresponding alcohol. See e.g., Imai, Drug Metab Pharmacokinet. (2006) 21(3):173-85, entitled "Human carboxylesterase isozymes: catalytic properties and rational drug design."

Pharmaceutical compositions for use in the present disclosure typically comprise an effective amount of a compound and a suitable pharmaceutical acceptable carrier. The preparations may 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 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.

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Generally, for pharmaceutical use, the compounds may be formulated as a pharmaceutical preparation comprising at least one compound and at least one pharmaceutically acceptable carrier, diluent or excipient, and optionally one or more further pharmaceutically active compounds.

The pharmaceutical preparations of the disclosure are preferably in a unit dosage form, and may 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 may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 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 between 0.01 to 1000 mg per kilogram body weight of the patient per day, more often between 0.1 and 500 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses. The effective amount can also be administered as a set dose, such as between 1 and 1600 mg, including for example 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600 mg. These combinations of active ingredients can be coformulated with a similar or different amount in a single pill, for example, EIDD-2023 and vapendavir. The amount(s) to be administered, the route of administration and the further treatment regimen may 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 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.

For an oral administration form, the compound can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary

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methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, cornstarch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

As described herein, compositions and methods using a combination therapy containing a nucleoside or nucleotide compound described herein and a second antiviral agent, such as disoxaril, pleconaril, pirodavir, vapendavir pocapavir, or combinations thereof are provided. Typically, when the nucleoside or nucleotide compound described herein is used in combination with a second antiviral agent, the dose of each antiviral agent can be either the same as or less than that when the antiviral agent is used alone. Thus, the combination therapy can result in synergy and/or reduced side effects of the co-administered antiviral agents compared to their administration alone. Appropriate doses will be readily appreciated by those skilled in the art.

The formulations containing the nucleoside or nucleotide compound described herein and a second antiviral agent, can be provided separately in the combination or provided in a single composition. If provided and administered separately, the combined compounds can be manufactured and/or formulated by the same or different manufacturers. The combination partners may thus be entirely separate pharmaceutical dosage forms or pharmaceutical compositions that are also sold independently of each other. For example, the two antiviral partners may be prepared in a manner known per se and are suitable for enteral, such as oral or rectal, topical and parenteral administration to subject in need thereof. In embodiments, instructions for their combined use are provided: (i) prior to release to physicians (e.g. in the case of a "kit" comprising the nucleoside or nucleotide compound of the disclosure and the second antiviral compound); (ii) by the physicians themselves (or under the guidance of a physician) shortly before administration; (iii) the patient themselves by a physician or medical staff. The antiviral agents can be co-administered simultaneously or near simultaneously, sequentially or intermittently in any order. For example, co-administration

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includes administration of unit dosages of the nucleoside or nucleotide compound before or after administration of unit dosages of the second antiviral agent, for example, administration of the nucleoside or nucleotide compound within seconds, minutes, or hours of the administration of the the second antiviral agent. For example, a unit dose of a nucleoside or nucleotide compound can be administered first, followed within seconds or minutes by administration of a unit dose of the second antiviral agent. Alternatively, a unit dose of the the second antiviral agent can be administered first, followed by administration of a unit dose of a nucleoside or nucleotide compound within seconds or minutes. In some cases, it may be desirable to administer a unit dose of the nucleoside or nucleotide compound first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of the second antiviral agent. In other cases, it may be desirable to administer a unit dose of the second antiviral agent first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of the nucleoside or nucleotide compound.

In certain embodiments, the combination composition can be processed to prepare a final dosage form, such as a tablet or a capsule. This can be achieved by compressing the final blend of the combination (that is, the nucleoside or nucleotide compound and the second antiviral agent), optionally together with one or more excipients. The compression can be achieved for example with a rotary tablet press. The tablets or capsule if not indicated otherwise, can be prepared in a manner known per se, e.g. by means of mixing, granulating, sugar-coating processes.

When administered by nasal aerosol or inhalation, the compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the disclosure or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation may additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the compounds, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds may also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion

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preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, sugar solutions such as glucose or mannitol solutions, or mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, the formulations may be prepared by mixing the compounds of formula I with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

In certain embodiments, it is contemplated that these compositions can be extended release formulations. Typical extended release formations utilize an enteric coating. Typically, a barrier is applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric coatings prevent release of medication before it reaches the small intestine. Enteric coatings may contain polymers of polysaccharides, such as maltodextrin, xanthan, scleroglucan dextran, starch, alginates, pullulan, hyaloronic acid, chitin, chitosan and the like; other natural polymers, such as proteins (albumin, gelatin etc.), poly-L-lysine; sodium poly(acrylic acid); poly(hydroxyalkylmethacrylates) (for example poly(hydroxyethylmethacrylate)); carboxypolymethylene (for example Carbopol™); carbomer; polyvinylpyrrolidone; gums, such as guar gum, gum arabic, gum karaya, gum ghatti, locust bean gum, tamarind gum, gellan gum, gum tragacanth, agar, pectin, gluten and the like; poly(vinyl alcohol); ethylene vinyl alcohol; polyethylene glycol (PEG); and cellulose ethers, such as hydroxymethylcellulose (HMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), methylcellulose (MC), ethylcellulose (EC), carboxyethylcellulose (CEC), ethylhydroxyethylcellulose (EHEC), carboxymethylhydroxyethylcellulose (CMHEC), hydroxypropylmethyl-cellulose (HPMC), hydroxypropylethylcellulose (HPEC) and sodium carboxymethylcellulose (Na-CMC); as well as copolymers and/or (simple) mixtures of any of the above polymers. Certain of the above-mentioned polymers may further be crosslinked by way of standard techniques.

The choice of polymer will be determined by the nature of the active ingredient/drug that is employed in the composition of the disclosure as well as the desired rate of release. In particular, it will be appreciated by the skilled person, for example in the case of HPMC, that

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a higher molecular weight will, in general, provide a slower rate of release of drug from the composition. Furthermore, in the case of HPMC, different degrees of substitution of methoxyl groups and hydroxypropoxyl groups will give rise to changes in the rate of release of drug from the composition. In this respect, and as stated above, it may be desirable to provide compositions of the disclosure in the form of coatings in which the polymer carrier is provided by way of a blend of two or more polymers of, for example, different molecular weights in order to produce a particular required or desired release profile.

Microspheres of polylactide, polyglycolide, and their copolymers poly(lactide-co-glycolide) may be used to form sustained-release protein delivery systems. Proteins can be entrapped in the poly(lactide-co-glycolide) microsphere depot by a number of methods, including formation of a water-in-oil emulsion with water-borne protein and organic solvent-borne polymer (emulsion method), formation of a solid-in-oil suspension with solid protein dispersed in a solvent-based polymer solution (suspension method), or by dissolving the protein in a solvent-based polymer solution (dissolution method). One can attach poly(ethylene glycol) to proteins (PEGylation) to increase the in vivo half-life of circulating therapeutic proteins and decrease the chance of an immune response.

Liposomal suspensions (including liposomes targeted to viral antigens) may also be prepared by conventional methods to produce pharmaceutically acceptable carriers. This may be appropriate for the delivery of free nucleosides, acyl nucleosides or phosphate ester prodrug forms of the nucleoside compounds according to the present disclosure.

It is appreciated that nucleosides of the present disclosure have several chiral centers and may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present disclosure encompasses any racemic, optically active, diastereomeric, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the disclosure, which possess the useful properties described herein. It is well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Carbons of the nucleoside are chiral, their nonhydrogen substituents (the base and the CHOR groups, respectively) can be either cis (on the same side) or trans (on opposite sides) with respect to the sugar ring system. The four optical isomers therefore are represented by the following configurations (when orienting the sugar moiety in a horizontal plane such that the oxygen atom is in the back): cis (with both groups "up", which corresponds to the

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configuration of naturally occurring β-D nucleosides), cis (with both groups "down", which is a nonnaturally occurring β-L configuration), trans (with the C2' substituent "up" and the C4' substituent "down"), and trans (with the C2' substituent "down" and the C4' substituent "up"). The "D-nucleosides" are cis nucleosides in a natural configuration and the "L-nucleosides" are cis nucleosides in the nonnaturally occurring configuration.

Likewise, most amino acids are chiral (designated as L or D, wherein the L enantiomer is the naturally occurring configuration) and can exist as separate enantiomers.

Examples of methods to obtain optically active materials are known in the art, and include at least the following. i) physical separation of crystals-a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct; ii) simultaneous crystallization-a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state; iii) enzymatic resolutions-a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme; iv) enzymatic asymmetric synthesis-a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer; v) chemical asymmetric synthesis--a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries; vi) diastereomer separations-a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer; vii) first- and second-order asymmetric transformations-a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer; viii) kinetic resolutions-this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic

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conditions; ix) enantiospecific synthesis from non-racemic precursors--a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis; x) chiral liquid chromatography--a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions; xi) chiral gas chromatography-a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase; xii) extraction with chiral solvents-a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent; xiii) transport across chiral membranes-a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through. Chiral chromatography, including simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

Some of the compounds described herein contain olefinic double bonds and unless otherwise specified, are meant to include both E and Z geometric isomers.

In addition, some of the nucleosides described herein, may exist as tautomers, such as, keto-enol tautomers. The individual tautomers as well as mixtures thereof are intended to be encompassed within the compounds of the present disclosure. The nucleoside or nucleotide compounds of the formulas herein, its pharmaceutically acceptable salts, and the second antiviral agents may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the

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ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant disclosure may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The present disclosure comprises all polymorphs and pseudopolymorphs of the compounds and their pharmaceutically acceptable salts.

Provided herein is the crystal form of the compounds of this disclosure, including EIDD-2023/2024/1911 combined with the crystal form of an additional antiviral compound, such as vapendavir.

The nucleoside or nucleotide compounds of the formulas herein, its pharmaceutically acceptable salts, and the second antiviral agents may may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises use of all amorphous forms of the compounds described herein and their pharmaceutically acceptable salts.

EXAMPLES

Example 1.

Conjugate Preparation

Mono and diphosphate prodrugs have been prepared by several groups. See Jessen et al., Bioreversible Protection of Nucleoside Diphosphates, Angewandte Chemie-International Edition English 2008, 47 (45), 8719-8722, hereby incorporated by reference. In order to prevent rupture of the P-O-P anhydride bond, one utilizes a pendant group that fragments rapidly (e.g. bis-(4-acyloxybenzyl)-nucleoside diphosphates (BAB-NDP) that is deacylated by an endogenous esterase) to generate a negative charge on the second phosphate. See also Routledge et al., Synthesis, Bioactivation and Anti-HIV Activity of 4-Acyloxybenzyl-bis(nucleosid-5'-yl) Phosphates, Nucleosides & Nucleotides 1995, 14 (7), 1545-1558 and Meier et al., Comparative study of bis(benzyl)phosphate triesters of 2',3'-dideoxy-2',3'-didehydrothymidine (d4T) and cycloSal-d4TMP -hydrolysis, mechanistic insights and anti-HIV activity, Antiviral Chemistry and Chemotherapy 2002, 13,101-114, both hereby incorporated by reference. Once this occurs, the P-O-P anhydride bond is less susceptible to

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cleavage and the remaining protecting group can then do its final unraveling to produce the nucleoside diphosphate.

Other methods to prepare diphosphate and monothiodiphosphate prodrugs are shown in Figure 5. Standard coupling conditions are used to prepare sphingolipid- nucleoside monophosphate prodrugs. The corresponding diphosphate prodrugs may be prepared according to the protocols shown in Figure 5 and as provided in Smith et al., Substituted Nucleotide Analogs. U.S. Patent Application 2012/0071434; Skowronska et al., Reaction of Oxophosphorane-Sulfenyl and Oxophosphorane-Selenenyl Chlorides with Dialkyl Trimethylsilyl Phosphites - Novel Synthesis of Compounds Containing a Sulfur or Selenium Bridge Between 2 Phosphoryl Centers, Journal of the Chemical Society-Perkin Transactions 1 1988, 8, 2197-2201; Dembinski et al., An Expedient Synthesis of Symmetrical Tetra-Alkyl Monothiopyrophosphates, Tetrahedron Letters 1994, 35 (34), 6331-6334; Skowronska et al., Novel Synthesis of Symmetrical Tetra-Alkyl Monothiophosphates, Tetrahedron Letters 1987, 28 (36), 4209-4210; and Chojnowski et al., Methods of Synthesis of O,O-Bis TrimethylSilyl Phosphorothiolates. Synthesis-Stuttgart 1977, 10, 683-686, all hereby incorporated by reference in their entirety.

Example 2.

Activity of 2-Fluoronucleosides

Ribonucleoside analogs when activated to their corresponding triphosphate inhibit RNA-dependent RNA viral replication by acting as competitive substrate inhibitors of the virally encoded RdRp. Compounds in this therapeutic class are useful in the treatment of viruses found in but not limited to the arenaviridae, bunyaviridae, flaviviridae, orthomyxoviridae, paramyxoviridae, and togaviridae viral families. Certain compounds disclosed herein are contemplated to have advantages such as a high genetic barrier for antiviral resistance; broad spectrum activity within viral families; and high oral bioavailability with targeted delivery to sites of infection.

The nucleoside analogs were designed with a 2'-alpha-fluorine substituent to mimic natural ribonucleosides. The C-F bond length (1.35 Å) is similar to the C-O bond length (1.43 Å) and fluorine is a hydrogen-bond acceptor making the fluorine substituent an isopolar and isosteric replacement of a hydroxyl group. Unlike ribonucleoside analogs currently in clinical trials for treating HCV infections, in certain embodiments, the 2', 3'-dideoxy-2'-

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fluoronucleoside analogs covered by this disclosure lack a 3'-hydroxyl group and are thus obligate chain terminators of viral replication. Once the nucleosides are converted to their triphosphates, they act as competitive substrate inhibitors of the virally encoded RdRp. After incorporation of the chain terminator into nascent RNA, viral replication ceases. One advantage to obligate chain terminators is that they are not mutagenic to the host when treating chronic diseases.

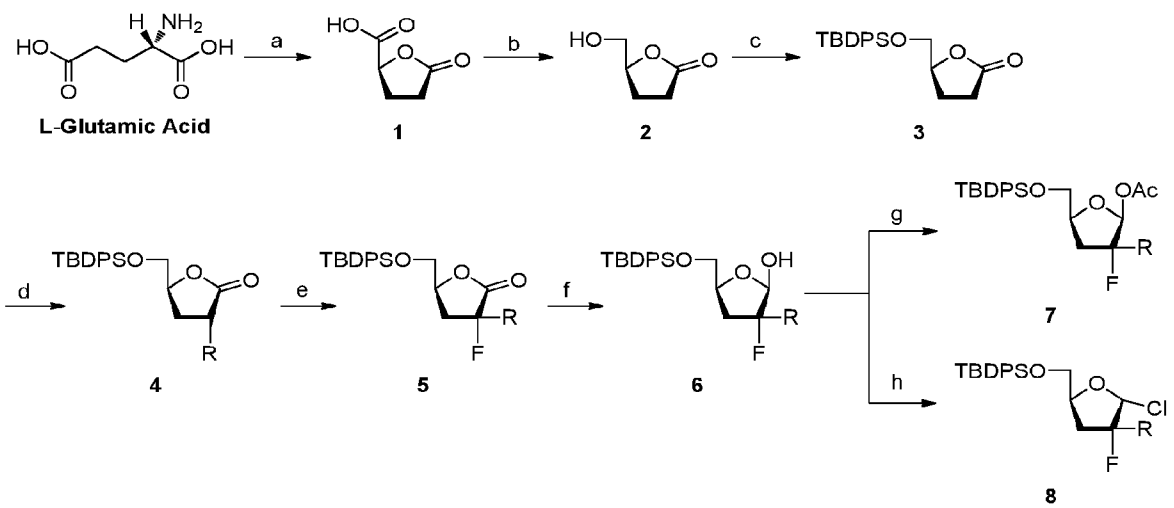
Example 3.

Synthesis of Sphingolipids and Derivatives

The preparation of sphingolipids is provided for in PCT/US12/57448 hereby incorporated by reference in its entirety.

Example 4.

General Synthesis of 2', 3'-Dideoxy-2'-β -Substituted-2'-α-Fluoronucleosides

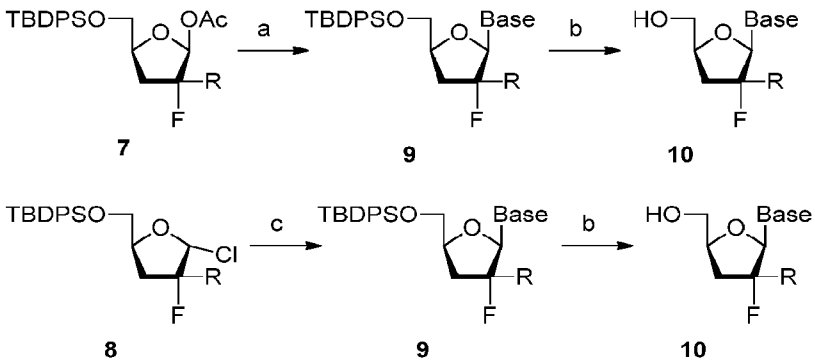


Reagents and conditions: a) $NaNO_2$, $HCl_{(aq)}$; b) $BH_3 \cdot SMe_2$; c) TBDPSCl, DMAP, pyridine; d) i. LiHMDS, ii. RX (X = Cl, Br, I, etc.); e) i. TBSOTf, Et_3N, ii. NFSi; f) DIBAL; g) Ac_2O, DMAP; h) HMPT, CCl_4

Example 5.

Base Coupling and Deprotection

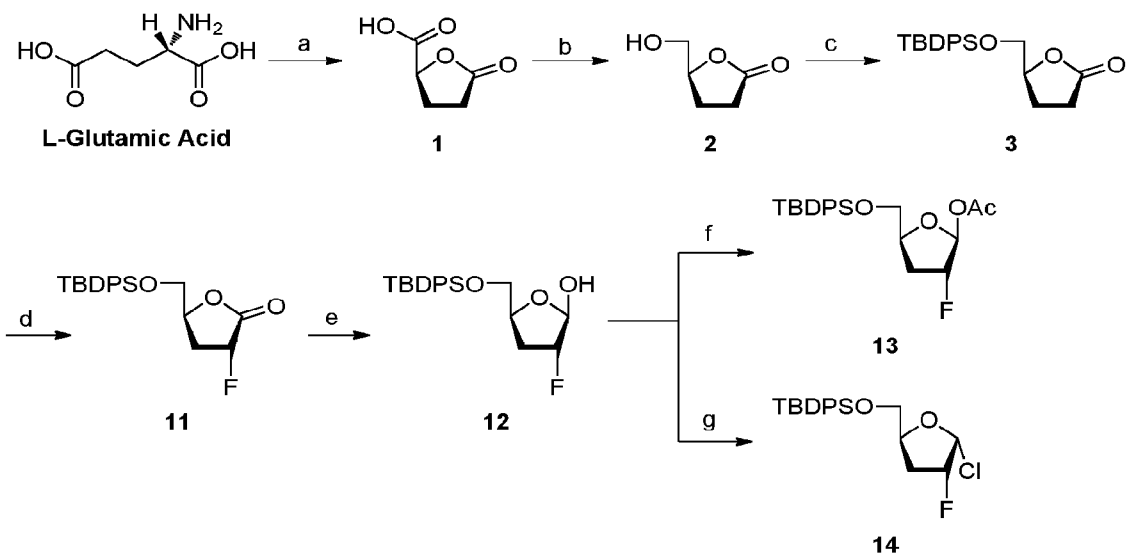
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Reagents and conditions: a) silylated base, TMSOTf, DCE; b) TBAF, THF; c) nucleobase, TDA-1, KOH, MeCN

Example 6.

Synthesis of 2',3'-Dideoxy-2'-α-Fluoronucleosides

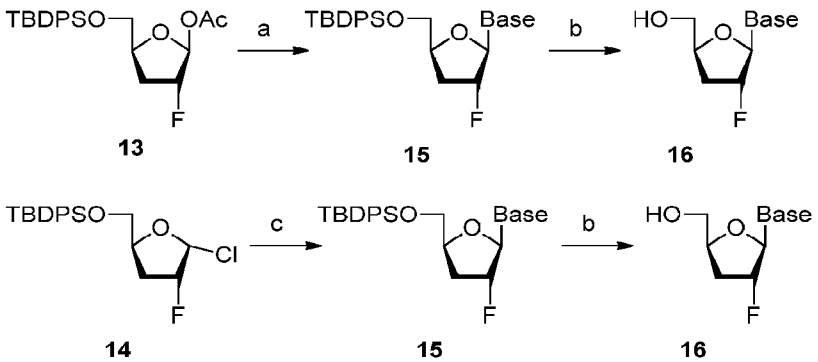


Reagents and conditions: a) $NaNO_2$, $HCl_{(aq)}$; b) $BH_3 \cdot SMe_2$; c) TBDPSCl, DMAP, pyridine; d) i. LiHMDS, ii. NFSi; e) DIBAL; f) Ac_2O, DMAP; g) HMPT, CCl_4

Example 7.

Base Coupling and Deprotection

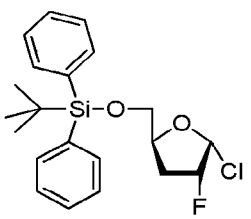
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Reagents and conditions: a) silylated base, TMSOTf, DCE; b) TBAF, THF; c) nucleobase, TDA-1, KOH, MeCN

Example 8.

1-Chloro-2,3-dideoxy-2-fluoro-5-*tert*-butyldimethylsilylribose 17



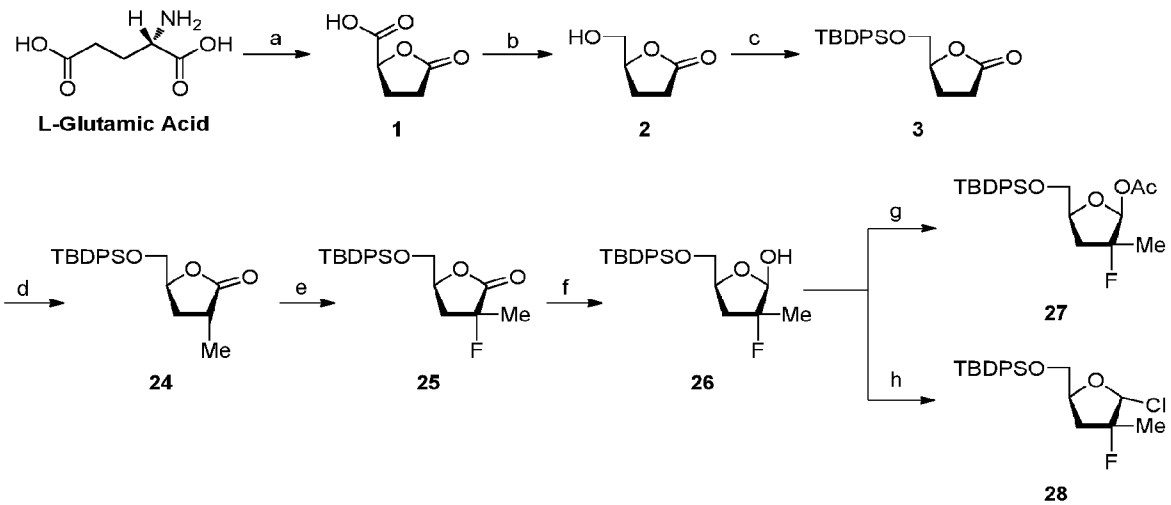
A mixture of 2,3-dideoxy-2-fluoro-5-*tert*-butyldimethylsilylribose (840 mg, 2.24 mmol) and carbon tetrachloride (1.55g, 10.09 mmol) in anhydrous toluene (15 mL) at -50°C was treated dropwise with a solution of hexamethylphosphorous triamide (440 mg, 2.69 mmol) in toluene (15 mL) over a 35 min period. The mixture was stirred with gradual warming to 0°C and maintained at this temperature for 3h. After cooling to -20°C, the mixture was diluted with cold toluene (50 mL) and quenched by dropwise addition of cold brine (5mL at -10°C). After 10 min the organic layer was separated and washed again with cold brine (10 ML). After drying over sodium sulfate, the organic phase was filtered and concentrated by rotary evaporator (bath set at 20°C) to give crude **17** (900 mg) in a 9:1 α:□ ratio. Crude material was used in next step without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.58 (m, 5H), 7.46 – 7.32 (m, 7H), 6.28 (d, *J* = 4.1 Hz, 1H), 5.36 (td, *J* = 8.4, 4.2 Hz, 1H), 5.22 (td, *J* = 8.3, 4.1 Hz, 1H), 4.55 (ddt, *J* = 7.6, 5.2, 2.8 Hz, 1H), 3.78 (ddd, *J* = 11.5, 2.7, 1.8 Hz, 1H), 3.60 (dd, *J* = 11.5, 2.8 Hz, 1H), 2.44 – 2.35 (m, 2II).

Example 9.

Synthesis of 2',3'-Dideoxy-2'-α-Methyl-2'-α-Fluoronucleosides

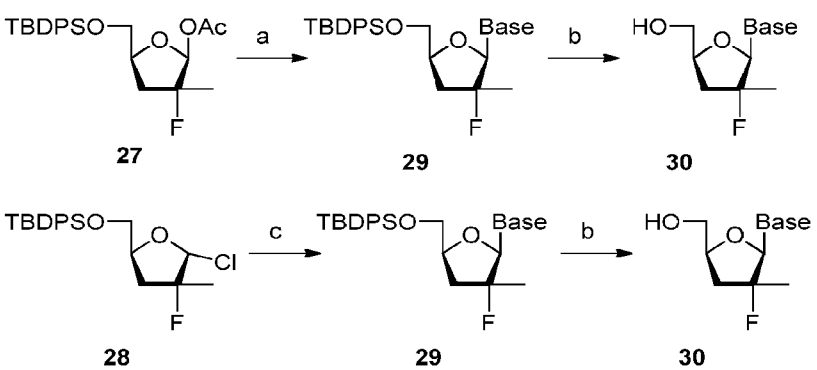
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Reagents and conditions: a) $NaNO_2$, $HCl_{(aq)}$; b) $BH_3 \cdot SMe_2$; c) TBDPSCl, DMAP, pyridine; d) i. LiHMDS, ii. MeI; e) i. TBSOTf, Et_3N, ii. NFSi; f) DIBAL; g) Ac_2O, DMAP; h) HMPT, CCl_4

Example 10.

Base coupling and Deprotection

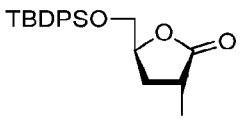


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) TBAF, THF; c) nucleobase, TDA-1, KOH, MeCN

Example 11.

(3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-methyldihydrofuran-2(3H)-one (31)

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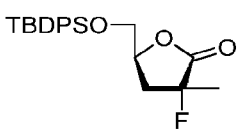


To a solution of diisopropylamine (2.01 ml, 14.1 mmol) in dry THF (20 ml) at 0°C, under an inert atmosphere, was added n-butyllithium (8.83 ml of a 1.6 M solution in hexane, 14.13 mmol). After 30 minutes of stirring, the solution was cooled to -78°C, and a solution of (4S)-4-tert-butyldiphenylsiloxymethyl-4-butanolide (5.01 g, 14.13 mmol) in dry THF (5 ml) was added drop-wise over a period of 5 minutes. After stirring for a further 30 minutes at -78°C, iodomethane (1.31 ml, 21.0 mmol) was added, and the reaction vessel removed from the ice bath. After 30 minutes at ambient temperature, deionised water (40 ml) was added to the solution, and the organics extracted with ether (3 x 15 ml). The combined organic layer was washed with 1M HCl (3 x 20 ml) and once more with brine, before being dried over Mg_2SO_4. The crude product was purified by silica chromatography (product Rf = 0.26 in 4:1 hexane:ethyl acetate), eluting with 85:15 hexane:ethyl acetate to afford the final product as a white, crystalline solid. Stereochemistry was established based on comparison of NMR data with reported data.

^{1}H NMR (400 MHz, $CDCl_3$): □ 7.67-7.65 (m, 4H), 7.48-7.39 (m, 6H), 4.58-4.53 (m, 1H), 3.86 (dd, *J* = 3.2, 10.8 Hz, 1H), 3.68 (dd, *J* = 3.2, 11.2 Hz, 1H), 2.90-2.81 (m, 1H), 2.45 (ddd, *J* = 3.2, 9.2, 12.8 Hz, 1H), 1.98 (dt, *J* = 8.8, 12.4 Hz, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.06 (s, 9H).

Example 12.

(3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-fluoro-3-methyldihydrofuran-2(3H)-one (32)



Compound **31** (0.1000 g, 0.27 mmol) was placed in a dry flask under argon atmosphere and was dissolved in dry DCM (5 mL). Next, TBSOTf (0.075 mL, 0.33 mmol) was added dropwise to the stirring DCM solution of lactone at room temperature followed by the dropwise addition of neat triethylamine (0.057 mL, 0.41 mmol) also at room temp. The reaction mixture was allowed to stir at room temp under nitrogen for 2 hours with monitoring by TLC. Next, NFSi (0.1280 g, 0.41 mmol) was dissolved in 2 mL of dry DCM and was added dropwise to the silyl enol ether at room temp under nitrogen. The reaction mixture turned dark red. The reaction mixture was allowed to stir over night. The reaction mixture

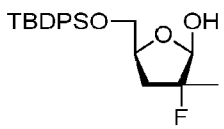
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was quenched with sat. NH4Cl and was diluted with ether. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated. The product was purified on silica eluting with 8:1 hexanes/ethyl acetate.

^{1}H NMR (400 MHz, $CDCl_3$): □ 7.67-7.64(m, 4H), 7.48-7.39 (m, 6H), 4.75-4.70 (m, 1H), 3.96 (dd, *J* = 3.6, 12 Hz, 1H), 3.71 (dd, *J* = 3.6, 11.6 Hz, 1H), 2.53 (ddd, *J* = 6.4, 14.6, 22.8 Hz, 1H), 2.37 (ddd, *J* = 8.8, 14.6, 35.2 Hz, 1H), 1.66 (d, *J* = 22.8 Hz, 3H), 1.05 (s, 9H).

Example 13.

(2R,3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-fluoro-3-methyltetrahydrofuran-2-ol (33)

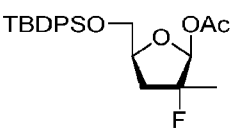


Compound **33** was prepared following the procedure outlined by JOC (1998), 63, 2161-2167.

^{1}H NMR (400 MHz, $CDCl_3$): □ 7.70-7.67 (m, 4H), 7.47-7.39 (m, 6H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.50 (m, 1H), 3.87 (dd, *J* = 2.4, 11.2 Hz, 1H), 3.46 (dd, *J* = 2.4, 11.2 Hz, 1H), 2.27-2.11 (m, 2H), 1.57 (d, *J* = 21.6 Hz, 3H), 1.09 (s, 9H).

Example 14.

(2S,3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-fluoro-3-methyltetrahydrofuran-2-yl acetate (34)



Compound **34** was prepared following the procedure outlined by JOC (1998), 63, 2161-2167.

^{1}H NMR (400 MHz, $CDCl_3$): □ 7.69-7.66 (m, 4H), 7.46-7.37 (m, 6H), 6.13 (d, *J* = 10.4 Hz, 1H), 4.53-4.47 (m, 1H), 3.79 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.72 (dd, *J* = 4.4, 11.6 Hz, 1H), 2.27-2.02 (m, 2H), 1.92 (s, 3H), 1.50 (d, *J* = 21.6 Hz, 3H), 1.07 (s, 9H).

Example 15.

General Nucleobase Coupling Conditions

The desired nucleobase (5 equivalents) was transferred to a dry flask under an argon atmosphere and suspended in HMDS (2 mL/mmol nucleobase). Catalytic ammonium sulfate (1-3 mgs) was added to the reaction vessel, and the suspension was allowed to reflux for 1-3

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hours. During the course of reaction, the white suspension turned clear. The reaction vessel was allowed to cool to room temperature, and the excess HMDS was removed under reduced pressure. The resulting residue was dissolved in dry DCE (5 mL/mmol compound **34**) followed by the addition of compound **34** at room temperature. Finally, neat TMSOTf (5.5 equivalents) was added to the stirring solution. The reaction was quenched with saturated sodium bicarbonate. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired protected nucleoside was purified on silica gel eluting with 9:1 DCM/MeOH.

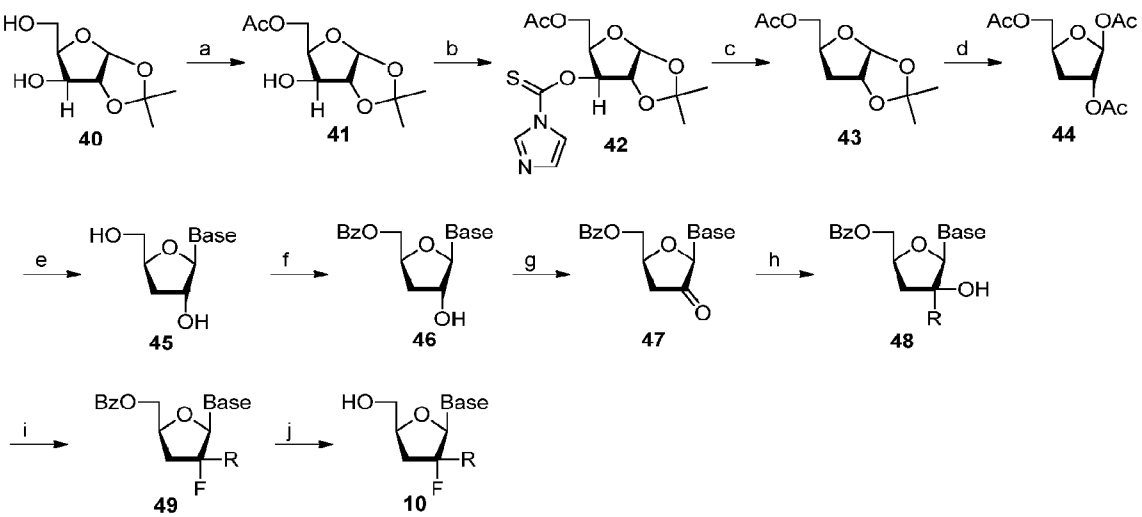
Example 16.

General Deprotection Conditions

A solution of protected nucleoside dissolved in dry THF (10 ml/mmol of protected nucleoside) was treated with tetrabutylammonium fluoride (TBAF, 1 M solution in THF, 1.1 equivalents), and let to stir at room temperature for 3 hours. The crude mixture was concentrated in vacuo, and the resulting residue was purified on silica gel (0-10% methanol in dichloromethane) to give the desired nucleoside.

Example 17.

Alternative Route for the Synthesis of 2',3'-Dideoxy-2'-□-Substituted-2'-□-Fluoronucleosides

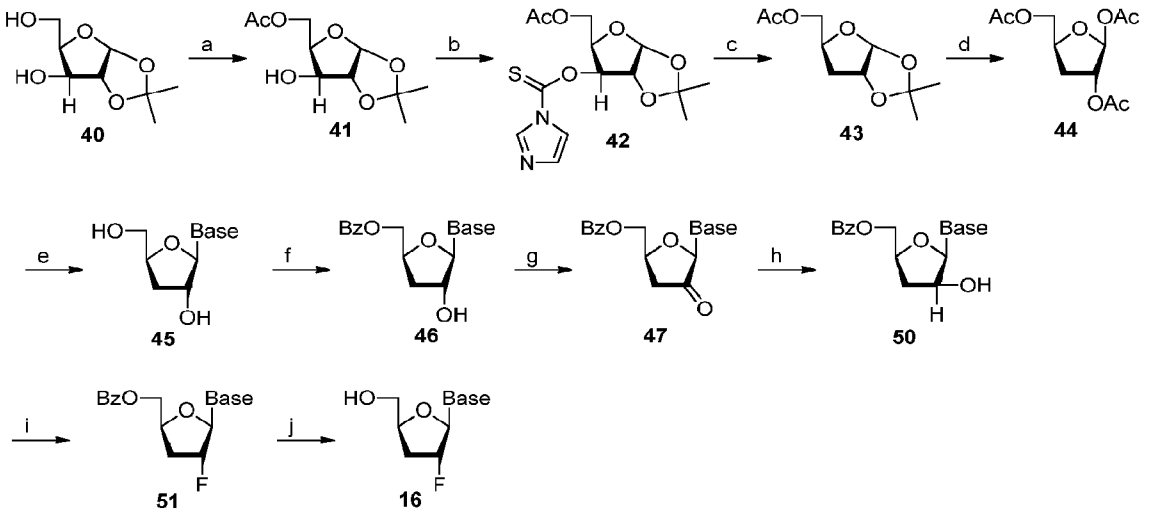


Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) Ac_2O, AcOH, H_2SO_4; e) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH; f) BzCl; g) DMP; h) RLi or RMgBr; i) DAST; j) NH_3, MeOH

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Example 18.

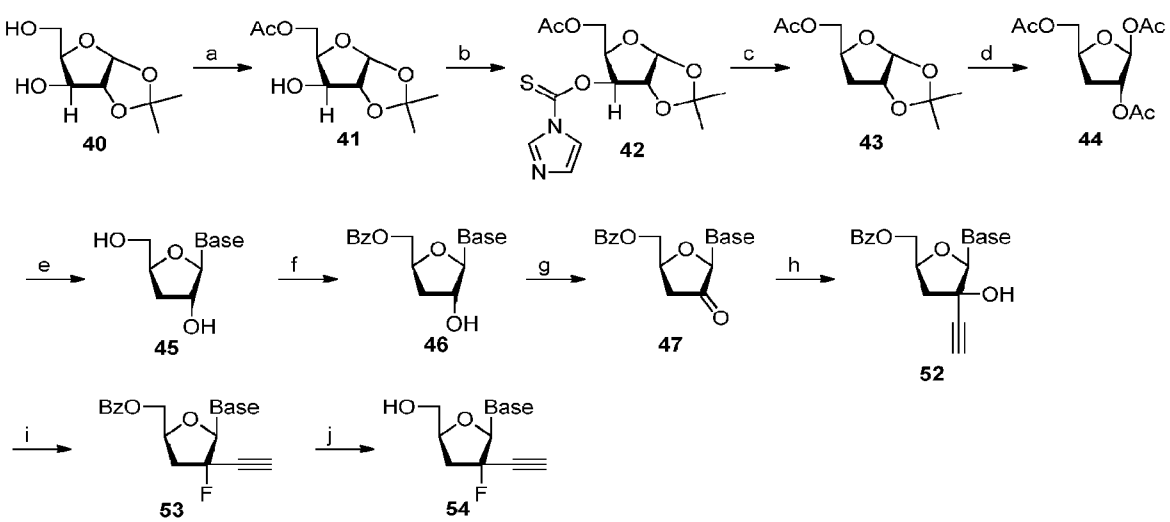
Alternative Route to 2',3'-Dideoxy-2'-α-Fluoronucleosides



Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) Ac_2O, AcOH, H_2SO_4; e) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH; f) BzCl; g) DMP; h) $NaBH_4$; i) DAST; j) NH_3, MeOH

Example 19.

2',3'-Dideoxy-2'-β-Ethynyl-2'-α-Fluoronucleosides

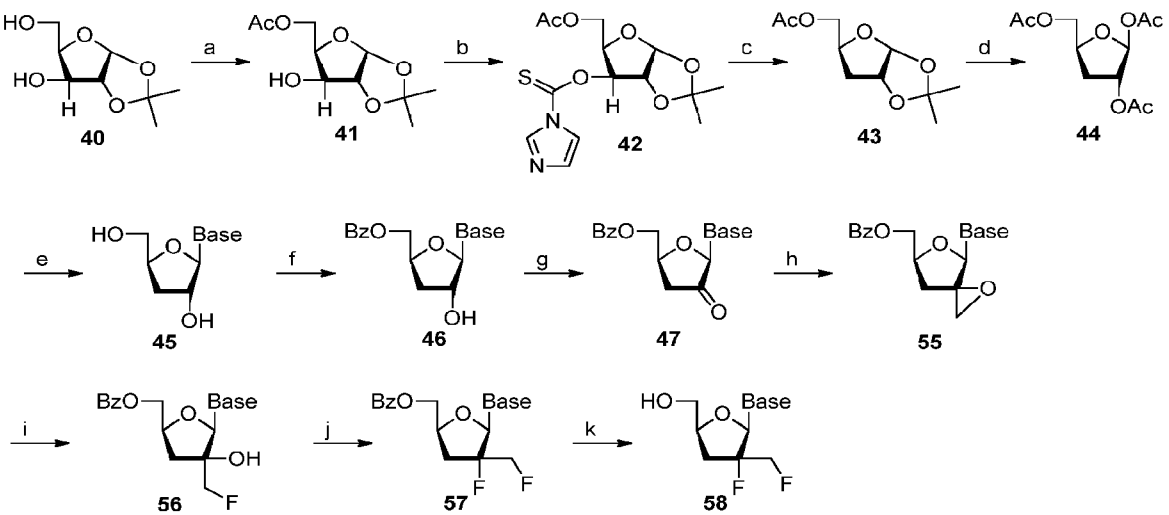


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Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) Ac_2O, AcOH, H_2SO_4; e) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH; f) BzCl; g) DMP; h) i.trimethylsilylacetylene, BuLi, ii. NH_4F, MeOH; i) DAST; j) NH_3, MeOH

Example 20.

2',3'-Dideoxy-2'-β-Fluoromethyl-2'-α-Fluoronucleosides

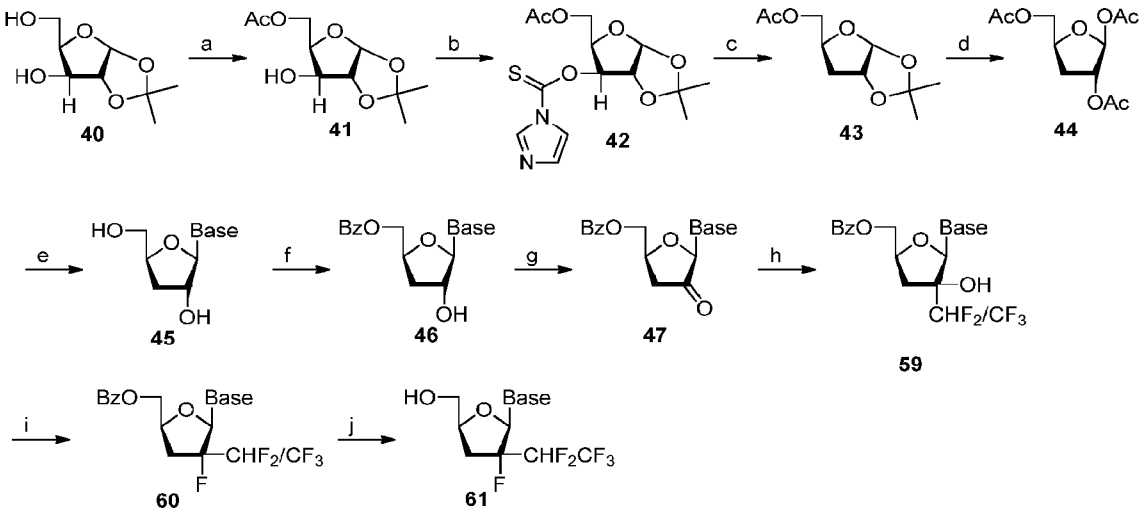


Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) Ac_2O, AcOH, H_2SO_4; e) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH; f) BzCl; g) DMP; h) $Me_3S(O)I$, NaH; i) KF, 18-crown-6; j) DAST; k) NH_3, MeOH

Example 21.

2',3'-Dideoxy-2'-β-Difluoromethyl OR Trifluoromethyl-2'-α-Fluoronucleosides

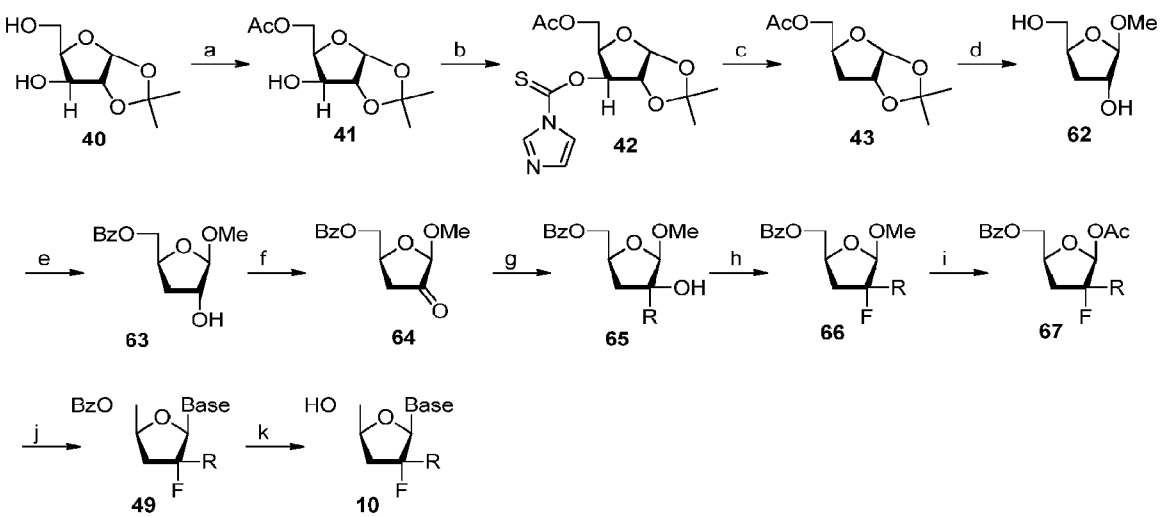
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Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) Ac_2O, AcOH, H_2SO_4; e) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH; f) BzCl; g) DMP; h) CHF_2: i. $PhSO_2CF_2H$, LiHMDS, ii. SmI_2 or CF_3: $TMSCF_3$, TBAF; i) DAST; j) NH_3, McOH

Example 22.

Alternative Route to 2',3'-Dideoxy-2'-β-Substituted-2'-α-Fluoronucleosides

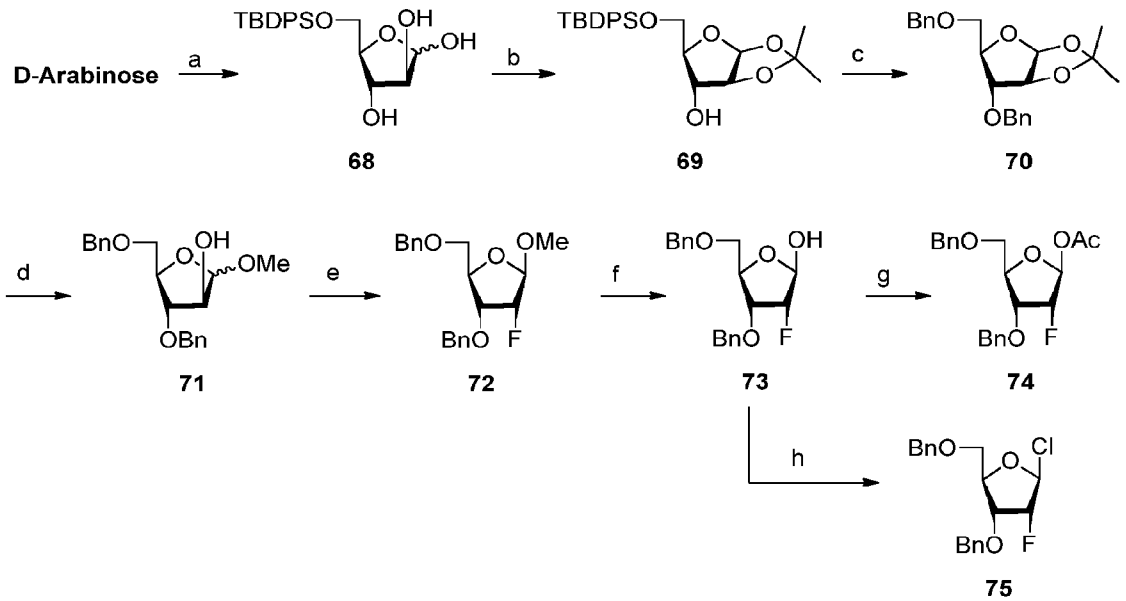


Reagents and conditions: a) AcCl, pyridine, DCM; b) TCDI, pyridine, DCM; c) Bu_3SnH, AIBN; d) i. H_2SO_4, MeOH ii. K_2CO_3, MeOH; e) BzCl, pyridine; f) DMP; g) RLi or RMgBr; h) DAST; i) Ac_2O, AcOH, H_2SO_4; j) silylated base, TMSOTf; k) NH_3, MeOH

Example 23.

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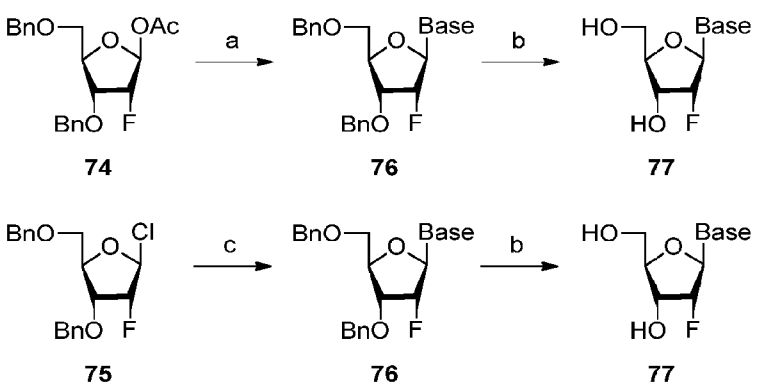
Synthesis of 2'-Deoxy-2'-α-Fluororibonucleosides



Reagents and conditions: a) TBDPSCl, imidazole; b) acetone, $CuSO_4$, H_2SO_4; c) KOH, BnCl; d) CSA, MeOH; e) i. Tf_2O, ii. TBAF; f) 90% $TFA_{(aq)}$; g) Ac_2O, DMAP; h) HMPT, CCl_4

Example 24.

Base Coupling and Deprotection

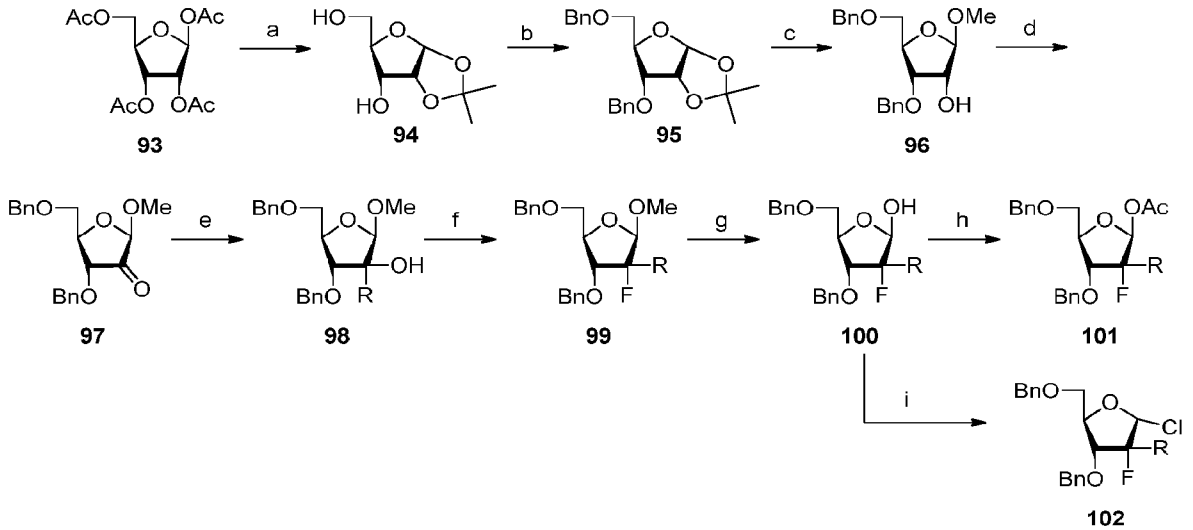


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) BCl_3, DCM; c) nucleobase, TDA-1, KOH, MeCN

Example 25.

Synthesis of 2'-Deoxy-2'-β-Substituted-2'-α-Fluororibonucleosides

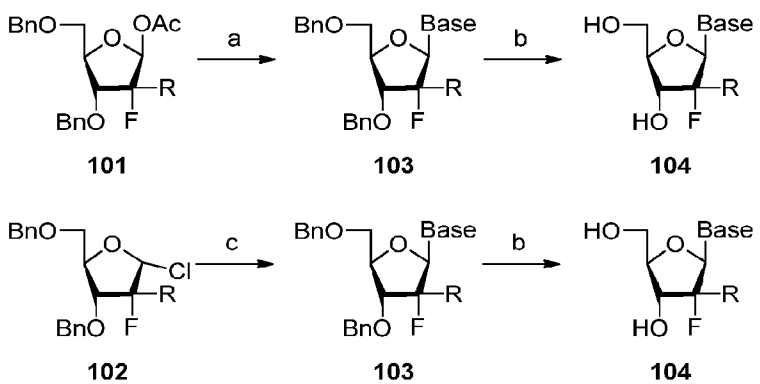
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Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) KOH, BnCl; c) H_2SO_4, MeOH; d) DMP; e) RLi or RMgBr; f) DAST; g) H_2SO_4, H_2O; h) Ac_2O, DMAP; i) HMPT, CCl_4

Example 26.

Base Coupling and Deprotection

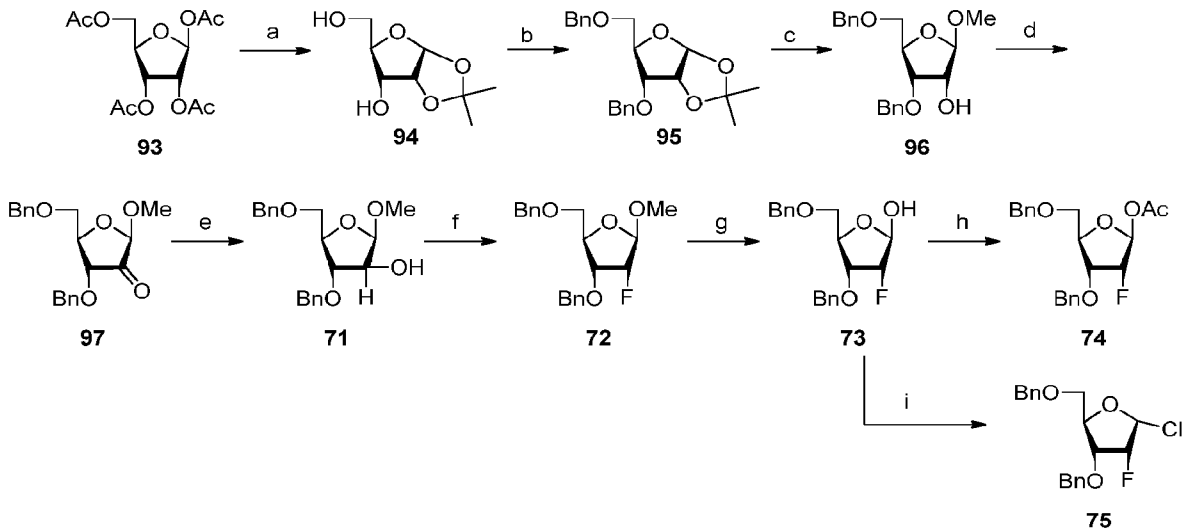


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) BCl_3, DCM; c) nucleobase, TDA-1, KOH, MeCN

Example 27.

Alternative Synthesis for 2'-Deoxy-2'-β-Fluororibonucleosides

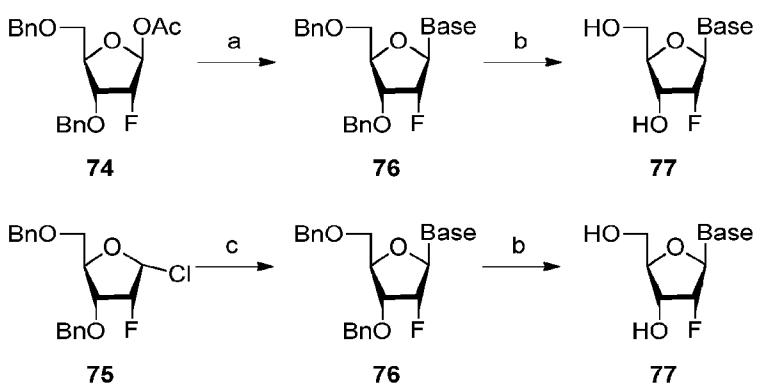
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Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) KOH, BnCl; c) H_2SO_4, MeOH; d) DMP; e) $NaBH_4$; f) DAST; g) H_2SO_4, H_2O; h) Ac_2O, DMAP; i) HMPT, CCl_4

Example 28.

Base Coupling and Deprotection

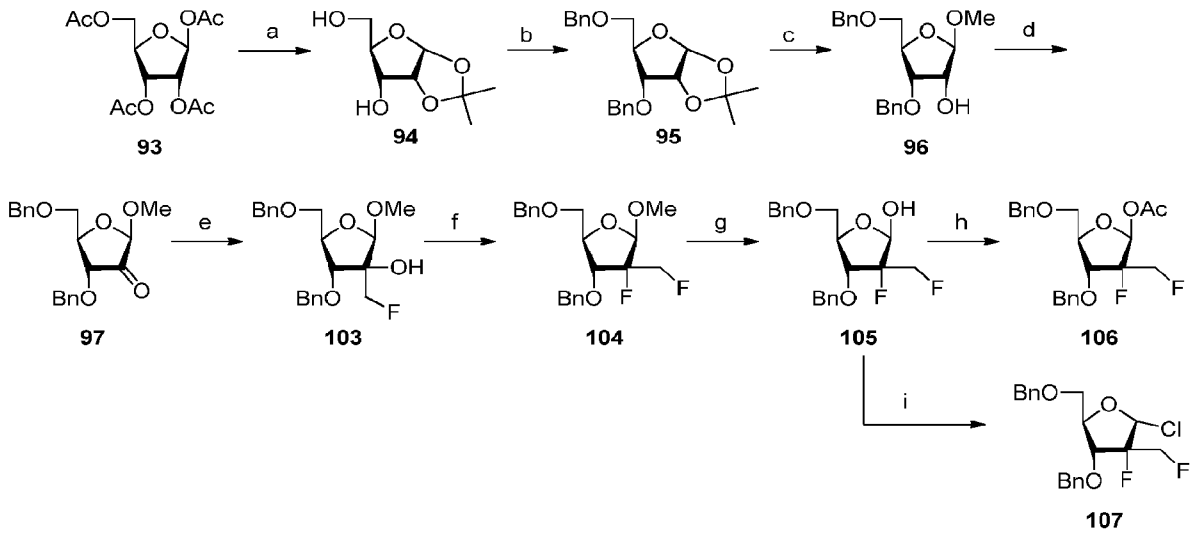


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) BCl_3, DCM; c) nucleobase, TDA-1, KOH, MeCN

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Example 29.

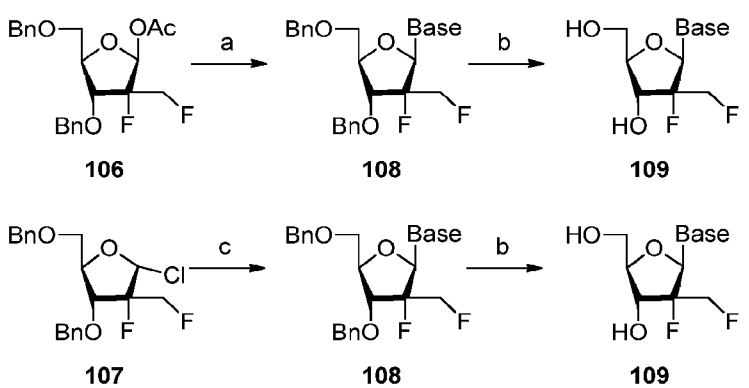
Synthesis of 2'-Deoxy-2'-β-Fluoromethyl-2'-α-Fluororibonucleosides



Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) KOH, BnCl; c) H_2SO_4, MeOH; d) DMP; e) i. $Me_3S(O)I$, NaH, ii. KF, 18-crown-6; f) DAST; g) H_2SO_4, H_2O; h) Ac_2O, DMAP; i) HMPT, CCl_4

Example 30.

Base Coupling and Deprotection

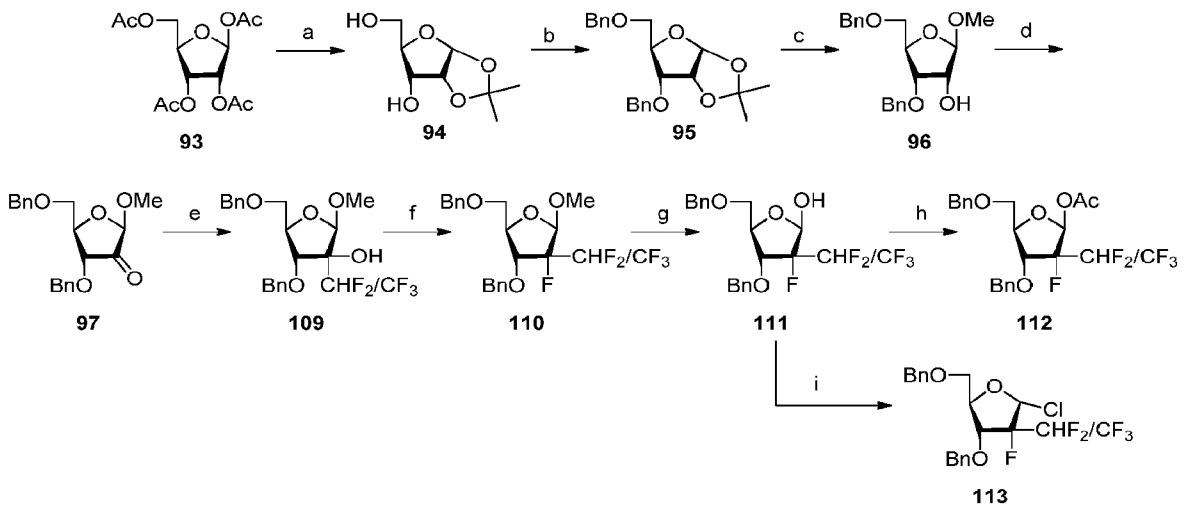


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) BCl_3, DCM; c) nucleobase, TDA-1, KOH, MeCN

Example 31.

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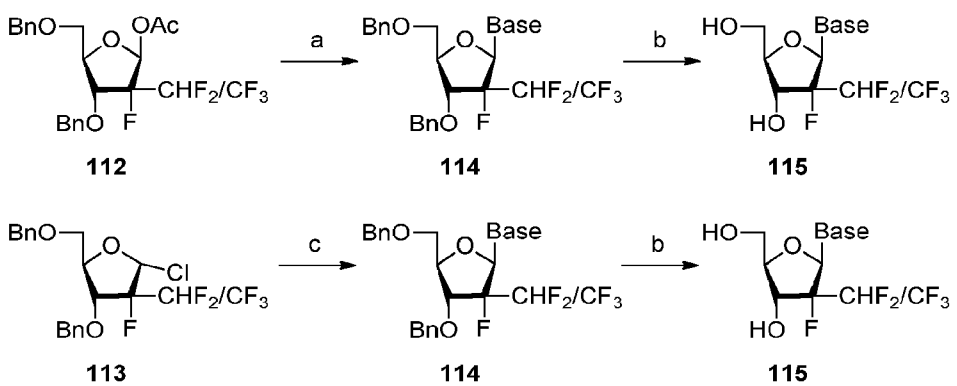
Synthesis of 2'-Deoxy-2'-β-Difluoromethyl OR Trifluoromethyl-2'-α-Fluororibonucleosides



Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) KOH, BnCl; c) H_2SO_4, MeOH; d) DMP; e) CHF_2: i. $PhSO_2CF_2H$, LiHMDS, ii. SmI_2 or CF_3: $TMSCF_3$, TBAF; f) DAST; g) H_2SO_4, H_2O; h) Ac_2O, DMAP; i) HMPT, CCl_4

Example 32.

Base Coupling and Deprotection

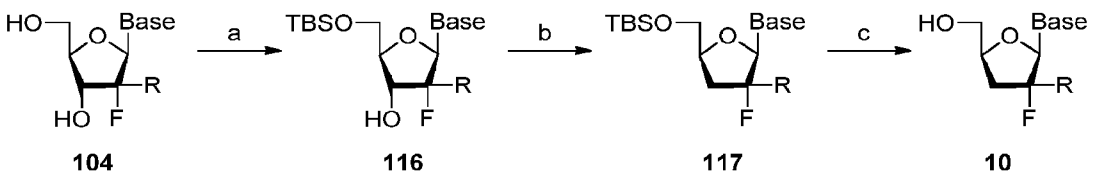


Reagents and conditions: a) silylated base, TMSOTf, DCE; b) BCl_3, DCM; c) nucleobase, TDA-1, KOH, MeCN

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Example 33.

Alternative Synthesis of 2',3'-Dideoxy-2'-β-Substituted-2'-α-Fluoronucleosides

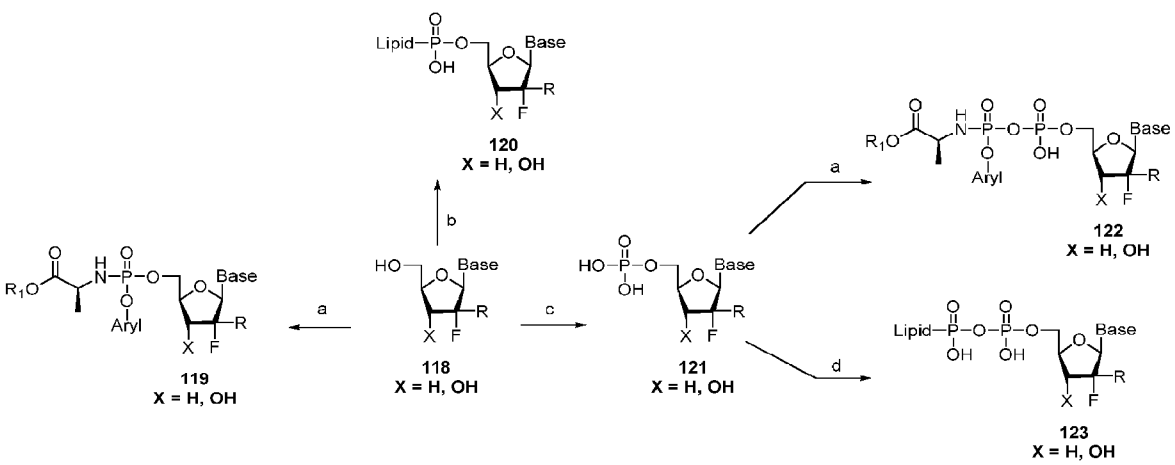


104 **116** **117** **10**

Reagents and conditions: a) TBSCl, Et_3N, DMAP; b) i. phenylchlorothionoformate, ii. AIBN; c) TBAF

Example 34.

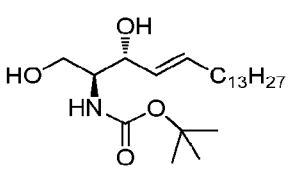
Monophosphate and Diphosphate Prodrug Synthesis



Reagents and conditions: a) chlorophosphoramidate, imidazole; b) DIC, lipid-1-phosphate; c) $POCl_3$, $O=P(OMe)_3$; d) i. DIC, morpholine, ii. Sphingoid base-1-phosphate, tetrazole

Example 35.

***N-tert*-Butyloxycarbonyl-sphingosine (124)**



124

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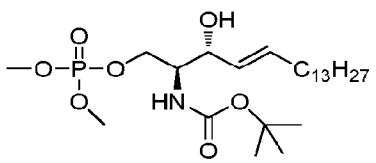
Prepared according to Boumendjel, Ahcene and Miller, Stephen *Journal of Lipid Research* **1994**, *35*, 2305.

A mixture of sphingosine (450 mg, 1.50 mmol) and di-*tert*-butyl dicarbonate (0.656 g, 3.01 mmol) in methylene chloride (100 mL) at 4°C was treated dropwise with diisopropylethylamine (0.53 mL, 3.01 mmol). After gradual warming to rt, the mixture was stirred for an additional 12 h and then diluted with methylene chloride (100 mL) followed by a wash with water (30 mL) and brine (30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to dryness. The crude residue was purified by flash column chromatography over silica gel (19 mm x 175 mm) using 50% ethyl acetate in hexanes to give *N-tert*-butyloxycarbonyl-sphingosine (540 mg, 90%) as a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.77 (dt, *J* = 15.4, 8.4 Hz, 1H), 5.52 (dd, J= 15.4, 8.4 Hz, 1H), 3.93 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.70 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.59 (s, 3H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.52 (s, 9H), 1.25 (s, 22 H), 0.87 (t, *J* = 6.5 Hz, 3H).

Example 36.

***N-tert*-Butyloxycarbonyl-sphingosine-1-*O*-dimethylphosphate (125)**



125

N-tert-Butyloxycarbonyl-sphingosine **124**(540 mg, 1.35 mmol) was rendered anhydrous by co-evaporation with anhydrous pyridine (2 x 12 mL). The residue was then dissolved in anhydrous pyridine and treated with carbon tetrabromide (622 mg, 1.88 mmol). The mixture was cooled to 0°C and treated dropwise with a solution of trimethylphosphite (0.25 mL, 2.10 mmol) in anhydrous pyridine (3 mL) over a 30 min period. After an additional 12 h at rt, both LCMS and tlc (5% methanol in methylene chloride) analysis indicated complete conversion. The mixture was quenched with water (2 mL) and then concentrated to dryness. The resulting dark oil was dissolved in ethyl acetate (150 mL) and washed with 3% HCL solution (2 x 20 mL) followed by saturated sodium bicarbonate solution (30 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography over silica gel (19 mm x 175 mm) using 2% methanol in methylene chloride to give ***N-tert*-butyloxycarbonyl-sphingosine-1-*O*-dimethylphosphate 125** (350 mg, 51%) as a gum.

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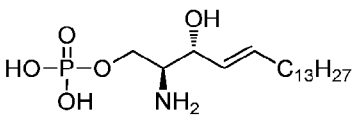
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (dt, *J* = 15.4, 7.1 Hz, 1H), 5.48 (dd, *J* = 15.4, 7.1 Hz, 1H), 4.99 (d, *J* = 8.9 Hz, 1H), 4.32 (ddd, *J* = 10.7, 8.0, 4.6 Hz, 1H), 4.11 (ddt, *J* = 10.7, 7.4, 3.1 Hz, 2H), 3.77 (dd, *J* = 11.1, 2.1 Hz, 6H), 2.01 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.34 (m, 2H), 1.23 (m, 20H), 0.86 (t, *J* = 6.4 Hz, 3H).

^{31}P NMR (162 MHz, Chloroform-*d*) δ 2.00.

MS C17H25NO4 [M+Na+]; calculated: 330.2, found: 330.2.

Example 37.

Sphingosine-1-phosphate (126).



126

A solution of*N-tert*-butyloxycarbonyl-sphingosine-1-*O*-dimethylphosphate **125** (350 mg, 0.689 mmol) in anhydrous methylene chloride (8 mL) was treated dropwise with trimethylsilyl bromide (0.45 mL, 3.45 mmol) at 0°C. After warming to room temperature, the mixture was allowed to stir at rt for 6h and then concentrated to dryness. The resulting residue was co-evaporated with methylene chloride to remove excess trimethylsilyl bromide and then treated with 66% aqueous THF (6 mL). The resulting precipitate was collected by filtration to give sphingosine-1-phosphate **126** (218 mg, 83%) as a white solid.

^{1}H NMR (400 MHz, Methanol-d_4+ CD_3CO_2D) δ 5.84 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.46 (dd, *J* = 15.5, 6.7 Hz, 1H), 4.33 (t, *J* = 6.0 Hz, 1H), 4.13 (ddd, *J* = 11.8, 7.7, 3.6 Hz, 1H), 4.03 (dt, *J* = 11.8, 8.4 Hz, 1H), 3.47 (ddd, *J* = 8.3, 4.8, 3.2 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.37 (m, 2H), 1.24 (m, 20H), 0.83 (t, *J* = 6.4 Hz, 3H).

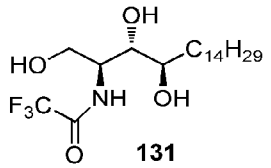
^{31}P NMR (162 MHz, Chloroform-*d*) δ 0.69.

MS $C_{18}H_{38}NO_5P$ [M-H^+]; calculated: 378.2, found: 378.2.

Example 38.

***N*-Trifluoroacetyl-phytosphingosine (131).**

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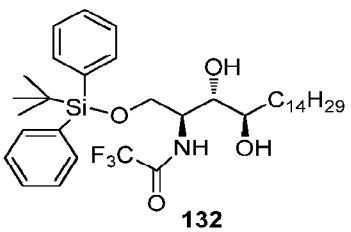
131

To a slurry of phytosphingosine (4 g, 12.6 mmol) and anhydrous powdered potassium carbonate (5.22 g, 37.8 mmol) in methylene chloride (85 mL) was added trifluoroacetic anhydride (1.96 mL, 13.9 mmol). The mixture was stirred at rt for 18 h and then diluted with methylene chloride (500 mL). The mixture was washed with water (100 mL). Methanol (60 mL) was added to break the emulsion. The organic phase was then dried over sodium sulfate, filtered and concentrated to give **131** (4.9 g, 94 %) as a white solid

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 4.90 – 4.68 (m, 1H), 4.56 (d, J = 6.1 Hz, 1H), 4.43 (s, 1H), 3.97 (d, J = 7.6 Hz, 1H), 3.65 (d, J = 10.8 Hz, 1H), 3.46 (t, J = 10.2 Hz, 1H), 3.32 – 3.16 (m, 1H), 1.42 (tt, J = 15.7, 7.5 Hz, 2H), 1.20 (s, 24H), 0.83 t, J = 6.8 Hz, 3H).

Example 39.

1-*O-tert*-Butyldiphenylsilyl-2-*N*-trifluoroacetyl-phytosphingosine (132)



132

N-Trifluoroacetyl-phytosphingosine (**131**, 1.88 g, 4.5 mmol) in anhydrous pyridine (23 mL) was treated with DMAP (56 mg, 0.45 mmol) and then dropwise with tert-butyldiphenylsilyl chloride (1.38 g, 5.0 mmol). After 18 h concentrated to dryness. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with saturated ammonium chloride (2x 50 mL) and then brine (50 mL). The aqueous phases was back-extracted with ethyl acetate (50 mL). Combined organic phases were dried over sodium sulfate and concentrated to give crude 1-*O-tert*-Butyldiphenylsilyl-2-*N*-trifluoroacetyl-phytosphingosine **132** (3g, 100%) as a gum. The material was used in the next step without further purification.

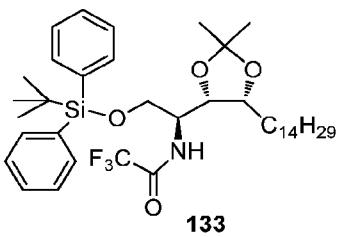
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (m, 2H), 7.60 – 7.56 (m, 2H), 7.47 – 7.31 (m, 6H), 7.07 (d, J = 8.4 Hz, 1H), 4.23 (dd, J = 8.5, 4.1 Hz, 1H, 4.04 (dt, J = 11.0, 2.5 Hz, 1H), 3.82

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(ddd, J = 11.0, 4.3, 1.8 Hz, 1H), 3.64 (dq, J = 10.6, 6.0, 4.3 Hz, 2H), 1.45 (m, 2H), 1.39 – 1.15 (m, 24H), 1.05 (m, 9H), 0.94 – 0.80 (t, J = 6.9 Hz 3H).

Example 40.

1-*O*-*tert*-Butyldiphenylsilyl-3,4-*O*-isopropylidene-2-*N*-trifluoroacetyl-phytosphingosine (133)



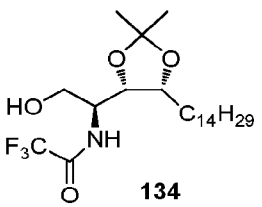
133

A solution of 1-*O*-*tert*-Butyldiphenylsilyl-2-*N*-trifluoroacetyl-phytosphingosine **132** (3g,4.5 mmol) in 1/1 (v/v) 2,2-dimethoxypropane/THF was treated with catalytic amount of *p*-toluenesulfonic acid (87 mg, 0.45 mmol) and allowed to stir for 16h at rt. The mixture was quenched with saturated sodium bicarbonate (30 mL) and then excess THF/2,2-dimethoxypropane was removed under vacuum. The mixture was extracted with ethyl acetate (200 mL). After washing with brine, the organic layer was dried over sodium sulfate, filtered and concentrated. The crude oil was purified by column chromatography (25 mm x 175mm) over silica gel with a hexanes/ethyl acetate mobile phase to give **133**(2.45 g, 78%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.63 (m, 2H), 7.63 – 7.57 (m, 2H), 7.39 (m, 6H), 6.54 (d, J = 9.4 Hz, 1H), 4.23 (dd, J = 8.2, 5.6 Hz, 1H), 4.12 (ddd, J = 13.3, 6.9, 3.8 Hz, 2H), 3.96 (dd, J = 10.5, 3.9 Hz, 1H), 3.69 (dd, J = 10.5, 2.9 Hz, 1H), 1.52 – 1.36 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H), 1.24 (m, 24H), 1.03 (s, 9H), 0.86 (t, J = 53.7, 6.9 Hz, 3H).

Example 41.

3,4-*O*-Isopropylidene-2-*N*-Trifluoroacetyl-phytosphingosine (134).



134

A solution of 1-*O*-*tert*-Butyldiphenylsilyl-3,4-*O*-isopropylidene-2-*N*-trifluoroacetyl-phytosphingosine **133** (2.45 g, 3.54 mmol)in THF (18 mL) was treated with tetrabutylammonium fluoride (4.25 mL of a 1.0 M solution in THF, 4.25 mmol) and stirred

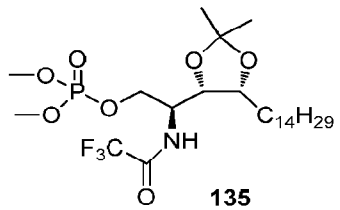
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at rt for 12h. The mixture was diluted with ethyl acetate (100 mL) and saturated ammonium chloride (2 x 50 mL) and then brine (50 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated to give a white solid that was further purified by column chromatography (25 mm x 175 mm) over silica gel with a 9:1 hexanes: ethyl acetate mobile phase to afford **134**(1.5g, 93%) as a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.92 (d, *J* = 8.7 Hz, 1H), 4.31 – 4.16 (m, 2H), 4.11 (dq, *J* = 11.7, 3.7 Hz, 1H), 4.00 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.70 (dd, *J* = 11.5, 3.6 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.25 (m, 26H), 0.88 (t, *J* = 6.9 Hz 3H).

Example 42.

3,4-*O*-Isopropylidene-2-*N*-trifluoroacetyl-phytosphingosine-1-*O*-dimethylphosphate (135)



135

A solution of 3,4-*O*-Isopropylidene-2-*N*-Trifluoroacetyl-phytosphingosine **134**(630 mg, 1.39 mmol) was rendered anhydrous by co-evaporation with anhydrous pyridine (2 x 12 mL). The residue was then dissolved in anhydrous pyridine (12 mL) and treated with carbon tetrabromide (533 mg, 1.67 mmol). The mixture was cooled to 0°C and treated dropwise with a solution of trimethylphosphite (0.23 mL, 1.95 mmol) in anhydrous pyridine (3 mL) over a 30 min period. After an additional 12 h at rt, both LCMS and tlc (5% methanol in methylene chloride) analysis indicated complete conversion. The mixture was quenched with water (2 mL) and then concentrated to dryness. The resulting dark oil was dissolved in ethyl acetate (100 mL) and washed with 3% HCL solution (2 x 20 mL) followed by saturated sodium bicarbonate solution (30 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography over silica gel (19 mm x 175 mm) using 2% methanol in methylene chloride to give **135** (650 mg, 83%).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.8 Hz, 1H), 4.36 (td, *J* = 10.9, 5.0 Hz, 1H), 4.25 (m, 1H), 4.19 (m, *J* = 6.5, 2.0 Hz, 3H), 3.77 (dd, *J* = 11.2, 7.5 Hz, 6H), 1.44 (s, 3H), 1.33 (s, 3H), 1.25 (m, 26H), 0.87 (t, *J* = 6.6 Hz, 3H).

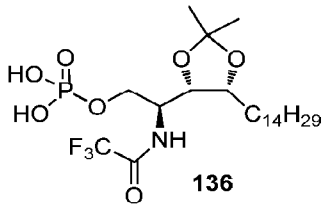
^{31}P NMR (121 MHz, Chloroform-*d*) δ 1.69.

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MS $C_{25}H_{47}F_3NO_7P$ [M-H$^+$]; calculated: 560.3, found: 560.2.

Example 43.

3,4-*O*-Isopropylidene-2-*N*-trifluoroacetyl-phytosphingosine-1-phosphate (136)



136

A solution of 3,4-*O*-Isopropylidene-2-*N*-trifluoroacetyl-phytosphingosine-1-*O*-dimethylphosphate **135** (650 mg, 1.16 mmol) in anhydrous methylene chloride (12 mL) was treated dropwise with trimethylsilyl bromide (0.81 mL, 6.23 mmol) at 0°C. After 12h at rt, the mixture was concentrated to dryness and the resulting residue co-evaporated with methylene chloride (3 x 50 mL) to remove excess trimethylsilyl bromide. The residue then was dissolved in cold (4°C) solution of 1% NH_4OH while maintaining pH 7-8. After 10 min at rt, the mixture was concentrated to dryness, and the resulting solid triturated with methanol/acetonitrile. The solid was collected by filtration, washed with acetonitrile, and dried under high vacuum to give **136** (500 mg, 75%) as a white solid.

^{1}H NMR (300 MHz, Methanol-d_4) δ 4.31 (dd, J = 8.7, 5.4 Hz, 1H), 4.09 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.31 (m, 26H), 0.89 (t, J = 6.4 Hz, 3H).

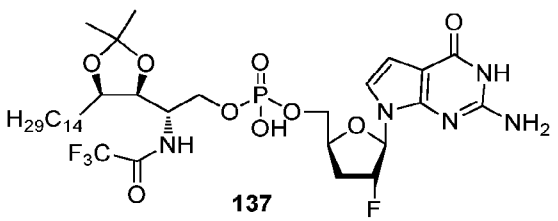
^{31}P NMR (121 MHz, Methanol-d_4) δ 1.28.

^{19}F NMR (282 MHz, Methanol-d_4) δ -77.13.

HRMS $C_{23}H_{42}F_3NO_7P$ [M-H$^+$]; calculated: 532.26565, found: 532.26630.

Example 44.

2',3'-dideoxy-2'-fluoro-5'-(*N*-trifluoroacetyl-3,4-O-isopropylidene-phytosphingosine-1-phospho)-7-deazaguanosine (137)



137

A mixture of *N*-trifluoroacetyl-phytosphingosine-1-phosphate **136**(200mg, 0.373

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mmol) and 2',3'-dideoxy-2'-fluoro-7-deazaguanine (100 mg, 0.373 mmol) was rendered anhydrous by co-evaporation with anhydrous pyridine (3 x 10 mL). The resulting residue then was dissolved in anhydrous pyridine (4 mL) and treated with diisopropylcarbodiimide (127 mg, 1.01 mmol) and HOBt (60 mg, 0.447 mmol). After 24 h at 75°C, the reaction mixture was cooled to rt and concentrated to dryness. The crude material was purified by flash column chromatography (19 mm x 170 mm) over silica gel using a solvent gradient from 5 to 7.5% methanol in chloroform with 1% (v/v) NH_4OH to give **137**(80 mg, 27%) as a white solid.

^1H NMR (300 MHz, Methanol-d_4) δ 6.88 (d, J = 3.8 Hz, 1H), 6.46 (d, J = 3.8 Hz, 1H), 6.24 (d, J = 19.9 Hz, 1H), 5.34 (dd, J = 52.4, 4.6 Hz, 1H), 4.53 (s, 1H), 4.34 – 3.97 (m, 6H), 2.63 – 2.17 (m, 2H), 1.40 (s, 3H), 1.30 (s, 3H), 1.27 (m, 26H), 0.89 (t, J = 6.6 Hz, 3H).

^{31}P NMR (121 MHz, Methanol-d_4) δ 12.50.

^{19}F NMR (282 MHz, Methanol-d_4) δ -77.10 , -179.69 – -180.25 (m).

MS $C_{34}H_{52}2F_4N_5O_9P$ [M-H^+]; calculated: 781.3, found: 782.2.

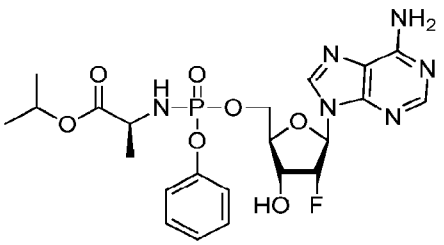
Example 45.

Experimental procedure for synthesis of prodrugs

A solution of isopropyl 2-((chloro(phenoxy)phosphoryl)amino)propanoate (0.397 g, 1.300 mmol) in anhydrous THF (5 ml) was added to a -78 °C stirred solution of 2'-deoxy-2'-fluoronucleoside (0.812 mmol) and 1-methyl-1H-imidazole (0.367 ml, 4.63 mmol) in pyridine (10.00 ml). After 15 min the reaction was allowed to warm to room temperature and was stirred for an additional 3 hours. Next, the solvent was removed under reduced pressure. The crude product was dissolved in 120 ml of DCM and was washed with 20 ml 1 N HCl solution followed by 10 ml water. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residues were separated over silica column (neutralized by TEA) using 5% MeOH in DCM as a mobile phase to yield the respective products as diastereomers.

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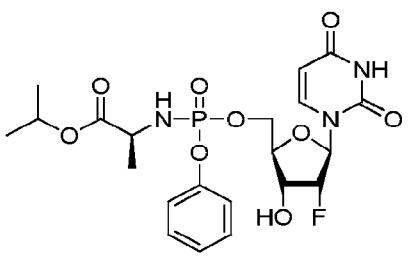
Example 46.



139

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 – 1.06 (m, 9H), 4.04 – 3.84 (m, 1H), 4.60 – 4.14 (m, 3H),4.86 – 4.64 (m, 1H), 5.11 – 4.90 (m, 1H), 5.61 – 5.19 (m, 1H), 6.32 – 5.94 (m, 3H), 7.44 – 7.02 (m, 5H), 8.11 – 7.89 (m, 1H), 8.46 – 8.20 (m, 1H). LC-MS *m/z* 589.4 ($M+H^+$).

Example 47.

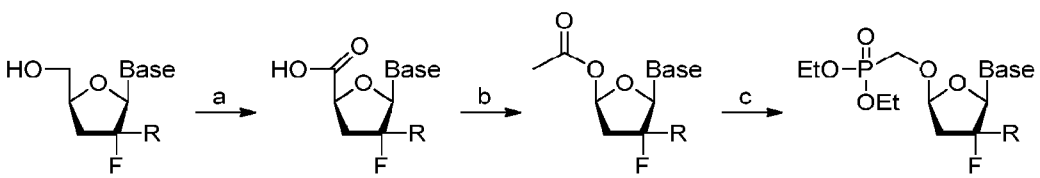


140

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 – 1.29 (m, 6H), 1.31 – 1.43 (m, 3H), 3.83 – 4.07 (m, 2H), 4.15 – 4.54 (m, 3H), 4.91 – 5.11 (m, 1H), 5.61 – 5.74 (m, 1H), 5.81 – 5.97 (m, 1H), 7.14 – 7.24 (m, 3H), 7.27 – 7.44 (m, 2H), 7.48 – 7.51 (m, 1H), 7.80 (t, *J* = 7.96, 7.96 Hz, 0H), 9.30 (s, 1H). LC-MS m/z 516.3 ($M+1^+$)

Example 48.

Phosphonate Synthesis

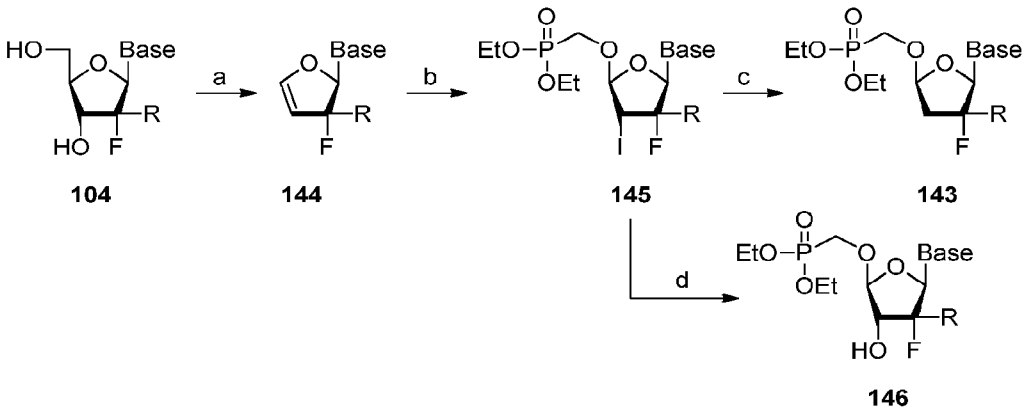


10 141 142 143

Reagents and conditions: a) BAIB, TEMPO; b) $Pb(OAc)_4$; c) $(EtO)_2POCH_2OH$, pTSA

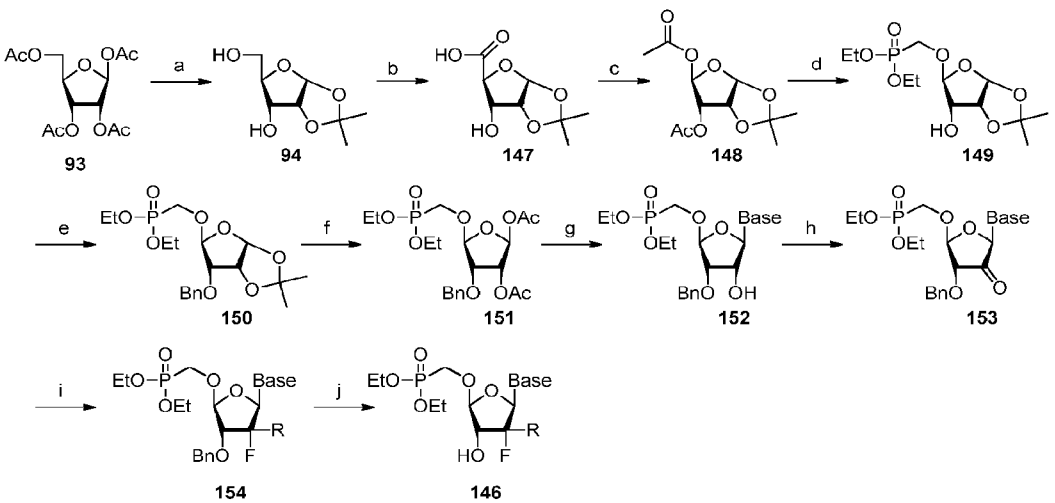
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Example 49.



Reagents and conditions: a) i. Pt/C, O_2, ii. DMF-dineopentyl acetal; b) IBr, $(EtO)_2POCH_2OH$; c) AIBN, Bu_3SnH; d) i. AgOAc, ii. NaOMe, MeOH, iii. PPh_3, DIAD, 4-$NO_2C_6H_4COOH$, iv. NaOMe, MeOH.

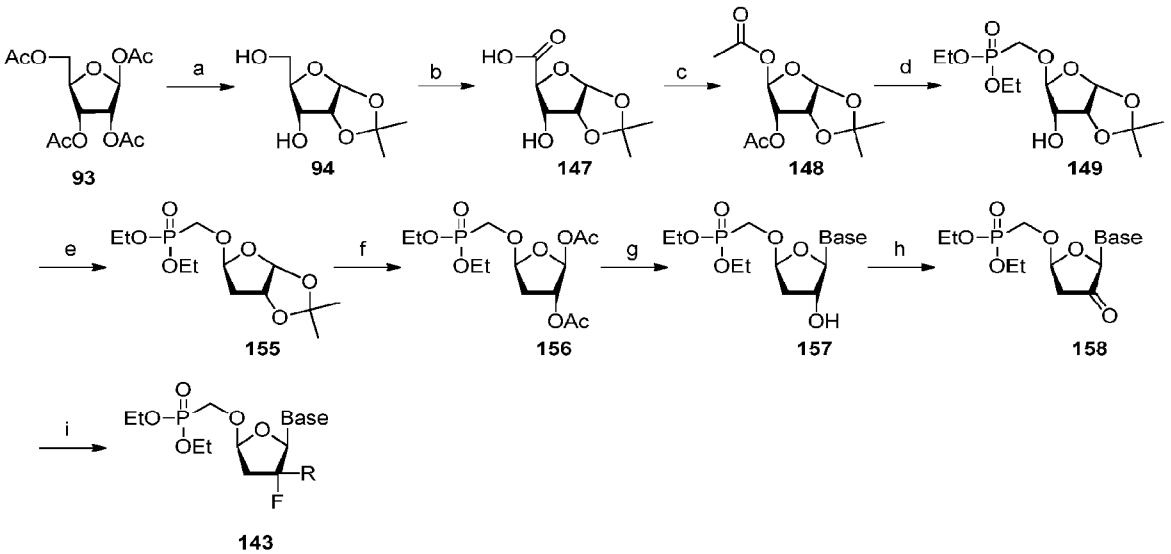
Example 50.



Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) Pt/C, O_2; c) i. $Pb(OAc)_4$, ii. Ac_2O, DMAP; d) i. $(EtO)_2POCH_2OH$, pTSA, ii. K_2CO_3, MeOH; e) BnCl, KOH; f) Ac_2O, AcOH, H_2SO_4; g) i. silylated base, TMSOTf, ii.K_2CO_3, MeOH; h) DMP; i) i. RLi or RMgBr, ii. DAST; j) H_2, Pd/C.

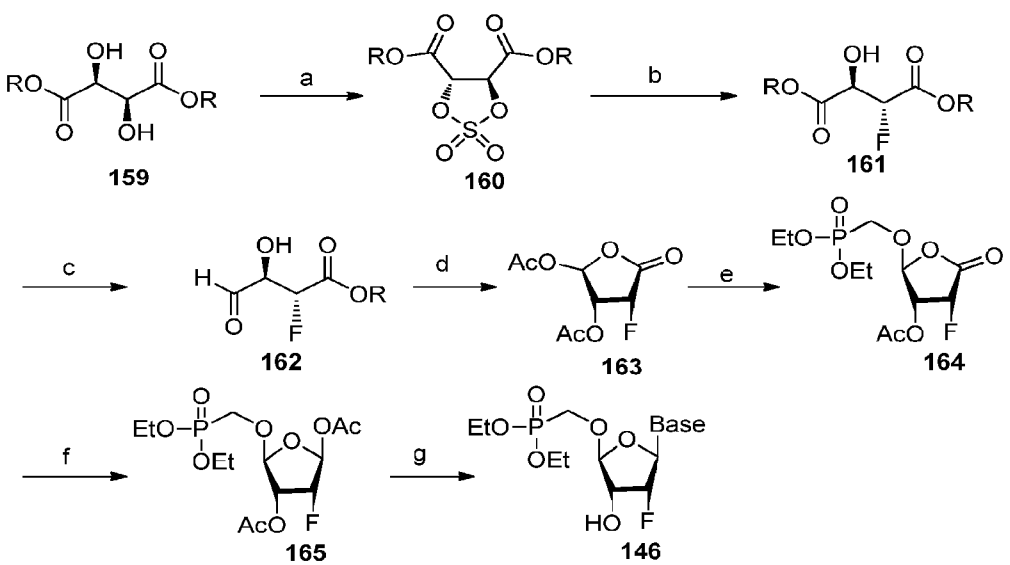
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Example 51.



Reagents and conditions: a) i. I_2, acetone, ii. K_2CO_3, MeOH; b) Pt/C, O_2; c) i. $Pb(OAc)_4$, ii. Ac_2O, DMAP; d) i. $(EtO)_2POCH_2OH$, pTSA, ii. K_2CO_3, MeOH; e) i. TCDI, pyridine, ii.Bu_3SnH, AIBN; f) Ac_2O, AcOH, H_2SO_4; g) i. silylated base, TMSOTf, ii.K_2CO_3, MeOH; h) DMP; i) i. RLi or RMgBr, ii. DAST

Example 52.

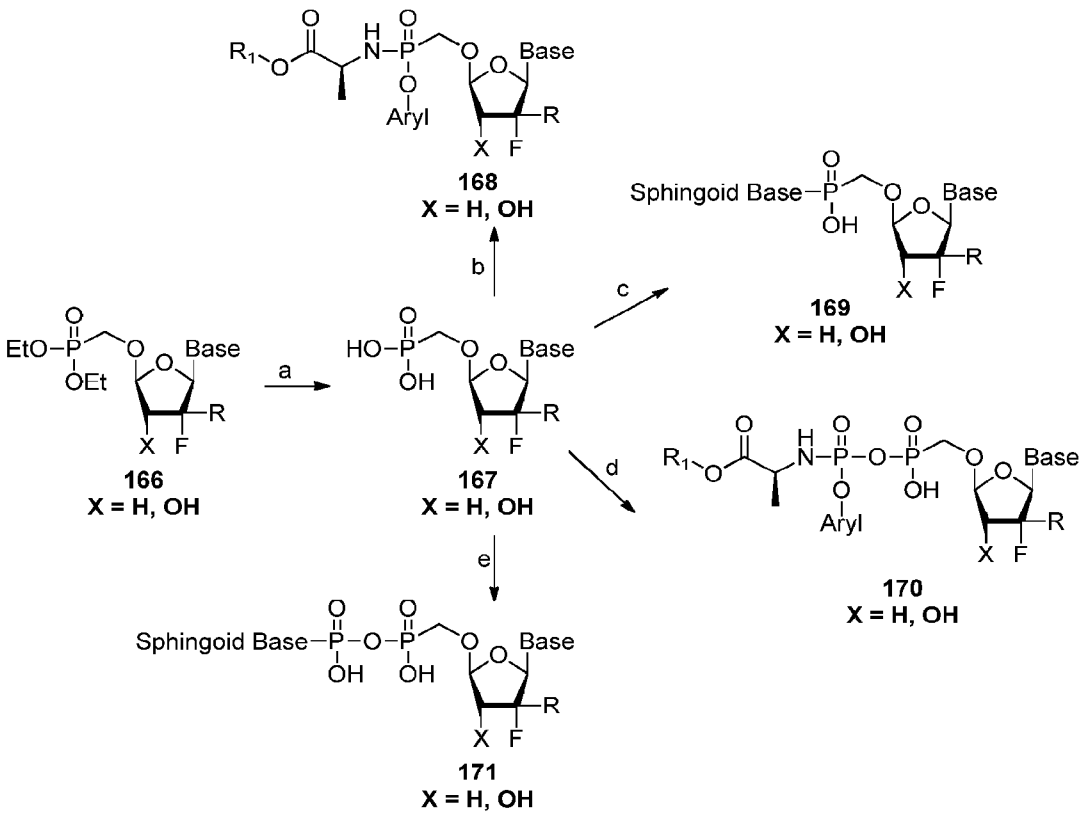


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Reagents and conditions: a) i. $SOCl_2$, ii. $NaIO_4$, $RuCl_3$; b) TBAF; c) $BF_3 \cdot OEt_2$, DIBAL; d) Ac_2O, AcOH, H_2SO_4; e) $(EtO)_2POCH_2OH$, pTSA; f) i. DIBAL, ii. Ac_2O, Et_3N, DMAP; g) i. silylated base, TMSOTf, ii. K_2CO_3, MeOH

Example 53.

Phosphonate Prodrug Synthesis

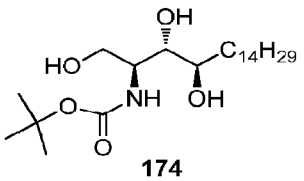


Reagents and conditions: a) TMSBr; b) amino ester, ArOH, Et_3N, 2,2'-dithiodipyridine, PPh_3; c) i. DIC, sphingoid base, ii. TFA; d) chlorophosphoramidate, Et_3N; e) DIC, sphingoid base-1-phosphate

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Example 54.

***N-tert*-Butyloxycarbonyl-phytosphingosine (174)**



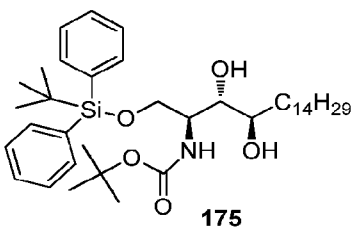
174

A suspension of phytosphingosine (10.6 g, 33.5 mmol) and triethylamine (5.6 ml, 40.2 mmol) in THF (250 mL) was treated dropwise with di-tert-butyl dicarbonate (8.6 mL, 36.9 mmol). After 12h at rt, the mixture was concentrated to dryness and the resulting white solid was recrystallized from ethyl acetate (80 mL) and then dried under high vacuum at 35°C for 12h to give **174**(10.5 g, 75%).

^{1}H NMR (400 MHz, Chloroform-*d*) □ 5.31 (d, *J* = 8.5 Hz, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.83 (s, 2H), 3.74 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.65 (d, *J* = 8.3 Hz, 1H), 3.61 (d, *J* = 3.9 Hz, 1H), 1.43 (s, 9H), 1.23 (s, 27H), 0.86 (t, *J* = 6.4 Hz, 3H).

Example 55.

2-*O-tert*-Butyldiphenylsilyl-1-*N-tert*-butyloxycarbonyl-phytosphingosine (175)



175

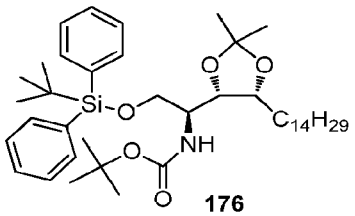
A solution of *N-tert*-Butyloxycarbonyl-phytosphingosine **174** (9.5 g, 22.65 mmol) and triethylamine (3.8 mL, 27.2 mmol) in anhydrous methylene chloride/DMF (120 mL/10 mL) was treated dropwise with *tert*-butylchlorodiphenylsilane (7 mL, 27.25 mmol). After 18h at rt, the mixture was diluted with methylene chloride (200 mL) and washed with 0.2N HCl (100 mL) and then brine (100 mL). The organic phase was dried over sodium sulfate, filtered and then concentrated to give **175** (14.9 g) as an oil which was used in the next reaction without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) □ 5.31 (d, *J* = 8.5 Hz, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.83 (m, 1H), 3.74 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.65 (d, *J* = 8.3 Hz, 1H), 3.61 (d, *J* = 3.9 Hz, 1H), 1.43 (s, 9H), 1.23 (s, 27H), 0.86 (t, *J* = 6.4 Hz, 3H).

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Example 56.

2-*O*-*tert*-Butyldiphenylsilyl-1-*N*-*tert*-butyloxycarbonyl-3,4-*O*-isopropylidene-phytosphingosine (176)



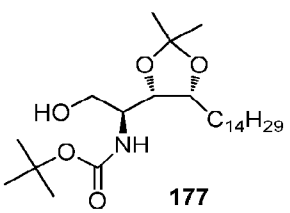
176

A solution of 2-*O*-*tert*-Butyldiphenylsilyl-1-*N*-*tert*-butyloxycarbonyl-phytosphingosine (**175**, 14.9 g, 22.65 mmol) in 1/1 (v/v) THF/2,2-dimethoxypropane was treated with catalytic *para*-toluenesulfonic acid (860 mg, 4.53 mmol). After 24h, the mixture was quenched with saturated sodium bicarbonate solution (50 mL). The mixture was concentrated and then dissolved in ethyl acetate (200 mL) and washed with brine (2 x 50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to give **176** (15.7 g) as a gum which was used in the next step without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) □ 7.66 (m, 4H), 7.51 – 7.27 (m, 6H), 4.78 (d, *J* = 10.0 Hz, 1H), 4.18 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.89 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.80 (d, *J* = 9.9 Hz, 1H), 3.72 (d, *J* = 9.9 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 3H), 1.35 (s, 3H), 1.25 (s, 27H), 1.05 (s, 9H), 0.87 (t, *J* = 6.5 Hz, 3H).

Example 57.

1-*N*-*tert*-butyloxycarbonyl-3,4-*O*-isopropylidene-phytosphingosine (177).



177

A solution of 2-*O*-*tert*-Butyldiphenylsilyl-1-*N*-*tert*-butyloxycarbonyl-3,4-*O*-isopropylidene-phytosphingosine **176** (15.7 g,22.6 mmol) in THF at 0°C was treated dropwise with a solution of tetrabutylammonium fluoride (1.0 M in THF, 24.9 mL, 24.9 mmol) over a 20 min period. After 16h at rt, tlc (3:1 hexanes:ethyl acetate) indicated complete conversion. The mixture was concentrated to dryness and the resulting residue was dissolved in ethyl acetate (300 mL) and washed with water (3 x 100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. The resulting oil purified by flash

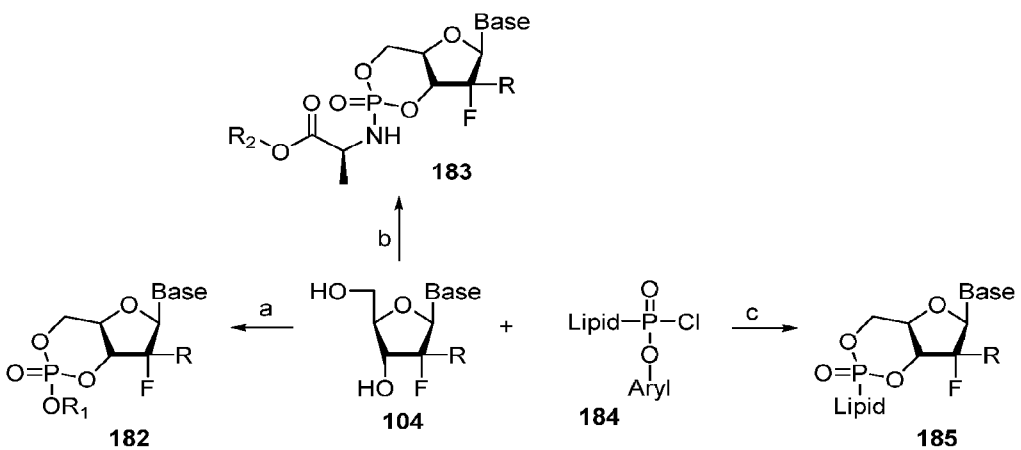
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column chromatography (35 mm x 180 mm) using a solvent gradient from 25 to 50% ethyl acetate in hexanes to give **177** (7.3 g, 71% over 3 steps) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) □ 4.93 (d, *J* = 9.1, 1H), 4.16 (q, *J* = 7.1, 6.4 Hz, 1H), 4.07 (t, *J* = 6.5 Hz, 1H), 3.83 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.76 (m, 1H), 3.67 (dd, *J* = 11.2, 3.6 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 9H), 1.32 (s, 3H), 1.23 (s, 27H), 0.86 (t, *J* = 6.9 Hz, 3H).

Example 58.

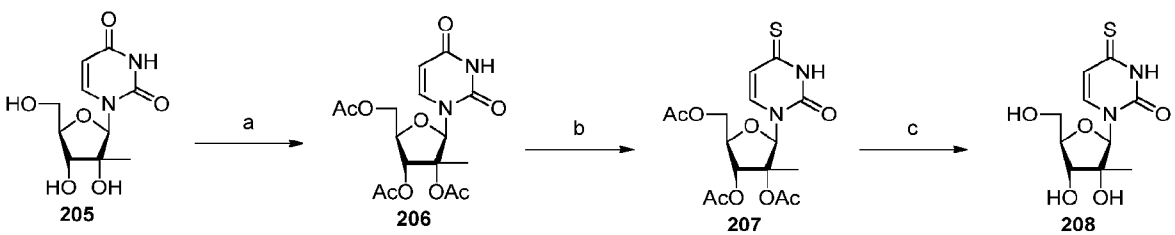
Synthesis of Cyclic Phosphate Prodrugs



Reagents and conditions: a) i. $R_1OP(NiPr_2)_2$, DCI, ii. mCPBA; b) i. chlorophosphoramidate, imidazole, ii. t-BuOK; c) i. imidazole, ii. t-BuOK

Example 59.

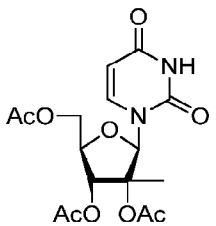
General Method for the Synthesis of 4-Thiouridine Nucleoside Analogs



Reagents and conditions: a) Ac_2O, Et_3N, DMAP; b) Lawesson's reagent, dioxane, reflux; c) NH_3, MeOH

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Example 60.

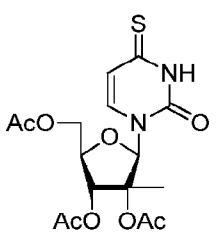


206

A suspension of 2'-Methyluridine (0.258 g, 0.999 mmol) in Ac_2O (4.00 ml) in the presence of DMAP (0.024 g, 0.200 mmol) and Et_3N (0.139 ml, 0.999 mmol) was stirred at r.t. overnight. The reaction mixture became homogeneous and yellowish upon stirring. The reaction was condensed on rotavap, and co-evaporated with EtOH (15 mL x 3). The product was purified *via* ISCO to give a white solid with a yield of >95%.

Physical data: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.519 (s, 3H), 2.087 (s, 6H), 2.099 (s, 3H), 4.265 (m, 1), 4.369 (m, 2H), 5.220 (d, 1H, J = 6 Hz), 5.756 (d, 1H, J = 8 Hz), 6.217 (s, 1H), 7.407 (d, 1H, J = 8 Hz), 9.744 (s, 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 17.773, 20.520, 20.687, 21.461, 62.649, 74.313, 79.284, 84.195, 89.409, 102.364, 140.530, 150.040, 163.071, 169.643, 169.742, 170.318; MS: m/z 273.1 (M-uracil+H); LC-MS 99.6% purity; HRMS Calc. for $C_{16}H_{21}O_9N_2$ (M+H): 385.12416, Found: 385.12420.

Example 61.

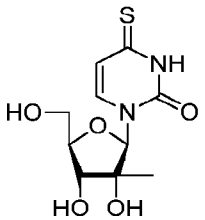


207

A mixture of per-Ac-2'-methyluridine (0.100 g, 0.260 mmol) and Lawesson's Reagent (0.127 g, 0.315 mmol) in dry Dioxane (1.301 ml) was refluxed under nitrogen for 2 hrs. The reaction was condensed on rotavap and the obtained yellow residue was loaded on ISCO and eluted with 3% MeOH/CH_2Cl_2. The obtained yellow foam was used in next step without further purification, and LC-MS showed 53% purity.

Example 62.

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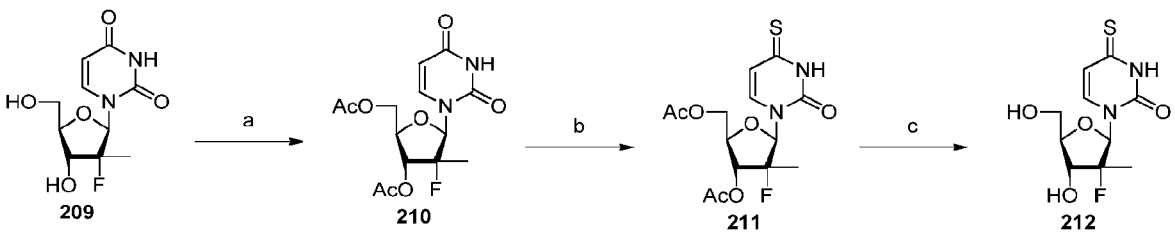


208

A solution of crude per-Ac-5-thio-2'-methyluridine obtained from previous step (0.126 g, 0.315 mmol) in NH_3 in MeOH (7 M, 1.573 ml, 11.01 mmol) was stirred at r.t. in a sealed tube for 4.5 hrs. The yellow solution was condensed on rotavap and loaded on ISCO (4g column, 8% → 15% MeOH/CH_2Cl_2) to give a yellow foam with a 55% yield in two steps.

Physical data: ^{1}H NMR (400Hz, CD_3OD): δ 1.201 (s, 3H), 3.835 (m, 2H), 3.983 (m, 2H), 5.595 (s, 1H), 6.396 (d, 1H, J = 7.6 Hz), 8.006 (d, 1H, J= 7.2 Hz); ^{13}C NMR (100Hz, CD_3OD): δ 20.983, 61.259, 74.123, 80.862, 84.809, 94.144, 114.863, 137.236, 150.806, 192.972; MS: m/z 275.0 (M+H); LC-MS 95.9% purity; HRMS Calc. for $C_{10}H_{15}O_5N_2S$ (M+H): 275.06962, Found: 275.06967.

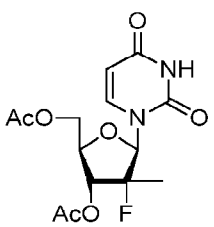
Example 63.



209 210 211 212

Reagents and conditions: a) Ac_2O, Et_3N, DMAP; b) Lawesson's reagent, dioxane, reflux; c) NH_3, MeOH

Example 64.



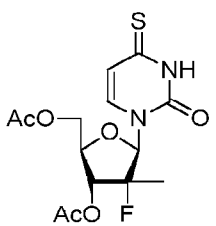
210

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A brownish suspension of 2'-F-2'-Methyluracil (0.120 g, 0.461 mmol) in Ac_2O (1.845 ml) in the presence of DMAP (5.63 mg, 0.046 mmol) was stirred at r.t. for 2 hrs. The reaction mixture became homogeneous upon stirring. The reaction was condensed on rotavap, and co-evaporated with MeOH (5 mL x 2). The obtained residue was purified *via* ISCO (12g column, 40% → 80% EtOAc/Hexanes) to give a white solid with 81% yield.

Physical data: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.398 (d, 3H, J = 22 Hz), 2.142 (s, 3H), 2.183 (s, 3H), 4.379 (m, 3H), 5.128 (dd, 1H, J_1 = 21.2 Hz, J_2 = 8.8 Hz), 5.788 (d, 1H, J = 8.4 Hz), 6.179 (d, 1H, J = 18.4 Hz), 7.549 (d, 1H, J = 8 Hz), 8.882 (s 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 17.113, 17.363, 20.490, 20.672, 61.457, 71.498, 71.665, 98.539, 100.390, 103.085, 138.990, 149.911, 162.312, 169.924; MS: m/z 345.0 (M-uracil+H); LC-MS 95% purity; HRMS Calc. for $C_{14}H_{18}FO_7N_2$ (M+H): 345.10926, Found: 345.10906.

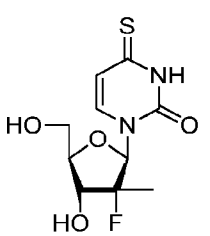
Example 65.



211

A yellow suspension of per-Ac-2'-F-2'-Methyluracil (0.129 g, 0.375 mmol) and Lawesson's Reagent (0.183 g, 0.453 mmol) in dry Dioxane (1.873 ml) was refluxed under argon for 1 hr, which became homogenous upon heating. The reaction was condensed on rotavap and the yellow residue was loaded on ISCO (12 g column, 20% → 100% EtOAc/Hexanes). The obtained yellow foam showed 74% purity of the desired product on LC-MS, which was used in next step without further purification.

Example 66.



212

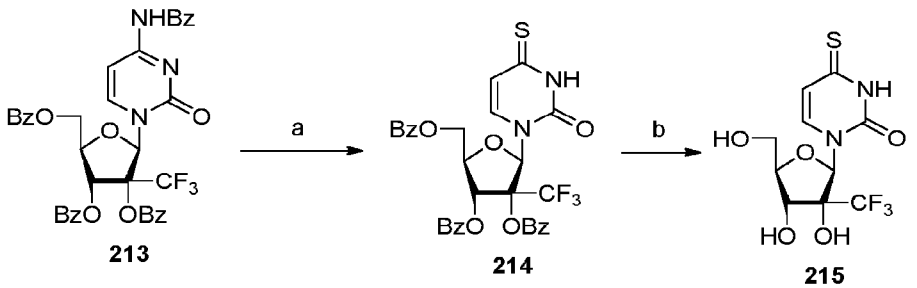
A solution of per-Ac-2'-F-2'-methyl-4-thiouracil (0.135 g, 0.375 mmol) in NH_3 in MeOH (7 M, 1.873 ml, 13.11 mmol) was stirred at r.t. in a sealed tube for 4.5 hrs (10:04:05

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AM).The yellow solution was condensed on rotavap and loaded on ISCO (4 g column, 5% → 12% MeOH/CH_2Cl_2). The obtained product is a yellow foam with a 73% yield in two steps.

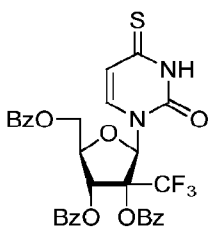
Physical data: ^{1}H NMR (400Hz, CD_3OD): δ 1.367 (d, 3H, J = 22.4 Hz), 3.794 (dd, 1H, J_1 = 12.4 Hz, J_2 = 2.4Hz), 3.971 (m, 3H), 6.094 (d, 1H, J = 18 Hz), 6.368 (d, 1H, J = 7.6 Hz), 7.888 (d, 1H, J = 7.6 Hz). ^{13}C NMR (100Hz, CD_3OD): δ 16.757 (d, J = 25 Hz), 59.951, 72.276, 83.395, 90.704 (d, J = 34.9 Hz), 101.894 (d, J = 179.9 Hz), 114.435, 135.602, 149.733, 192.200; MS: m/z 277.0 (M+H); LC-MS 100% purity; HRMS Calc. for $C_{10}H_{14}FO_4N_2S$ (M+H): 277.06528, Found: 277.06496.

Example 67.



Reagents and conditions: a) dioxane, Lawesson's reagent, reflux; b) NH_3/MeOH

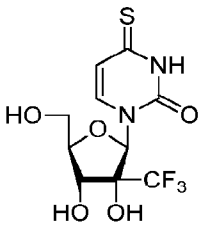
Example 68.



A stirred solution of benzoate (1g, 1.37mmol) in dioxane (6.9mL, .2M) was charged with Lawesson's reagent(673mg, 1.66mmol) and was heated to reflux, during which time reaction became homogeneous and brown. After 2h, reaction was concentrated and purified by silica gel chromatography 10-30% ethyl acetate in hexanes to provide 600mg of thiouridine 68%.

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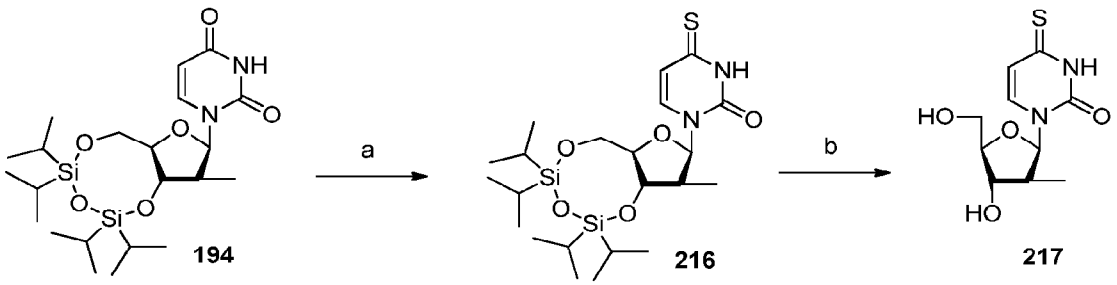
Example 69.



215

A stirred solution of benzoate (600mg, 2.08mmol) in ammonia (9mL, 7M in methanol) was prepared. After 16H, reaction was concentrated and purified by silica gel chromatography 2-15% methanol in dcm to provide 269 mg of thiourdine 87%.

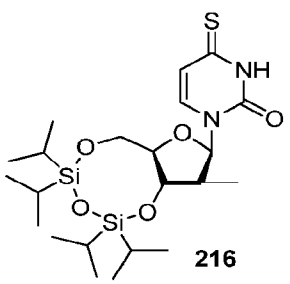
Example 70.



194 216 217

Reagents and conditions: a) dioxane, Lawesson's reagent, reflux; b) TBAF, THF

Example 71.



216

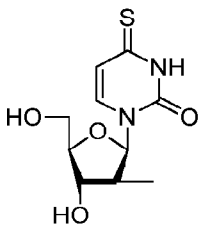
1-((6aR,8R,9S,9aR)-2,2,4,4-tetraisopropyl-9-methyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1H,3H)-dione (0.16 g, 0.33 mmol) was heated with Lawesson's reagent (0.17 g, 0.43 mmol) in dry 1,4-dioxane (1.65 mL) under argon for 1 h. Then solvent was removed in vacuo and the crude material was purified by ISCO column chromatography eluting from 10% to 40% EtOAc in hexanes to afford 1-((6aR,8R,9S,9aR)-2,2,4,4-tetraisopropyl-9-methyltetrahydro-6H-furo[3,2-

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f][1,3,5,2,4]trioxadisilocin-8-yl)-4-thioxo-3,4-dihydropyrimidin-2(1H)-one (0.11 g, 67%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (bs, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 6.40 (dd, *J* = 7.6, 1.6 Hz), 6.20 (d, *J* = 7.2 Hz, 1H), 4.18 (d, *J* =13.6 Hz, 1H), 4.04 – 3.89 (m, 2H), 3.78 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.71 – 2.62 (m, 1H), 1.12 – 0.84 (m, 31H).

Example 72.



217

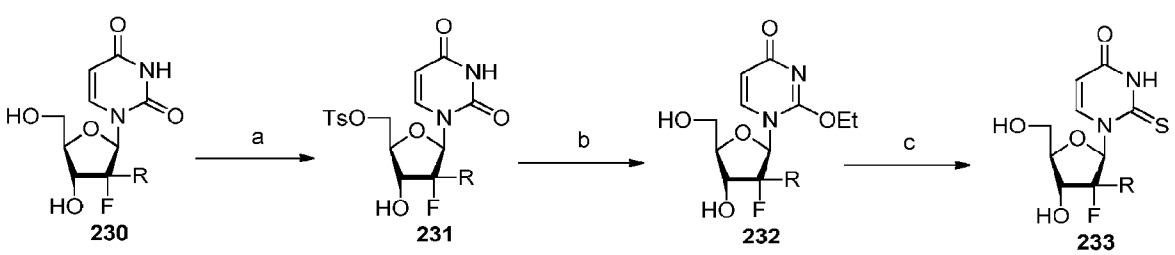
1-((6aR,8R,9S,9aR)-2,2,4,4-tetraisopropyl-9-methyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-4-thioxo-3,4-dihydropyrimidin-2(1H)-one (0.11 g, 0.22 mmol) was stirred with TBAF (1.0 M in THF, 0.44 mL, 0.44 mmol) at rt overnight. Then solvent was removed in vacuo and the crude material was purified by SiO2 column chromatography eluting from 100% DCM to 4% MeOH in DCM to afford 1-((2R,3S,4R,5R)-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-4-thioxo-3,4-dihydropyrimidin-2(1H)-one (33 mg, 58%) as a yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 7.6 Hz 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 6.17 (d, *J* = 7.6 Hz, 1H), 3.96 – 3.71 (m, 4H), 2.53 – 2.50 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H).

LCMS $C_{10}H_{13}N_2O_4S$ [M+H$^+$]; calculated: 257.1, found 256.9.

Example 73.

Synthetic Route for the Synthesis of 2'-Fluoro-2-Thiouridine Nucleoside Analogs



230 **231** **232** **233**

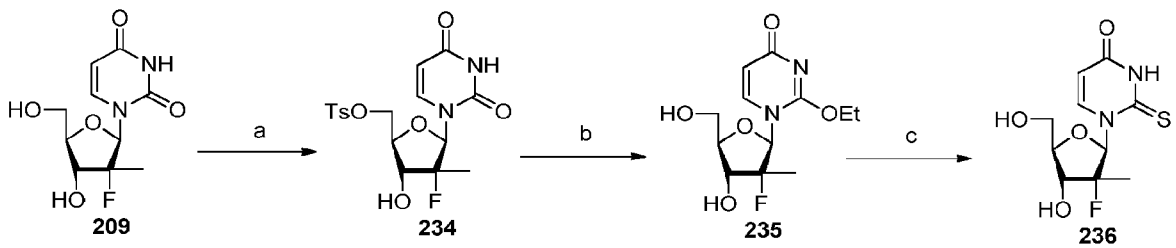
Reagents and conditions: a) tosyl chloride, Et_3N, DMAP; b) $NaHCO_3$, ethanol, reflux; c) NaSH, DMF

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2'-Fluoro-2-thiouridine nucleoside analogs can be made by treating the parent nucleoside (1 equivalent) with tosyl chloride (1.2 equivalents) dissolved in pyridine:DCM (1:1) under an inert atmosphere. The resulting 5'-tosyl nucleoside analog can then be treated with sodium bicarbonate (5 equivalents) in reflux ethanol to obtain the 2-ethoxy nucleoside. Finally, the desired 2-thionucleoside analog can be obtained by treating the 2-ethoxy intermediate with sodium hydrosulfide (10 equivalents) in a polar solvent such as DMF.

Example 74.

Synthetic Route for the Synthesis of 2'-Fluoro-2'-Methyl--2-Thiouridine Nucleoside Analogs

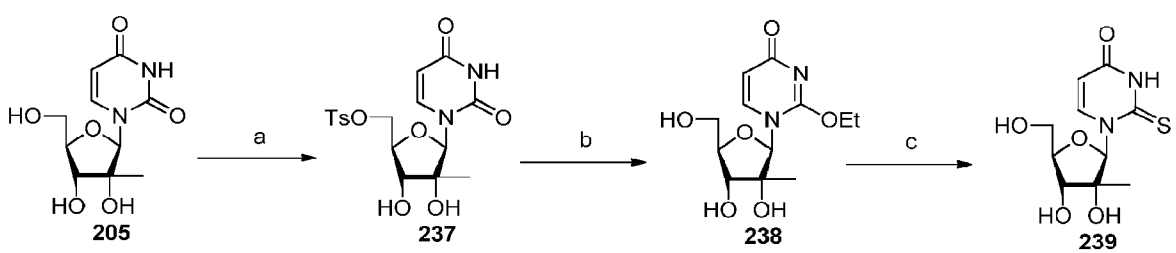


Reagents and conditions: a) tosyl chloride, Et_3N, DMAP; b) $NaHCO_3$, ethanol, reflux; c) NaSH, DMF

2'-Fluoro-2'-methyl-2-thiouridine nucleoside analogs can be made by treating the parent nucleoside (1 equivalent) with tosyl chloride (1.2 equivalents) dissolved in pyridine:DCM (1:1) under an inert atmosphere. The resulting 5'-tosyl nucleoside analog can then be treated with sodium bicarbonate (5 equivalents) in reflux ethanol to obtain the 2-ethoxy nucleoside. Finally, the desired 2-thionucleoside analog can be obtained by treating the 2-ethoxy intermediate with sodium hydrosulfide (10 equivalents) in a polar solvent such as DMF.

Example 75.

Synthetic Route for the Synthesis of 2'-C-Methyl--2-Thiouridine Nucleoside Analogs



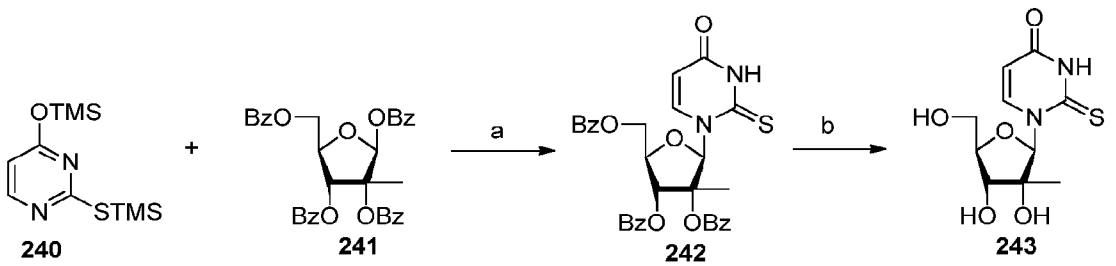
Reagents and conditions: a) tosyl chloride, Et_3N, DMAP; b) $NaHCO_3$, ethanol, reflux; c) NaSH, DMF

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2'-C-methyl-2-thiouridine nucleoside analogs can be made by treating the parent nucleoside (1 equivalent) with tosyl chloride (1.2 equivalents) dissolved in pyridine:DCM (1:1) under an inert atmosphere. The resulting 5'-tosyl nucleoside analog can then be treated with sodium bicarbonate (5 equivalents) in reflux ethanol to obtain the 2-ethoxy nucleoside. Finally, the desired 2-thionucleoside analog can be obtained by treating the 2-ethoxy intermediate with sodium hydrosulfide (10 equivalents) in a polar solvent such as DMF.

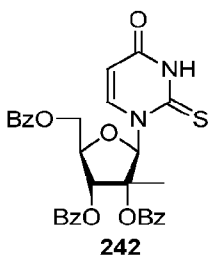
Example 76.

Alternative Synthetic Route for the Synthesis of 2'-C-Methyl--2-Thiouridine Nucleoside Analogs



Reagents and conditions: a) $SnCl_4$, DCE, rt; b) NH_3/MeOH

Example 77.



The persilylated 2-thiouracil was prepared in a round bottom flask charged with 2-thiouracil (1.99 g, 15.5 mmol), chlorotrimethylsilane (1.55 mL, 12.21 mmol), and bis(trimethylsilyl)amine (46.5 mL, 222 mmol) under nitrogen. The mixture was refluxed with stirring overnight (16 h) until all solids dissolved and a blue-green solution formed. The mixture was cooled to room temperature and volatiles were removed by rotary evaporation followed by high vacuum to give persilylated 2-thiouracil as a light blue liquid. This compound was used immediately in the next step.

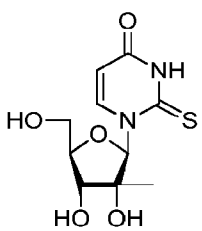
The freshly prepared persilylated 2-thiouracil **240** (4.22 g, 15.50 mmol) was dissolved in 1,2-dichloroethane (50 mL) under nitrogen with stirring at room temperature. A solution

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of **241** (4.50 g, 7.75 mmol) in 1,2-dichloroethane (50 mL) was added all at once to the stirred mixture.

To this mixture was added $SnCl_4$ (1.36 mL, 3.03 g, 11.63 mmol) dropwise via syringe, and the mixture was stirred at room temperature 6 h until all starting material was consumed. The mixture was cooled to 0°C and a sat. aq. $NaHCO_3$ solution (125 mL) was added. The mixture was warmed to room temperature and stirred 30 min. The mixture was extracted with EtOAc (2 x 200 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 to give 5.5 g crude product. The crude material was taken up in dichloromethane, immobilized on Celite, and subjected to flash chromatography on the Combiflash (120 g column, 5 to 50% EtOAc in hexanes gradient) to give **242** (2.41 g, 53%) as a clear sticky solid in ~90% purity. This material was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 9.37 (br s, 1H), 8.10-8.05 (m, 4H), 7.82 (d, J = 7.7 Hz, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.66-7.45 (m, 6H), 7.42 (t, J = 7.8 Hz, 2H), 7.27-7.21 (m, 2H), 5.88 (d, J = 8.2, 1H), 5.62 (d, J = 5.5 Hz, 1H), 4.91-4.83 (m, 2H), 4.77 (dd, J = 11.8 Hz, 4.7 Hz, 1H), 1.77 (s 3H).

Example 78.



243

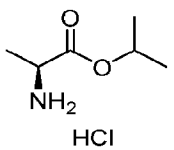
A round bottom flask was charged with **242** (2.41 g, 4.11 mmol) under nitrogen and cooled to 0°C. To this flask was added a ~7.0 N solution of ammonia in methanol (58.7 mL, 411 mmol) and the mixture was gently stirred and allow to warm to room temperature overnight. After 24 h stirring at room temperature, volatiles were removed by rotary evaporation to give 2.5 g of crude material. The crude material was taken up in MeOH, immobilized on Celite, and subjected to flash chromatography on the Combiflash (80 g column, 0 to 10% EtOH in EtOAc gradient) to give **243** (0.873 g, 41% two-step yield from scaffold) as an off-white solid. ^{1}H NMR (400 MHz, MeOH-d_4) □ ppm 8.27 (d, J = 8.2 Hz, 1H); 6.95 (s, 1H), 5.95 (d, 1H, J = 8.1 Hz), 3.98 (dd, J = 12.5 Hz, 2.1 Hz, 1H), 3.93 (dt, J = 9.3 Hz, 2.1 Hz, 1H), 3.84 (d, J = 9.4 Hz, 1H), 3.78 (dd, J = 12.5 Hz, 2.3 Hz), 1.24 (s, 3H).

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Example 79.

General Procedure for the Preparation of 5'-Phosphoramidate Prodrugs

Synthesis of chlorophosphoramidate:

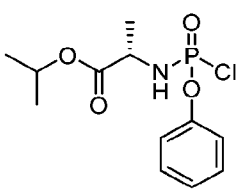


251

Thionyl chloride (80 g, 49.2 mL, 673 mmol) was added dropwise over a 30 min period to a suspension of L-alanine (50g, 561 mmol) in isopropanol (500 mL). The mixture was heated to a gentle reflux for 5h and then concentrated by rotary evaporator (bath set at 60°C). The resulting thick gum solidified upon trituration with ether (150 ml). The white powder was triturated a second time with ether (150 mL), collected by filtration while under a stream of argon, and then dried under high vacuum for 18h to give (S)-isopropyl 2-aminopropanoate hydrochloride (88 g, 94%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 3H), 5.10 – 4.80 (m, 1H), 3.95 (q, J = 7.2 Hz, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.22 (d, J = 4.6 Hz, 3H), 1.20 (d, J = 4.6 Hz, 3H).

Example 80.



252

A solution of phenyl dichlorophosphate (30.9 g, 146 mmol) in dichloromethane (450 mL) was cooled to 0°C then treated with (S)-isopropyl 2-aminopropanoate hydrochloride (24.5 g, 146 mmol). The mixture was further cooled to -78°C and then treated dropwise with triethylamine (29.6 g, 40.8 mL, 293 mmol) over a 30 min period. The mixture continued to stir at -78°C for an additional 2 h and then allowed to gradually warm to rt. After 18h the mixture was concentrated to dryness and the resulting gum dissolved in anhydrous ether (150 mL). The slurry was filtered while under a stream of argon, and the collected solid washed with small portions of anhydrous ether (3 x 30 mL). Combined filtrates were concentrated to

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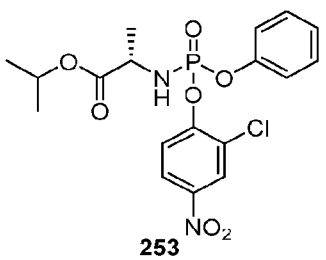
dryness by rotary evaporator to give a 1:1 diastereomeric mixture of phosphochloridate (41.5 g, 93%) as pale yellow oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.14 (m, 5H), 5.06 (m, 1H), 4.55 (dd, *J* = 14.9, 7.0 Hz, 1H), 4.21 – 4.01 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 2H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 5.8 Hz, 3H).

^{31}P NMR (121 MHz, Chloroform-*d*) δ 8.18 and 7.87.

Example 81.

Synthesis of 2-chloro-4-nitrophenyl phosphoramidate:



253

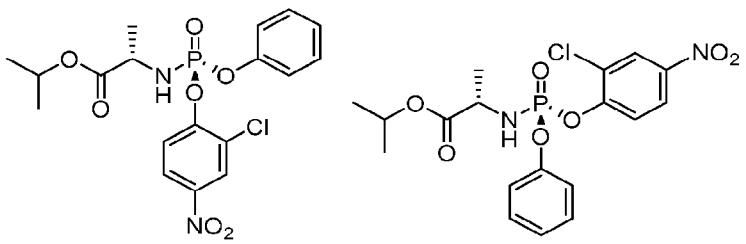
A solution of phenyl dichlorophosphate (60 g, 42.5 mL, 284 mmol) in dichloromethane (300 mL) was cooled to 0°C and then treated with (S)-isopropyl 2-aminopropanoate hydrochloride (47.7 g, 284 mmol). The mixture was further cooled to -78°C and treated dropwise with a solution of triethylamine (57.6 g, 79 mL, 569 mmol) in methylene chloride (300 mL) over a 1 h period. The reaction mixture was warmed to 0°C for 30 min and then treated with a preformed mixture of 2-chloro-4-nitrophenol (46.9 g, 270 mmol) and triethylamine (28.8 g, 39.6 mL, 284 mmol) in dichloromethane (120 mL) over a 20 min period. After 2 h at 0°C, the mixture was filtered through a fritted funnel, and the collected filtrate concentrated to dryness. The crude gum was dissolved MTBE (500 mL) and washed with 0.2 M K_2CO_3 (2 x 100 mL) followed by 10% brine (3 x 75 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to dryness by rotary evaporator to give a diastereomeric mixture (100 g, 93%) as a pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 2.7, 1.1 Hz, 1H, diastereomer 1), 8.31 (dd, *J* = 2.7, 1.1 Hz, 1H, diastereomer 2), 8.12 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.72 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.28 – 7.19 (m, 6H), 5.01 (pd, *J* = 6.3, 5.2 Hz, 1H), 4.22 – 4.08 (m, 1H), 3.96 (td, *J* = 10.7, 9.1, 3.6 Hz, 1H), 1.43 (dd, *J* = 7.0, 0.6 Hz, 3H), 1.40 (dd, *J* = 7.2, 0.6 Hz, 3H, diastereomer 2), 1.25 – 1.20 (m, 9H).

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Example 82.

Separation of compound 253 diastereomers:



Sp-diastereomer
254

Rp-diastereomer
255

The diastereomeric mixture **253** (28 g, 63.2 mmol) was dissolved in 2:3 ethyl acetate:hexanes (100 mL) and cooled to -20°C. After 16 h, the resulting white solid was collected by filtration and dried under high vacuum to give a 16:1 S_p:R_p-diastereomeric mixture (5.5 g, 19.6%). The mother liquor was concentrated and the resulting residue dissolved in 2:3 ethyl acetate:hexanes (50 mL). After 16h at -10°C, the resulting white solid was collected and dried under high vacuum to give a 1:6 S_p:R_p-diastereomeric mixture (4g, 14%). The 16:1 S_p:R_p-diastereomeric mixture (5.5 g, 12.4 mmol) was suspended in hot hexanes (50 mL) and treated slowly with ethyl acetate (approximately 10 mL) until complete dissolution. After cooling to 0°C, the resulting white solid was collected by filtration, washed with hexanes, and dried under high vacuum to give the S_p –diastereomer of **254** (4.2 g, 76%) as a single isomer.

^{1}H NMR (S_p-diastereomer, 400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 2.7, 1.1 Hz, 1H), 8.12 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.71 (dd, *J* = 9.1, 1.2 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.29 – 7.11 (m, 3H), 5.00 (m, 1H), 4.25 – 4.07 (m, 1H), 3.97 (dd, *J* = 12.7, 9.4 Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 2.2 Hz,3H), 1.21 (d, *J* = 2.2 Hz, 3H).

The 1:6 S_p:R_p-diastereomeric mixture (4 g, 12.4 mmol) was suspended in hot hexanes (50 mL) and treated slowly with ethyl acetate (approximately 5 mL) until complete dissolution. After cooling to 0°C, the resulting white solid was collected by filtration, washed with hexanes, and dried under high vacuum to give the R_p –diastereomer of **255** (3.2g, 80%) as a single isomer. Absolute stereochemistry was confirmed by X-ray analysis.

^{1}H NMR (R_p-diastereomer , 400 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 2.7, 1.1 Hz, 1H), 8.11 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.72 (dd, *J* = 9.1, 1.2 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.31 – 7.14 (m,

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3H), 5.01 (p, J = 6.3 Hz, 1H), 4.15 (tq, J = 9.0, 7.0 Hz, 1H), 4.08 – 3.94 (m, 1H), 1.40 (d, J = 7.0 Hz, 3H), 1.24 (d, J = 3.5 Hz, 3H), 1.22 (d, J = 3.5 Hz, 3H).

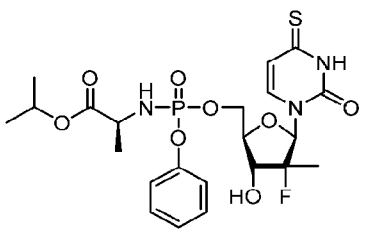
Example 83.

General procedure for phosphoramidate prodrug formation:

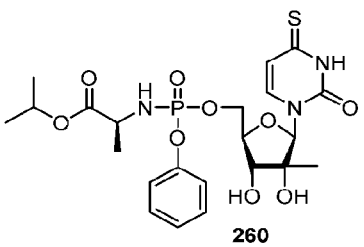
The desired nucleoside (1 equivalent) to be converted into its 5'-phosphoramidate prodrug was dried in a vaccum oven at 50°C overnight. The dry nucleoside is placed in a dry flask under an inert atmosphere and suspended in either dry THF or dry DCM to achieve a 0.05M solution. The flask was then cooled to 0°C, and the chlorophosphoramidate reagent (5 equivalents) was added to the suspended nucleoside. Next, 1-methylimidazole (8 equivalents) was added to the reaction mixture dropwise. The reaction was allowed to stir at room temperature for 12-72 hours. After the reaction was complete as judged by TLC, the reaction mixture was diluted with ethyl acetate. The diluted reaction mixture was then washed with saturated aqueous ammonium chloride solution. The aqueous layer was re-extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The concentrated crude product was then purified on silica eluting with a gradient of DCM to 5% MeOH in DCM.

Example 84.

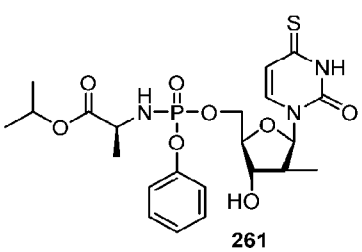
5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:



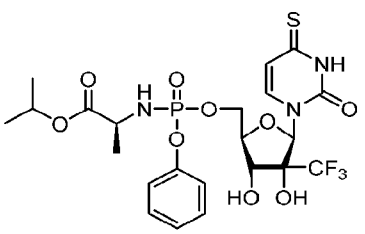
259



260



261

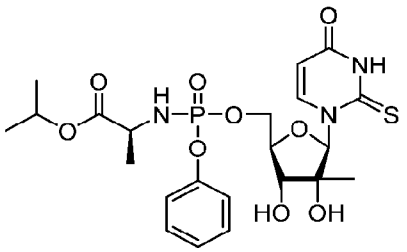


264

Example 85.

Procedure for Synthesis of 2'-C-Methyl-2-Thiouridine-5'-Phosphoramidate:

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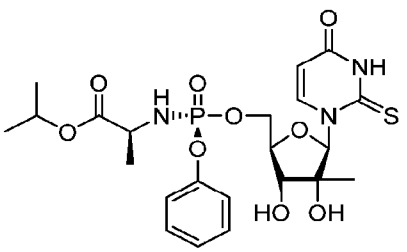


275

The desired nucleoside (1 equivalent) to be converted into its 5'-phosphoramidate prodrug was dried in a vaccum oven at 50°C overnight. To a stirred solution of 1-((2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (100 mg, 0.365 mmol) in THF (4 ml) at 0°C under nitrogen, was added (2S)-isopropyl 2-((chloro(phenoxy)phosphoryl)amino)propanoate (334 mg, 1.094 mmol) in THF (2.000 ml) dropwise via syringe. The stirred mixture was treated with 1-methyl-1H-imidazole (0.145 ml, 1.823 mmol) dropwise via syringe over 5 min. The mixture was slowly warmed to rt and stirred overnight. After 20 h stirring, the mixture was concentrated by rotary evaporation and taken up in 2 mL EtOH. A quick column on the Isco (12 g column, 0 to 3% EtOH in EtOAc) removed most baseline impurities to give 220 mg of compound. A second column on the Isco (12 g column, 0 to 3% EtOH in EtOAc) removed the less polar impurities but the more polar ones streaked with the product. 170 mg total were recovered. A third column on the Isco (12 g column, 0 to 10% MeOH in DCM) gave good separation and produced the desired product (93 mg, 0.171 mmol, 46.9 % yield).

Example 86.

Synthesis of (S,Sp)-diastereomer of compound 275:



276

To a dry 50 ml flask was added 1-((2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.5 g, 1.823 mmol) and THF (20 ml) and suspension was cooled in ice bath under nitrogen. tert-butylmagnesium chloride (2.260 ml, 2.260 mmol) was added via syringe and clear solution was formed. The mixture was stirred at ambient temp for 30 minutes and cooled to 0 °C again. A solution of

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compound **254** in THF (20 ml) was added via syringe over 10 min. period at O °C. The resulting yellowish color solution was stirred at RT for overnight.

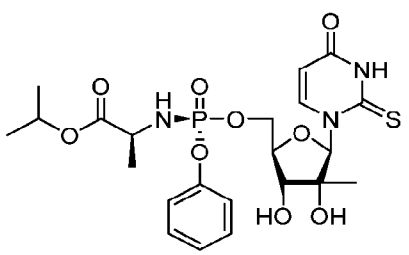
The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer washed with 5% K2CO3 solution, water and brine dried and concentrated under reduced pressure to give crude product. TLC 5% MeOH/DCM: SM Rf=0.25 and product Rf= 0.5. The product was purified on 20 g of SiO2 and eluting with 500 ml 3% MeOH in DCM. Desired fractions were combined and concentrated to give TLC single spot product. Small amount was crystallized as a plates by dissolving in toulene and allowing it to stand at RT for few weeks.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.76 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.34 – 7.13 (m, 3H), 6.98 (s, 1H), 5.87 (d, J = 8.1 Hz, 1H), 5.06 – 4.89 (m, 1H), 4.53 (ddd, J = 11.8, 5.8, 2.0 Hz, 1H), 4.39 (ddd, J = 11.9, 5.8, 3.3 Hz, 1H), 4.11 (dp, J = 7.9, 2.2 Hz, 1H), 3.92 (dq, J = 9.9, 7.0 Hz, 1H), 3.78 (d, J = 9.4 Hz,1H), 1.36 (dd, J = 7.2, 1.0 Hz, 3H), 1.24 (s, 3H), 1.23 (d, J = 1.5 Hz, 3H), 1.21 (d, J = 1.5 Hz, 3H).

MS $C_{22}H_{31}N_3O_9PS$ [M+H$^+$]; calculated: 544.1, found: 544.1.

Example 87.

Synthesis of (S,Rp)-diastereomer of compound 275:



277

To a dry 50 ml flask was added 1-((2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.5 g, 1.823 mmol) and THF (20 ml) and suspension was cooled in ice bath under nitrogen. tert-butylmagnesium chloride (2.260 ml, 2.260 mmol) was added via syringe and clear solution was formed. The mixture was stirred at ambient temp for 30 minutes and cooled to 0 °C again. A solution of compound **255** in THF (20 ml) was added via syringe over 10 min. period at O °C. The resulting yellowish color solution was stirred at RT for overnight.

The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer washed with 5% K2CO3 solution, water and brine dried

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and concentrated under reduced pressure to give crude product. TLC 5% MeOH/DCM: SM Rf=0.25 and product Rf= 0.5. The product was purified on 20 g of SiO2 and eluting with 500 ml 3% MeOH in DCM. Desired fractions were combined and conc to give TLC single spot product.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.31 – 7.14 (m, 3H), 6.98 (s, 1H), 5.91 (d, J = 8.1 Hz, 1H), 4.99 (mz, 1H), 4.60 (ddd, J = 11.9, 4.8, 2.1 Hz, 1H), 4.43 (ddd, J = 11.8, 5.3, 2.6 Hz, 1H), 4.18 – 3.98 (m, 1H), 3.90 (dq, J = 9.3, 7.2 Hz, 1H), 3.78 (d, J = 9.4 Hz, 1H), 1.32 (dd, J = 7.1, 1.3 Hz, 3H), 1.23 (m, 8H).

MS $C_{22}H_{31}N_3O_9PS$ [M+H$^+$]; calculated: 544.1, found: 544.1.

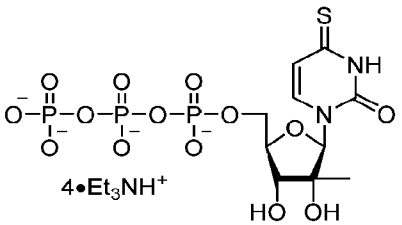
Example 88.

General Procedure for Preparation of 5'-Triphosphates:

Nucleoside analogue was dried under high vacuum at 50°C for 18h and then dissolved in anhydrous trimethylphosphate (0.3 M). After addition of proton-sponge® (1.5 molar equiv), the mixture was cooled to 0°C and treated dropwise with phosphoryl chloride (1.3 molar equiv) via microsyringe over a 15 min period. The mixture continued stirring at 0°C for 4 to 6 h while being monitored by tlc (7:2:1 isopropanol: conc. NH_4OH: water). Once greater than 85% conversion to the monophosphate, the reaction mixture was treated with a mixture of bis(tri-n-butylammonium pyrophosphate) (3 molar equiv) and tributylamine (6 molar equiv) in anhydrous DMF (1 mL). After 20 min at 0°C with monitoring by tlc (11:7:2 NH_4OH: isopropanol: water), the mixture was treated with 20 mL of a 100 mM solution of triethylammonium bicarbonate (TEAB), stirred for 1h at rt and then extracted with ether (3 x 15 mL). The aqueous phase was then purified by anion-exchange chromatography over DEAE Sephadex® A-25 resin (11 x 200 mm) using a buffer gradient from 50 mM (400 mL) to 600 mM (400 mL) TEAB. Fractions of 10 mL were analyzed by tlc (11:7:2 NH_4OH: isopropanol: water). Triphosphate (eluted @ 500 mM TEAB) containing fractions were combined and concentrated by rotary evaporator (bath < 25°C). The resulting solid was reconstituted in DI water (10 mL) and concentrated by lyophilization.

Example 89.

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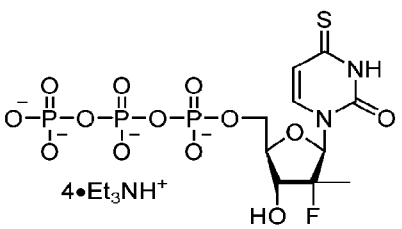


280

Triphosphate was prepared according to the general procedure.

Physical data: ^{1}H NMR (400Hz, D_2O): δ 1.226 (s, 3H), 1.280 (t, 36H, J = 7.2 Hz), 3.202 (q, 24H, J = 7.2 Hz), 4.143 (m, 2H), 4.363 (dq, 2H, J_1 = 12.8 Hz, J_2 = 1.2 Hz), 6.006 (s, 1H), 6.666 (d, 1H, J = 7.6 Hz), 7.889 (d, 1H, J = 7.2 Hz); MS (negative ion): m/z 512.9 (M-H).

Example 90.

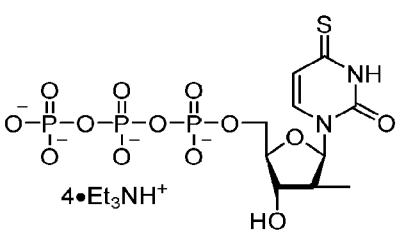


281

Triphosphate was prepared according to the general procedure.

Physical data: ^{1}H NMR (400Hz, D_2O): δ 1.402 (d, 3H, J = 23.2 Hz), 1.262 (t, 36H, J = 7.2 Hz), 3.186 (q, 24H, J = 7.2 Hz), 4.314 (m, 4H), 6.212 (d, 1H, J = 18.8 Hz), 6.650 (d, 1H, J = 7.6 Hz), 7.770 (d, 1H, J = 7.6 Hz); MS (negative ion): m/z 514.9 (M-H).

Example 91.



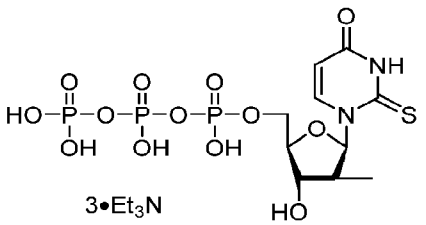
289

Following the General Procedure for making triphosphate, ((2R,3S,4R,5R)-3-hydroxy-4-methyl-5-(2-oxo-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate (4 mg, 3.5%) was obtained as a yellow solid as tetra-triethylammonium salt.

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^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.29 (d, *J* = 7.6 Hz, 1H), 4.33 (bs, 2H), 4.13 (t, *J* = 8.8, 1H), 4.00 (d, *J* = 7.2 Hz, 1H), 3.21 (q, *J* = 6.8 Hz, 24H), 2.72 – 2.64 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 36H).

Example 92.



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Following the General Procedure for making triphosphates, ((2R,3S,4R,5R)-3-hydroxy-4-methyl-5-(4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate (69 mg, 44%) was obtained as a white solid as a triple triethylamine salt.

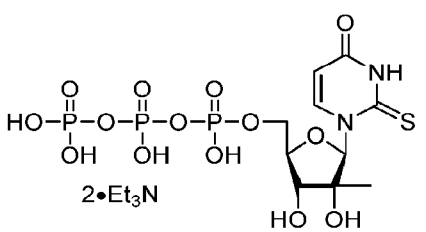
^{1}H NMR (400 MHz, D_2O) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.24 (d, *J* = 7.2 Hz, 1H), 4.35 (bs, 2H), 4.20 (t, *J* = 8.4 Hz, 1H), 4.03 – 4.01 (m, 1H), 3.21 (q, *J* = 7.6 Hz, 18H), 2.80 – 2.73 (m, 1H), 1.28 (t, *J* = 7.6 Hz, 27H), 1.00 (d, *J* = 7.2 Hz, 3H).

^{31}P NMR (121 MHz, D_2O) δ -6.03 (d, *J* = 21.1 Hz, γP), -10.52 (d, *J* = 20.2 Hz, αP), -21.76 (t, *J* = 20.7 Hz, βP).

HRMS $C_{10}H_{16}N_2O_{13}P_3S$ [M-H^+]; calculated: 496.9664, found 496.9586.

Example 93.

Method for the Synthesis of 2'-C-Methyl-2-Thiouridine-5'-Triphosphate



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After drying under high vacuum at 50°C for 18h, 2'-C-methyl-2-thiouridine (29 mg, 0.106 mmol) was dissolved in anhydrous trimethylphosphate (0.4 mL) and treated with proton-sponge® (34 mg, 0.159 mmol). The mixture was cooled to 0°C and treated dropwise with phosphoryl chloride (13 □L, 0.137 mmol, 1.3 equiv) via microsyringe over a 5 min

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period. After 2h at 0°C, tlc (7:2:1 isopropanol: conc. NH_4OH: water) showed mostly starting material indicating the parent nucleoside was slow to react under standard conditions. The mixture then was treated incrementally (10 µL/hr) with additional phosphoryl chloride (40 µL, 0.137 mmol, 4 equiv.), and after 5h tlc indicated complete conversion to the monophosphoryl dichloridate intermediate. While still at 0°C, the reaction mixture was treated dropwise with a solution containing bis(tri-n-butylammonium pyrophosphate) (145 mg, 0.264 mmol) and tributylamine (153 □L, 0.634 mmol) in anhydrous DMF (1 mL). After 20 min at 0°C, the mixture was quenched with 20 mL of a 100 mM solution of triethylammonium bicarbonate (TEAB), stirred for 1h with warming to rt and then extracted with ether (3 x 15 mL). The aqueous phase was purified by anion-exchange chromatography over DEAE Sephadex® A-25 resin (11 x 200 mm) using a buffer gradient from 50 mM (400 mL) to 600 mM (400 mL) TEAB. Fractions of 8 mL were first analyzed by tlc (11:7:2 NH_4OH: isopropanol: water), and then the triphosphate containing fractions were further analyzed by phosphorus NMR to ensure the product was free of inorganic phosphate (Product mixture contained high concentration of inorganic phosphate because of excess phosphoryl chloride needed to initiate phosphorylation of this unreactive nucleoside analogue). Pure triphosphate (eluted @ 500 mM TEAB) containing fractions were combined and concentrated by rotary evaporator (bath < 25°C). The resulting solid was reconstituted in DI water (10 mL) and concentrated by lyophilization to give 2'-C-methyl-2'-thiouridine-5'-triphosphate (25 mg, 33%) as a bis(triethylammonium salt) .

^{1}H NMR (400 MHz, Deuterium Oxide) δ 8.01 (d, J= 7.9 Hz, 1H), 7.08 (s, 2H), 6.20 (d, J = 7.9 Hz, 2H), 4.36 (m, 2H), 4.14 (m, 2H), 3.19 (q, J = 7.3 Hz, 12H), 1.27 (t, J = 7.3 Hz, 20H).

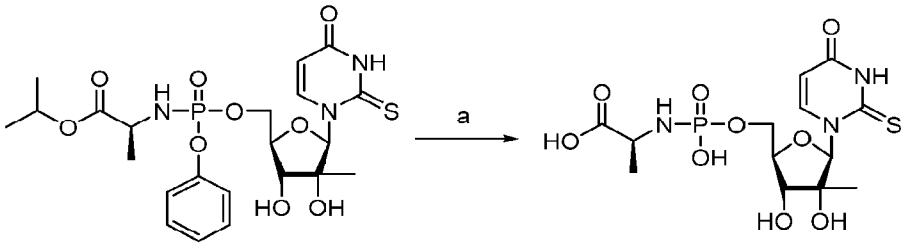
^{31}P NMR (162 MHz, Deuterium Oxide) δ -8.81 (d, J = 20.6 Hz), -13.70 (d, J = 19.9 Hz), -24.82 (t, J = 20.6 Hz).

HRMS $C_{10}H_{17}N_2O_{14}P_3S$ [M-H$^+$]; calculated: 512.95287, found: 512.95406.

Example 94.

Synthesis of Nucleotide Alaninyl Phosphate

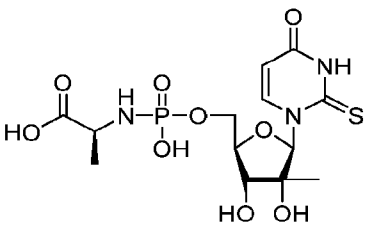
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275 294

Reagents and conditions: a) Et_3N, H_2O, 37°C

Example 95.



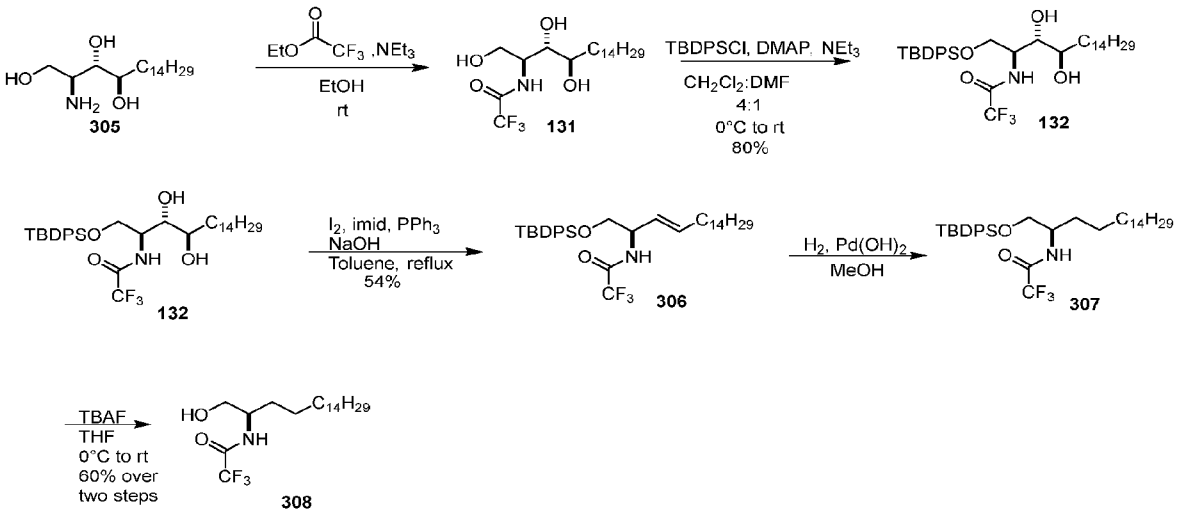
294

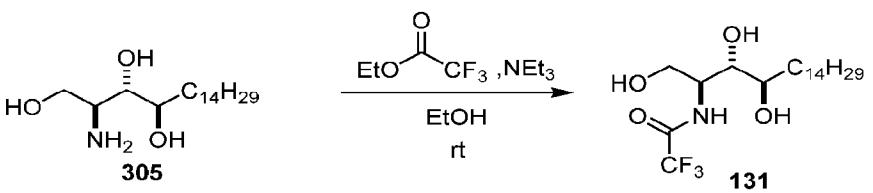
The parent nucleotide 5'-phosphoramidate (0.1mmol) was suspended in triethylamine (5 mL) and distilled water (5 mL) in a round bottom flask at room temperature. The reaction mixture was stirred at 37°C for 24 hours, and then the solvents were removed under reduced pressure. The crude residue was purified on silica eluting with 2-propanol, water, ammonia (8:1:1). The fractions containing the desired product were pooled and concentrated under reduced pressure to remove most of the volatiles. The remaining aqueous solution was transferred to a vial, and was then frozen in a dry ice/acetone bath. The material was then freeze-dried to provide the desired product as a white solid.

Example 96.

Synthesis of (R)-2,2,2-trifluoro-N-(1-hydroxyoctadecan-2-yl)acetamide

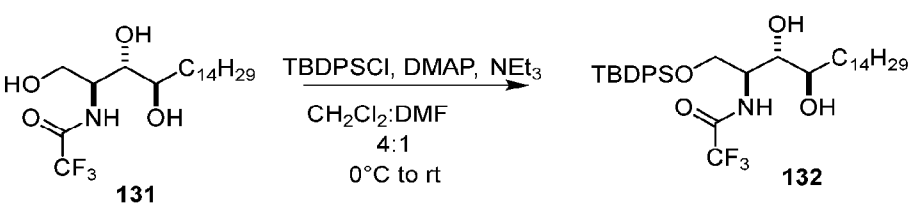
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Phytosphingosine (15.75 mmol) was dissolved in EtOH (0.5M) and ethyl trifluoroacetate (15.75 mmol) was added dropwise. NEt_3 (24.41mmol) was added next the reaction mixture stirred overnight. The solvent was removed in vacuo and the residue was taken up in EtOAc and brine, washed, dried and concentrated. The crude material that was a white powder was good enough to use in the next step without further purification. Characterization matched literature: *Synthesis*, **2011,** 867.

Example 97.



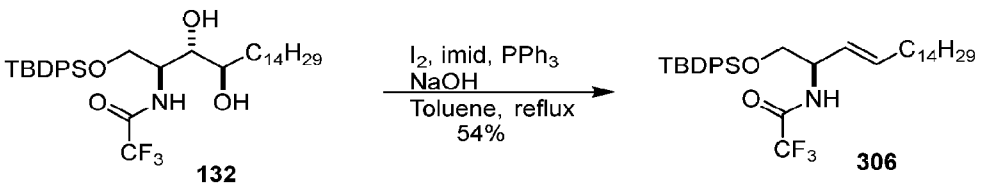
The primary alcohol (15.75 mmol), DMAP (1.575 mmol) and NEt_3 (39.4 mmol) were dissolved in CH_2Cl_2 and DMF (0.18M) mixture and cooled to 0°C. TBDPSCl (19.69 mmol)

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was added dropwise then the solution was allowed to warm to room temperature and stirred overnight.

NH_4Cl solution was added to quench. The reaction mixture was extracted with EtOAc and the combined organic layers were washed with water (x2) to remove DMF. It was then dried and concentrated. A column was run to purify the mixture. 10-20% EtOAc/Hex. Characterization matched literature: *Synthesis*, **2011,** 867.

Example 98.

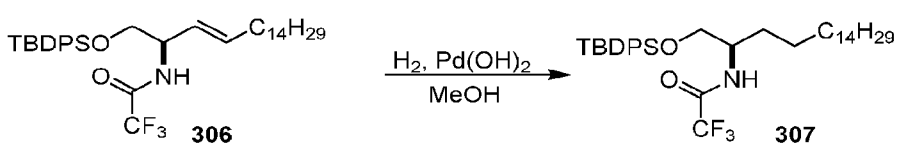


The diol (12.58 mmol), triphenylphosphine (50.3 mmol) and imidazole (50.03 mmol) were dissolved in toluene and reheated to reflux. The iodine (37.7 mmol) was then added slowly and the reaction mixture continued to be stirred at reflux. After three hours it was cooled to room temperature and 1 equivalent of iodine (12.58 mmol) was added followed by 8 equivalents of 1.5M NaOH (100.64 mmol). The reaction mixture was stirred until all the solids dissolved. The aqueous layer was removed in a separatory funnel and the organic layer was washed with $Na_2S_2O_3$ solution then $NaHCO_3$ solution then brine. It was dried and concentrated. A column was run to purify the mixture 0-20% EtOAc/Hex and a mixture of cis and trans was obtained but carried on to the next step.

δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (ddt, *J* = 7.8, 3.8, 1.7 Hz, 4H), 7.51 – 7.35 (m, 6H), 6.68 (dd, *J* = 16.0, 8.2 Hz, 1H), 5.6 – 5.40 (m, 2H), 4.57 – 4.46 (m, 1H), 3.84 – 3.62 (m, 2H), 2.04 (q, *J* = 7.0 Hz, 1H), 1.28-1.21 (m, 24H), 1.15 – 0.98 (m, 9H), 0.90 (t, *J* = 6.8 Hz, 3H).

HRMS: 617.38759.

Example 99.

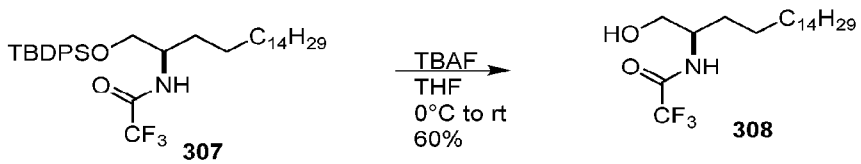


The alkene (2.91 mmol) was dissolved in MeOH (0.1M) and $Pd(OH)_2/C$ (0.146 mmol) was added. A Parr Hydrogenator was used at 40 psi. The palladium catalyst was

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carefully filtered off through celite and rinsed with EtOAc. The crude material was used in the next step and provided quantitative yield.

Example 100.

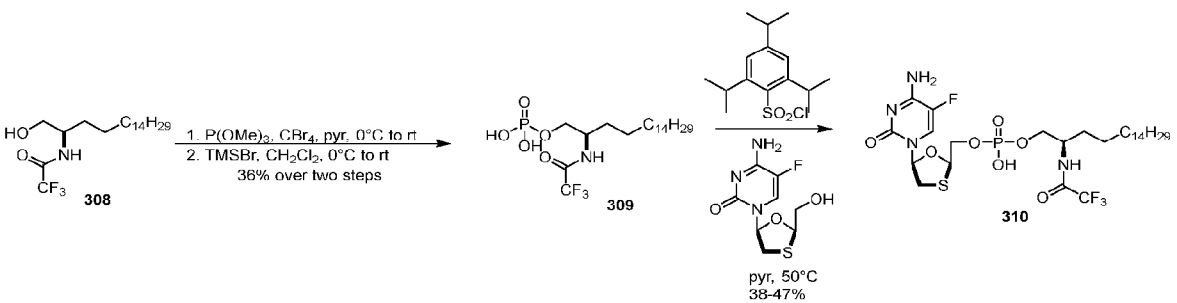


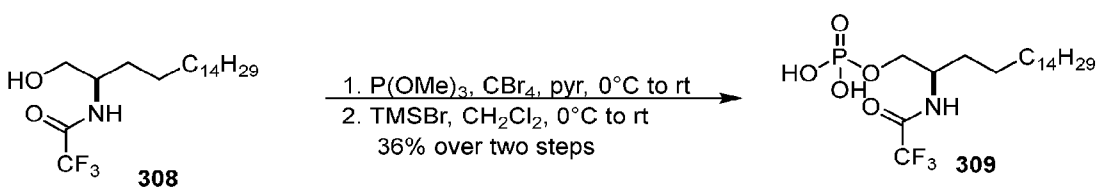
The silyl ether was dissolved in THF and cooled to 0ºC then TBAF was added dropwise. After stirring for 1 hour it was warmed to room temperature. After two hours NH4Cl solution was added and it was extracted with EtOAc, washed with brine and dried and concentrated. A column was run 10-50% EtOAc/Hex.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (tt, *J* = 7.0, 1.5 Hz, 2H), 7.48 – 7.33 (m, 4H), 3.73 3.61 (m, 1H), 1.24 (d, *J* = 3.5 Hz, 18H), 1.05 (s, 6H), 0.86 (t, *J* = 6.8 Hz, 3H). HRMS : 381.28546.

Example 101.

Synthesis of 2-Amino-Octadecyl-FTC-5'-Monophosphate Conjugates





Step 1: The alcohol (0.604 mmol) was dissolved in pyridine (0.1 M) and cooled to 0ºC then CBr_4 (0.755 mmol) was added followed by dropwise addition of $P(OMe)_3$ (0.845 mmol) over one hour. Once addition was complete the mixture was stirred at 0ºC for one hour then allowed to warm to room temperature. To quench water was added and the solvent was removed in vacuo. The residue was dissolved in EtOAc and washed with 3% HCl (x2) then $NaHCO_3$ solution and then brine. Bad emulsion took place especially after washing with

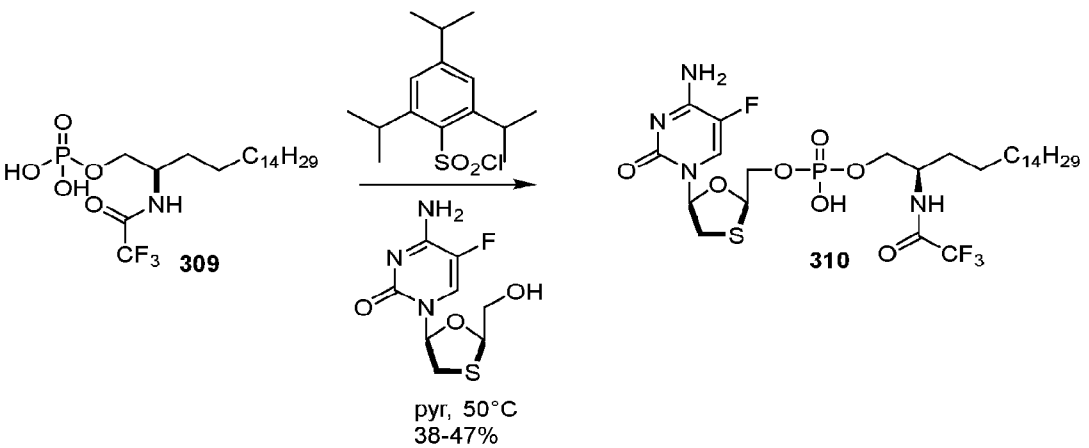
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$NaHCO_3$ solution. It was then dried and concentrated. The crude material was taken on to the next step although a column could have been run because some starting material is present because the reaction did not go to completion. Phosphate formation was confirmed by ^{31}P NMR and ^{1}H NMR.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.0 Hz, 1H), 4.10 (dq, *J* = 7.1, 4.4 Hz, 3H), 3.76 (dd, *J* = 11.2, 4.7 Hz, 6H), 1.67 – 1.56 (m, 2H), 1.23-1.18 (m, 28H), 0.91 – 0.76 (m, 3H).

HRMS : 489.28309.

Step 2: The dimethyl phosphate (0.291 mmol) was dissolved in dry CH_2Cl_2 (0.1 M) and cooled to 0°C with ice-bath and then treated dropwise via syringe pump with TMSBr (1.454 mmol) over a 30 min period. The mixture was allowed to warm to room temperature for one hour. It was concentrated to dryness after 4 hours and then co-evaporated with CH_2Cl_2 3x 50mL. The crude residue was cooled in ice-bath and treated with ice-cold mixture of approx. 1% aqueous NH_4OH/THF. The mixture was agitated at 4°C for 10 min and then concentrated to dryness. The crude material was analyzed by ^{1}H NMR and ^{31}P NMR and then triturated with methanol/ACN and then filtered. The collected off-white solid was washed with dry acetonitrile.



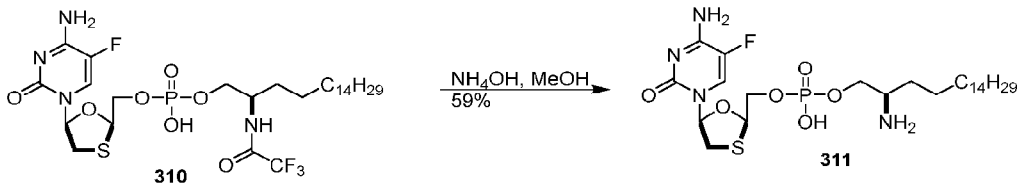
FTC (0.155 mmol) and the phosphate (0.155mmol) were dissolved in pyridine (0.05 M) and trisyl chloride was added. It was stirred at 50°C overnight. The solvent was removed in vacuo and the crude material was purified by column 5%-50% MeOH/NH_4OH/$CHCl_3$.

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^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 – 8.08 (m, 1H), 6.27 – 6.19 (m, 1H), 5.37 (t, J = 4.0 Hz, 1H), 4.19 – 4.10 (m, 1H), 4.07 (td, J = 7.7, 5.5, 3.1 Hz, 1H), 3.96 – 3.83 (m, 2H), 3.29 (s, 1H), 1.58 – 1.50 (m, 1H), 1.26-1.18 (m, 28H), 0.92 – 0.83 (m, 3H).

HRMS: 690.28392.

Example 102.



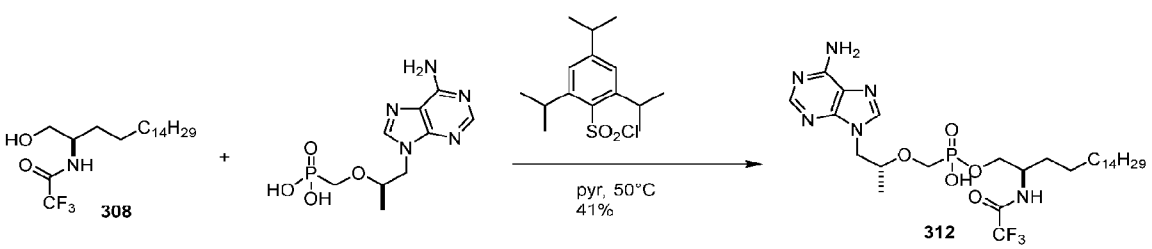
The phosphate was dissolved in MeOH (0.05M) and NH_4OH in a pressure tube and stirred at 40 ℃ overnight. This reaction was very stubborn and on more than one occasion the reaction was not complete after 24 hours. In those cases it was resubjected for another 24 hours.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.10 (t, J = 6.0 Hz, 1H), 6.24 (q, J = 5.4 Hz, 1H), 5.49 – 5.42 (m, 1H), 5.38 (dt, J = 9.2, 4.1 Hz, 1H), 4.26 – 4.10 (m, 2H), 4.07 (q, J = 5.0, 4.6 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.48 (dt, J = 9.5, 4.6 Hz, 1H), 3.32 (d, J = 3.6 Hz, 2H), 3.17 (ddd, J = 12.3, 7.7, 4.3 Hz, 1H), 1.61 (dt, J = 13.0, 7.2 Hz, 2H), 1.25 (d, J = 9.1 Hz, 28H), 0.87 (t, J = 5.7, 4.8 Hz, 3H).

HRMS: 594.30162.

Example 103.

Synthesis of 2-Amino-Octadecyl-Tenofovir-5'-Monophosphate Conjugates

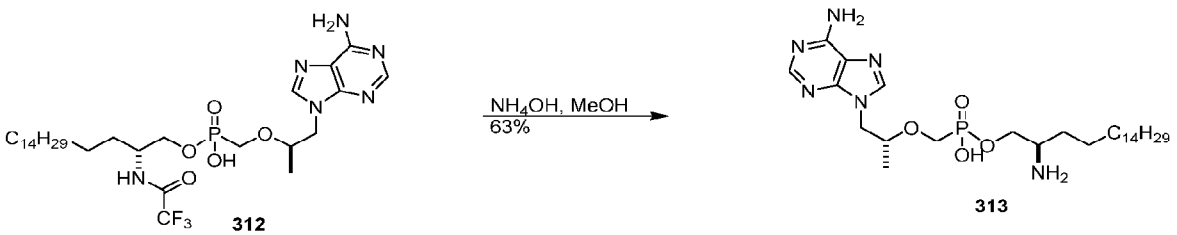


Tenofovir (0.149 mmol) and the alcohol (0.149 mmol) were dissolved in pyridine (0.05 M) and trisyl chloride (0.448 mmol) was added. It was stirred at 50°C overnight. The solvent was removed in vacuo and the crude material was purified by column using 5%-50% MeOH/NH_4OH/$CHCl_3$.

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^{1}H NMR (400 MHz, Methanol-d_4) δ 8.3 (s, 1H), 8.2 (s, 1H), 4.4-3.2 (m, 8H), 1.6 (m, 2H), 1.4-1.1 (m, 31H), 0.9 (t, 3H). HRMS: 650.35324.

Example 104.



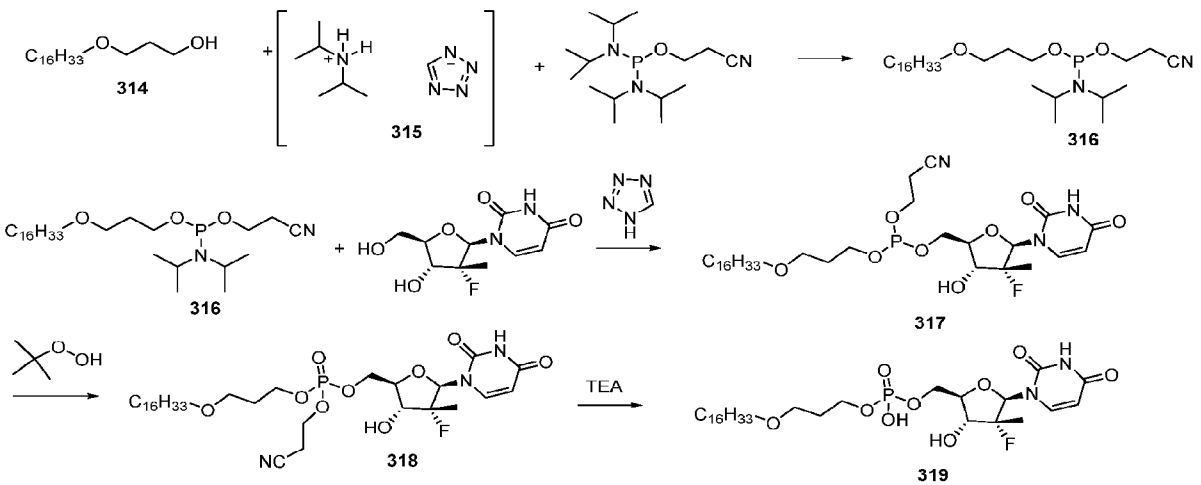
The phosphate was dissolved in MeOH (0.05M) and NH_4OH in a pressure tube and stirred at 40 ℃ overnight. This reaction was very stubborn and on more than one occasion the reaction was not complete after 24 hours. In those cases it was resubjected for another 24 hours.

^{1}H NMR (300 MHz, Methanol-d_4) δ 8.31 (d, J = 5.4 Hz, 1H), 8.21 (d, J = 5.5 Hz, 1H), 4.5-3.2 (m, 10H), 1.63 – 1.52 (m, 2H), 1.4-1.0 (m, 31H), 0.87 (t, J = 6.3 Hz, 3H).

HRMS : 554.37094.

Example 105.

Synthesis of 2'-Fluoro-2'-Methyluridine-5'-HDP-Monophosphate Conjugate



Compound 314 was prepared following literature procedure (Bioorganic & Medicinal Chemistry 20 (2012) 3658-3665).

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Compound 315: To a solution of 1H-tetrazole (0.415 g, 5.92 mmol) in 25 ml ether and 10 ml acetonitrile diisopropylamine (0.93 ml, 0.726 g, 7.03 mmol) was added. The precipitate was filtered off, washed with ether and dried under vacuum to give diisopropylammonium tetrazolide.

Compound 316: 3-(hexadecyloxy)propan-1-ol (0.301 g, 1.00 mmol) and diisopropylammonium tetrazolide (0.115 g, 0.67 mmol) were coevaporated with DCM-AcCN mixture(10:10) 3 times. Dried mixture was dissolved in 7 ml DCM and added 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (0.673 ml, 2.120 mmol). After 1 hour stirring at room temperature 1 ml methanol was added and stirred for 15 minutes. Then reaction was concentrated under vacuum; diluted with 10%TEA solution in EtOAc (100 ml) and washed with 10%NaHCO3 solution (2 x 50 ml) and water (2 x 50 ml); dried over anhydrous MgSO4; filtered off and evaporated. The crude product was purified with column chromatography using Hexanes:EtOAc:TEA (10:4:0.5).

^{1}H-NMR: 3.89-3.54 (m, 6H); 3.49 (t, 2H, J=6.4 Hz); 3.39 (t, 2H, J=6.4Hz); 2.63 (dt, 2H, J=1.6, 6.4 Hz); 1.89-1.83 (m, 1H); 1.57-1.51 (m, 1H); 1.24 (s, 24H); 1.19-1.16 (m, 16H); 0.87 (t, 3H, J=6.4 Hz).

Compound 317 318, 319: The amidophosphite (compound 3) (0.114 g, 0.228 mmol) and 1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (0.065 g, 0.248 mmol) were dried by coevaporating with anhydrous DCM (4 x 10 ml), dissolved in 4 ml DCM and a solution of 3% 1H-tetrazole in acetonitrile (0.75 ml, 0.320 mmol) was added. After 1 hour stirring at room temperature 5.5 M solution of tert-butyl peroxide (0.25 ml, 1.359 mmol) was added. After 40 minutes the solvents were evaporated and reaction mixture was dissolved in toluene and 1 ml TEA was added. It was stirred for 5 hours. All the solvents were evaporated and coevaporated with toluene (2 x 2 ml). Crude material was purified with column chromatography starting with CHCl3 and increased the polarity slowly with CHCl3:MeOH:NH4OH (75:25:5) to give compound **319**.

^{1}H-NMR: (CDCl3-CD3OD, 3:1) 1.024 (t, 3H, 6.4 Hz); 1.35-1.49 (m, 27H); 1.55 (d, 2H, 6.0 Hz); 1.63-1.70 (m, 2H); 2.011-2.067 (m, 2H); 3.47-3.49 (m, 2H); 3.54 (q; 2H, J=4.8 Hz); 3.65-3.70 (m, 2H); 4.07-4.20 (m, 3H); 4.23-4.42 (m, 2H); 5.99 (d, 1H, J=8.4 Hz); 6.32 (dd, 1H, J=19.2, 5.2 Hz); 8.125 (t, 1H, J=8.0 Hz).

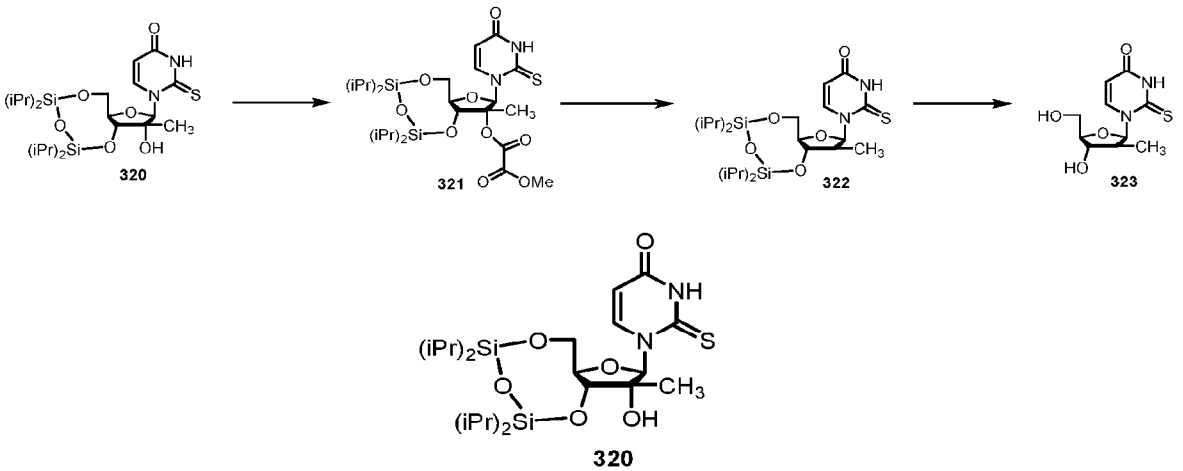
^{31}P-NMR: (CDCl3-CD3OD, 3:1) 17.95 ppm.

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HRMS: 623.34722.

Example 106.

Synthesis of 2'-Deoxy-2'-Beta-Methyl-2-Thiouridine

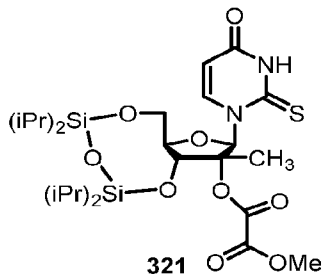


The nucleoside (4.15 g, 15.13 mmol) was dried by azeotroping residual water by dissolving in pyridine and removing volatiles by rotary evaporation (3 x 50 mL). The residue was dissolved in pyridine (200 mL) with stirring under nitrogen at 0°C, and 1,3-dichloro-1,1,3-3-tetraisopropyldisiloxane (5.81 mL, 18.2 mmol) was added dropwise via syringe over 5 min. The mixture was warmed to rt and stirred 16 h. The mixture was then concentrated by rotary evaporation and taken up in CH_2Cl_2 (500 mL). The solution was washed with sat. aq. $NaHCO_3$ (2 x 500 mL) and then dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give 12 g crude material. The mixture was taken up in CH_2Cl_2, and flash chromatography on the CombiFlash (120 g column, 5 to 30% EtOAc in hexanes gradient) gave **320** (6.55 g, 84%) as a white powdery solid.

^{1}H NMR (400 MHz, $CDCl_3$) □ 9.29 (br s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 6.87 (br s, 1H), 5.97 (d, J = 8.1 Hz, 1H), 4.24 (d, J = 13.6 Hz, 1H), 4.10 (dd, J = 9.1 Hz, 2.6 Hz, 1H), 4.02 (dd, J = 13.6 Hz, 2.8 Hz, 1H), 3.99 (d, J = 9.1 Hz, 1H), 1.33 (s, 3H), 1.14-1.05 (m, 28H).

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Example 107.

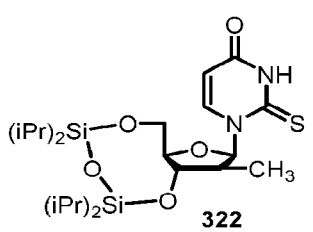


321

To a stirred solution of **320** (6.25 g, 12.09 mmol) and 4-DMAP (2.95 g, 24.19 mmol) in acetonitrile (121 mL) at rt under nitrogen, was added methyl-2-chloro-2-oxoacetate (1.67 mL, 18.14 mmol) dropwise via syringe. The mixture was stirred at rt for 2 h, and was then diluted with EtOAc (600 mL). This organic solution was washed sequentially with sat. aq. $NaHCO_3$, water, and brine (1 x 120 mL each), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The resulting crude was dried under high vacuum overnight to give **321** (7.60 g) as a pale yellow solid. The entirety of the crude product mixture was taken on to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.82 (1H, d, J = 8.2 Hz), 7.12 (s, 1H), 5.99 (d, J = 8.2 Hz, 1H), 4.25-4.18 (m, 2H), 4.10 (d, J = 9.3 Hz, 1H), 4.02 (dd, J = 13.7 Hz, 2.8 Hz, 1H), 3.91 (s, 3H), 1.86 (s, 3H), 1.15-0.90 (m, 28H).

Example 108.



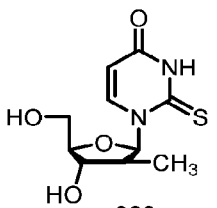
322

To a stirred solution of crude **321** (7.60 g) and tributyltin hydride (4.89 mL, 18.14 mmol) in toluene (216 mL) at reflux under nitrogen, was added solid AIBN (0.397 g, 2.42 mmol) all at once. The mixture was heated at reflux for 2 h and then cooled to rt. Volatiles were removed by rotary evaporation, and the crude residue was taken up in a small amount of PhMe. Flash chromatography on the Combiflash (120 g column, 1 to 30% EtOAc in hexanes gradient) gave **322** (5.30 g, ~79% yield) as a white solid of ~90 purity (remainder tributylstannane residues). NMR analysis showed a 10:1 □:□ dr at the C_2' position. The entirety of this mostly pure product was taken on to the next step without further purification.

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Major isomer ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.37 (br s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.96 (dd, *J* = 8.0 Hz, 2.1 Hz, 1H), 4.17 (d, *J* = 13.2 Hz, 1H), 4.03 (dd, *J* = 13.5 Hz, 2.8 Hz, 1H), 3.98 (t, *J* = 9.6 Hz, 1H), 3.78 (ddd, *J* = 8.8 Hz, 2.8 Hz, 1.0 Hz), 2.74 (m, 1H), 1.15-0.95 (m, 31 H). Signals for the minor isomer were also seen at ^{1}H NMR (400 MHz, $CDCl_3$) □ 8.08 (d, *J* = 8.2 Hz, 1H), 4.38 (dd, *J* = 9.1 Hz, 7.5 Hz, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 2.53 (m, 1H).

Example 109.



323

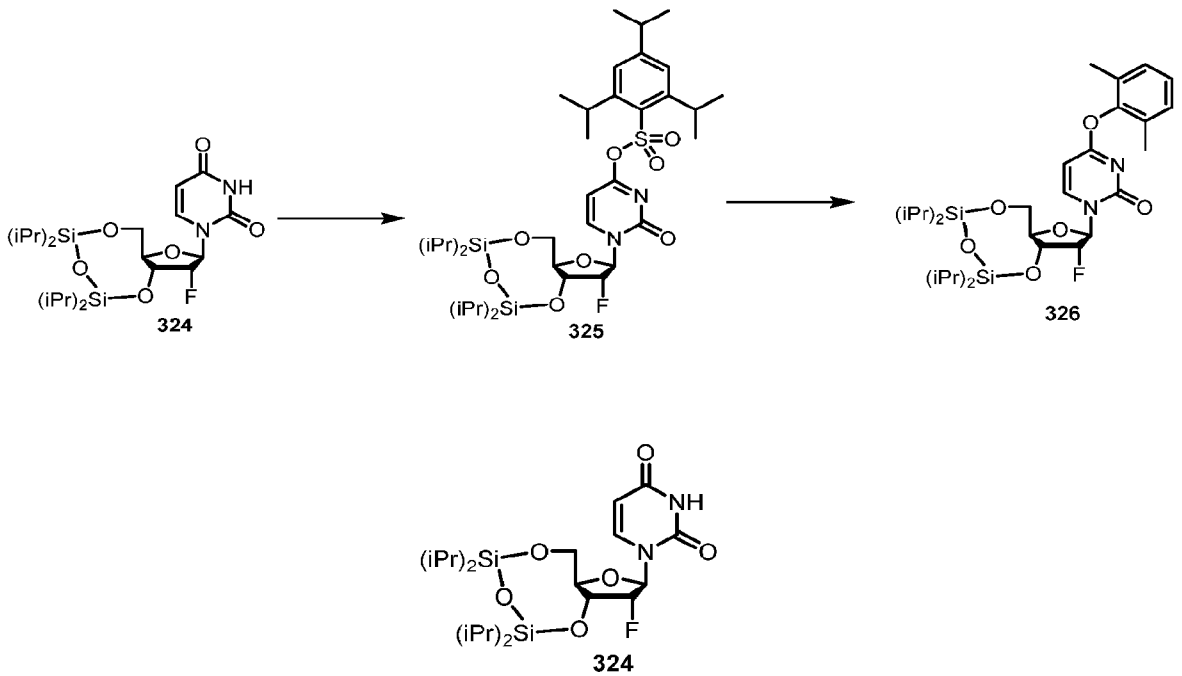
To a stirred solution of **322** (5.30 g, 10.58 mmol) in THF (106 mL) under nitrogen at 0°C, was added a solution of TBAF (1.0 M in THF, 21.17 mL) dropwise via syringe. The mixture was brought to rt and stirred 2 h. Volatiles were removed by rotary evaporation to give a crude yellow oil. The material was taken up in EtOAc and flash chromatography on the Combiflash (330 g column, 0 to 5% MeOH in DCM gradient) gave 2.8 g of mostly purified material as a white solid. This material was dissolved in methanol and immobilized on Celite, then loaded on top of a 10% w/w KF/silica column. Flash chromatography (10% MeOH in EtOAc) gave **323** (1.96 g, 63% yield over 3 steps) as a white solid. ^{1}H NMR analysis showed a 13:1 □:□ dr at the C_2'position (integration of methyl doublet).

Major isomer ^{1}H NMR (400 MHz, MeOH-d_4) □ 8.18 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 3.93 (dd, *J* = 12.2 Hz, 2.1 Hz, 1H), 3.89 (t, *J* = 8.2 Hz, 1H), 2.64 (m, 1H), 0.99 (d, 7.1 Hz, 3H). ES+APCI (70 eV) *m/z*: $[M+HCO_2]^-$ 302.9.

Example 110.

Synthesis of 2'-Deoxy-2'-Fluoro-2-Thiouridine

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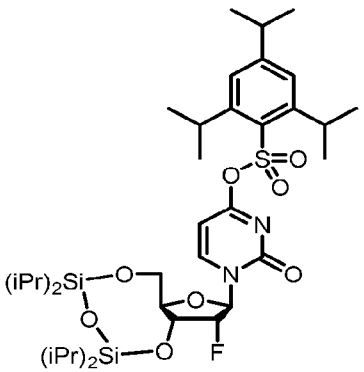


2'-Deoxy-2'-fluorouridine (4.92 g, 20.0 mmol) was dried by azeotroping residual water by dissolving in pyridine and removing volatiles by rotary evaporation (3 x 50 mL). The residue was dissolved in pyridine (100 mL) with stirring under nitrogen at 0°C, and 1,3-dichloro-1,1,3-3-tetraisopropyldisiloxane (7.68 mL, 24.0 mmol) was added dropwise via syringe over 5 min. The mixture was warmed to rt and stirred 16 h. The mixture was then concentrated by rotary evaporation and taken up in CH_2Cl_2 (500 mL). The solution was washed with sat. aq. $NaHCO_3$ (2 x 500 mL) and then dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give **324** (9.09 g, 93% yield) as a white solid of >95% purity by NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) □ 8.07 (br s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 5.90 (d, J = 16.2 Hz, 1H), 5.71 (dd, J = 8.2 Hz, 2.3 Hz, 1H), 4.90 (dd, J = 53.2 Hz, 3.4 Hz, 1H), 4.30 (ddd, J = 28.2 Hz, 9.6 Hz, 3.6 Hz, 1H), 4.29 (d, J = 14.3 Hz, 1H), 4.16 (d, J = 10.6 Hz, 1H), 4.02 (dd, J = 13.6 Hz, 2.5 Hz, 1H), 1.15-1.00 (m, 28H).

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Example 111.

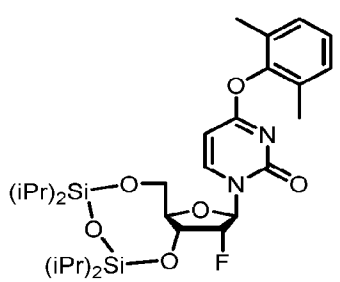


325

To a vigorously stirred biphasic mixture of **324** (4.89 g, 10.0 mmol) in CH_2Cl_2 (200 mL) and 0.2 M Na_2CO_3 (400 mL) at rt, was added solid *n*-Bu_4Br (1.29 g, 4.00 mmol) followed by 2,4,6-triisopropylbenzene-1-sulfonyl chloride (3.94 g, 13.0 mmol). The mixture was stirred vigorously for 20 h at rt, after which the organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation, followed by azeotropic removal of water by coevaporation with PhMe (100 mL) to give crude **325** as a yellow oil, also containing residues from excess reagents. The entirety of the crude was taken on to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) □ 8.28 (d, *J* = 7.3 Hz, 1H), 7.23 (s, 2H), 6.04 (d, *J* = 7.4 Hz, 1H), 5.86 (d, *J* = 15.2 Hz, 1H), 4.92 (dd, *J* = 52.4 Hz, 2.9 Hz, 1H), 4.30-4.05 (m, 5H), 3.99 (dd, *J* = 13.7 Hz, 2.3 Hz, 1H), 3.0-2.85 (m, 1H), 1.35-1.25 (m, 18H), 1.15-1.00 (m, 28H).

Example 112.



326

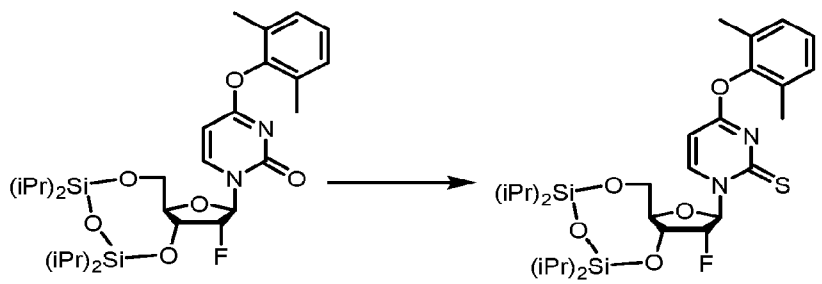
To a stirred solution of crude **325** in MeCN (100 mL) under nitrogen at rt, was added dropwise a solution of 2,6-dimethylphenol (1.22 g, 10.0 mmol), triethylamine (4.18 mL, 30.0 mmol), and DABCO (0.112 g, 1.00 mmol) in MeCN over 30 min. The mixture immediately

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turned deep red at the beginning of addition, and was stirred an additional 90 min after addition was completed. The reaction mixture was concentrated by rotary evaporation, and the residue was redissolved in $CHCl_3$ (300 mL). The solution was washed sequentially with sat. aq. $NaHCO_3$ (1 x 300 mL) and brine (2 x 300 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give a crude red oil. Flash chromatography on the Combiflash (330 g column, 5 to 20% EtOAc in hexanes gradient), gave **326** (5.02 g, 85% yield over 2 steps) as an off-white solid foam.

^{1}H NMR (400 MHz, $CDCl_3$) □ 8.20 (d, J = 7.4 Hz, 1H), 7.06 (s, 3H), 6.08 (d, J = 7.4 Hz, 1H), 5.94 (d, J = 15.9 Hz, 1H), 5.02 (dd, J = 52.1 Hz, 3.1 Hz, 1H), 4.31 (d, J = 13.8 Hz, 1H), 4.32-4.18 (m, 2H), 4.03 (dd, J = 13.6 Hz, 2.0 Hz, 1H), 2.13 (s, 6H), 1.15-0.97 (m, 28H).

Example 113.



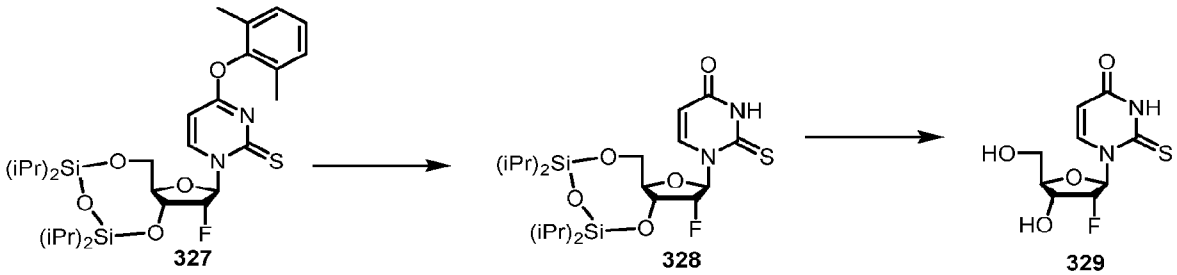
326 **327**

To a solution of **326** (4.50 g, 7.59 mmol) in PhMe (76 mL) under nitrogen with stirring was added Lawesson's reagent (4.61 g, 11.39 mmol) all at once as a solid. The mixture was refluxing with stirring under nitrogen for 2 h and was then cooled to rt. The mixture was filtered through Celite and the pad was rinsed with PhMe (2 x 30 mL). The combined filtrates were concentrated by rotary evaporation, the crude residue was taken up in CH_2Cl_2, and flash chromatography on the CombiFlash (120 g column, 1 to 15% EtOAc in hexanes gradient) gave **327** (2.80 g, 55% yield) as a fluffy yellow solid in approximate 90% purity as determined by ^{1}H NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$) □ 8.46 (d, J = 7.5 Hz, 1H), 7.08 (s, 3H), 6.57 (d, J = 14.6 Hz, 1H), 6.26 (d, J = 7.5 Hz, 1H), 5.23 (dd, J = 51.3 Hz, 3.4 Hz, 1H), 4.35-4.25 (m, 2H), 4.16 (ddd, J = 29.4 Hz, 10.3 Hz, 3.9 Hz, 1H), 4.03 (dd, J = 13.8 Hz, 2.5 Hz, 1H), 2.14 (s, 6H), 1.15-0.95 (m, 28H).

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Example 114.



To a stirred solution of **327** (2.70 g, 4.43 mmol) in MeCN (44 mL) at rt under nitrogen, was added a solution of 1,1,3,3-tetramethylguanidine (1.67 mL, 13.3 mmol) and (Z)-2-nitrobenzaldehyde oxime (2.21 g, 13.3 mmol) in MeCN (44 mL) dropwise via syringe over 5 min. The mixture was stirred for 20 h, then diluted with $CHCl_3$ (450 mL). The solution was washed with sat. aq. $NaHCO_3$ (1 x 450 mL) and brine (1 x 450 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Flash chromatography on the CombiFlash (40 g column, 1 to 25% EtOAc in hexanes gradient) gave an inseparable mixture of **328** and nitrobenzaldehyde oxime (~5:3 mole ratio by NMR) as a yellow oil. The entirety of this product was taken on to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) □ 9.72 (br s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 14.6 Hz, 1H), 5.98 (d, J = 8.4 Hz, 1H), 5.03 (dd, J = 51.8 Hz, 3.4 Hz, 1H), 4.32 (d, J = 13.7 Hz, 1H), 4.24 (dt, J = 9.8 Hz, 1.8 Hz, 1H), 4.16 (ddd, J = 28.0 Hz, 9.7 Hz, 3.3 Hz, 1H), 4.02 (dd, J = 13.7 Hz, 2.3 Hz, 1H), 1.15-0.95 (m, 28H).

To a stirred solution of **328** in THF (44 mL) at 0°C under nitrogen, was added a solution of TBAF (8.86 mL, 1.0 M in THF, 8.86 mmol) dropwise via syringe over 5 min. The mixture was warmed to rt and was stirred for 1 h. The mixture was concentrated by rotary evaporation, the crude residue was taken up in EtOAc, and flash chromatography on the CombiFlash (80 g column, 10% MeOH in EtOAc) removed bulk impurities to give 1.8 g impure product. The mixture was redissolved in MeOH and immobilized on Celite. A second flash chromatography column on the Combiflash (80 g, 1 to 10% MeOH in EtOAc gradient) gave **329** (0.940 g, 81% yield over 2 steps) as a white solid.

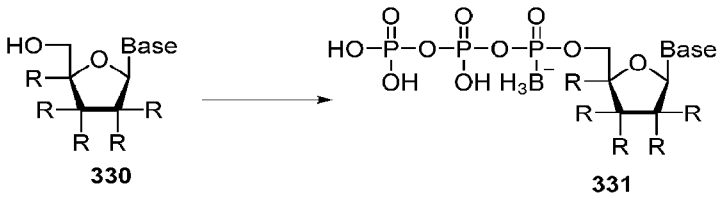
^{1}H NMR (400 MHz, MeOH-d_4) □ 8.36 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 15.6 Hz, 1H), 5.94 (d, J = 8.2 Hz, 1H), 5.03 (dd, J = 52.0 Hz, 4.0 Hz, 1H), 4.24 (ddd, J = 24.2 Hz, 9.0 Hz, 4.1 Hz, 1H), 4.08 (d, J = 8.9 Hz, 1H), 4.03 (d, J = 12.7 Hz, 1H), 3.81 (dd, J = 12.6 Hz, 2.2 Hz, 1H).

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ES+APCI (70 eV) *m/z*: $[M+H]^+$ 263.0.

Example 115.

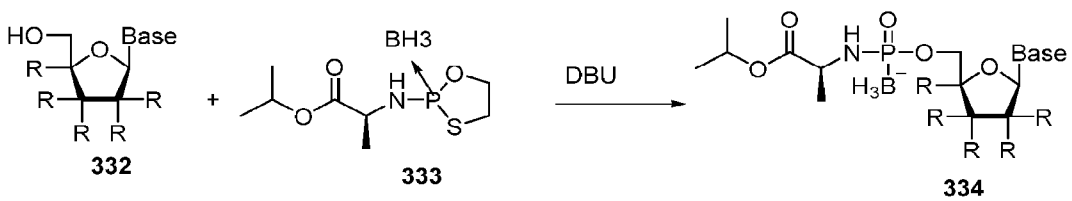
Synthesis of □-Boranotriphosphate Analogs



The nucleoside for conversion was dried overnight in a vacuum oven at 60°C. The dried nucleoside was suspended in dry THF in a dry flask under an argon atmosphere. The suspension was then treated with 2-chloro-4H-1,2,3-benzodioxaphosporin-4-one and tributylamine. After consumption of starting material, a 0.5M tributylammonium pyrophosphate solution in DMF and tributylamine was added. Next, a 2.0M dimethylsulfide borane complex in THF was added. The reaction mixture was quenched with a triethylamine/water (3:2) mixture. The desired product was purified on a DEAE column eluting with triethylammonium bicarbonate solution.

Example 116.

Synthesis of Nucleotide Amino Acid Boranophosphoramidate Analogs

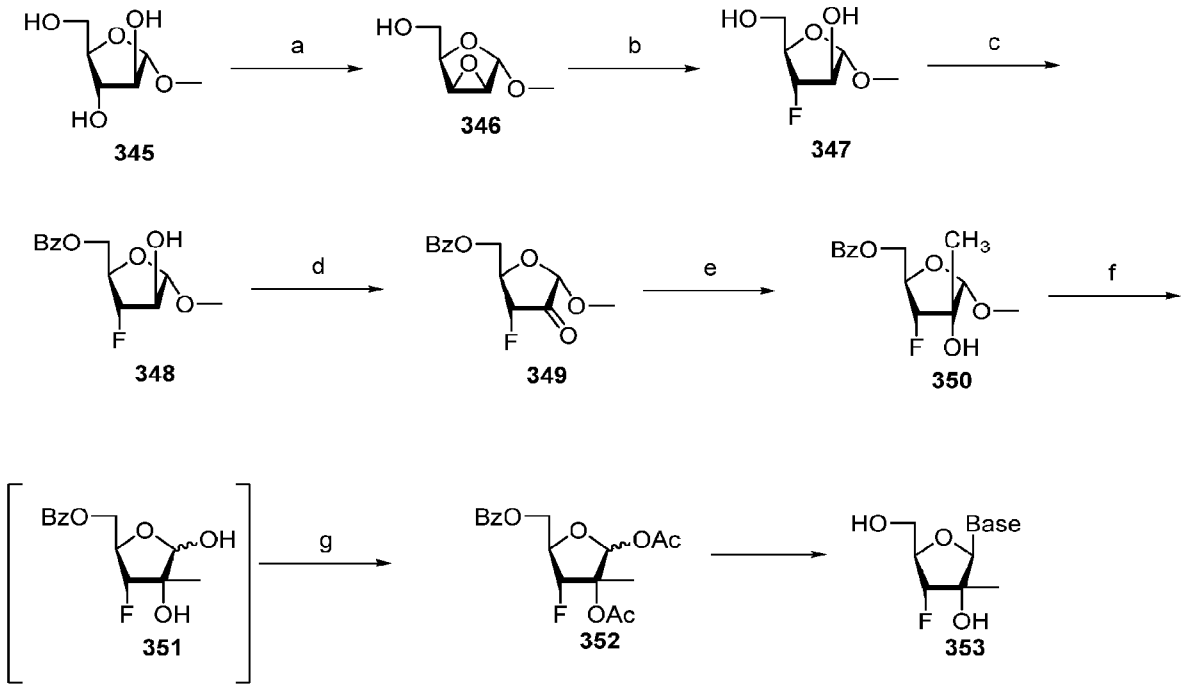


L-alanine isopropyl ester hydrochloride (0.5 mmol) was suspended in dry DCM in a dry flask under an argon atmosphere and was treated with DIPEA (1 mmol). After a clear solution formed, 2-chloro-1,3,2-oxathiaphospholane **333** (0.55 mmol) was added. After 30 minutes of stirring at room temperature, borane-dimethyl sulfide complex (2.5 mmol) was added. The reaction was allowed to stir for an additional 30 minutes. Next, the nucleoside (0.4 mmol) and DBU (1.5-5 equvilents) in dry acetonitrile was added to the reaction. The reaction was quenched with triethylamine/water (1:1 v/v) with stirring for 15 minutes. Solvents were then reduced under reduced pressure. The residue was then coevaporated with ethanol (3 x 15 mL). The desired product was purified on silica eluting with methanol (3-15%) in DCM containing 0.5% triethylamine.

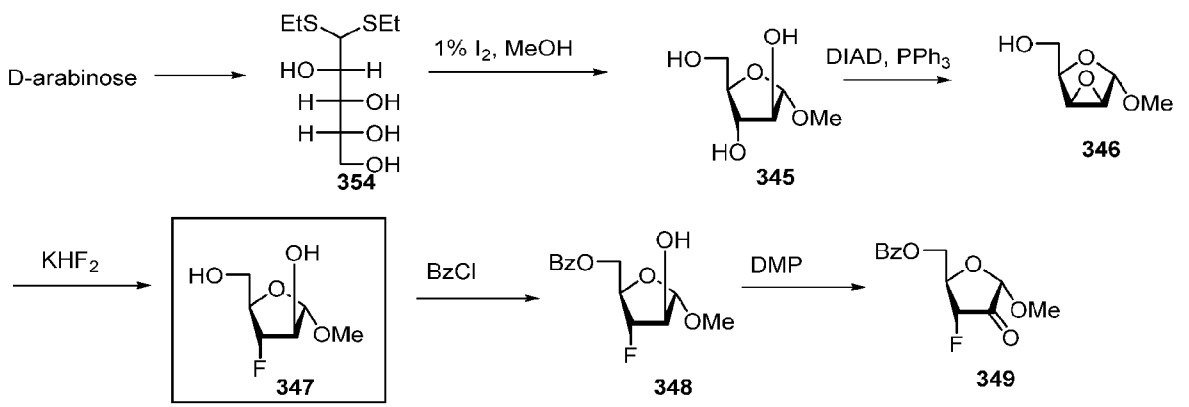
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Example 117.

Synthesis of 3'-Fluoro-2'-Substituted Ribonucleoside Analogs



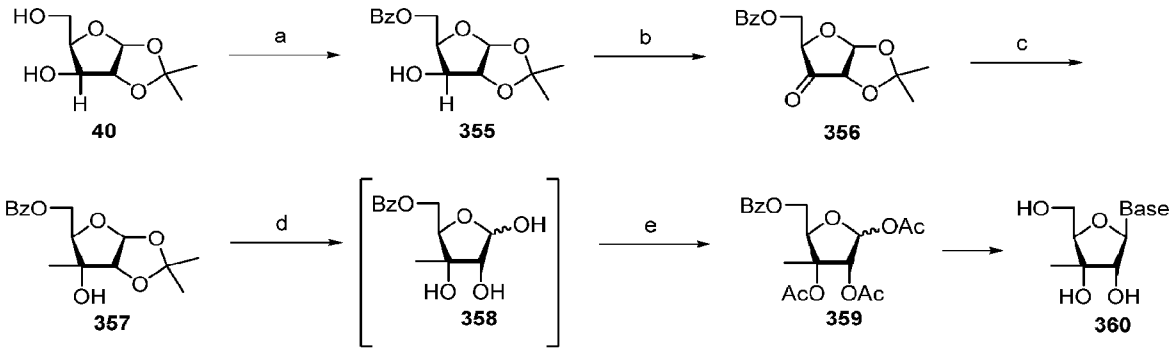
Example 118.



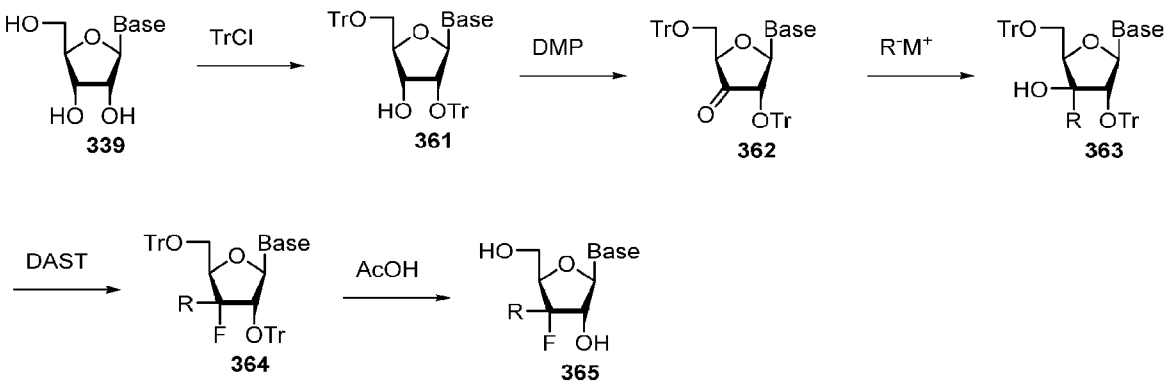
Example 119.

Synthesis of 3'-Substituted Ribonucleoside Analogs

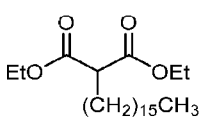
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Example 120.



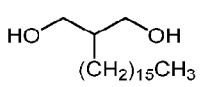
Example 121.



380

To 33.4 g sodium ethoxide solution (21% wt) in ethanol, diethyl malonate(15g) and then 1-bromohexadecane (31.5g) were added dropwise. After reflux for 8 hrs, ethanol was evaporated in vacuo. The remaining suspension was mixed with ice-water(200 ml) and extracted with diethyl ether (3 X 200ml). The combined organic layers were dried over MgSO4, filtered and the filtrate was evaporated in vacuo to yield a viscous oil residue. This residue was purified by column chromatography(silica: 500 g) using hexane/diethyl ether(12:1) as mobile phase to yield the main compound.

Example 122.

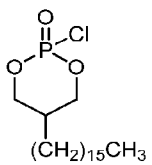


381

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In a 250 mL round-bottomed flask was aluminum lithium hydride (2.503 g, 66.0 mmol) in Diethyl ether (90 ml) to give a suspension. To this suspension was added diethyl 2-hexadecylmalonate (18.12 g, 47.1 mmol) dropwise and the reaction was refluxed for 6 h. The reaction was followed up by TLC using PMA and H2SO4 as drying agents. The excess lithium aluminium hydride was destroyed by 200ml of ice-water. 150 ml of 10 % H2SO4 was added to dissolve aluminium hydrate. The reaction mixture was extracted by diethyl ether (100 ml X 3). The organic layer including undissolved product was filtered. The collect solids were washed with ethyl acetate. The filtrate was dried over MgSO4, filtered and concentrated under reduced pressure. The product was purified on silica (100g) column eluting with Hexane:EtOAc (3:1) to (1:1).

Example 123.

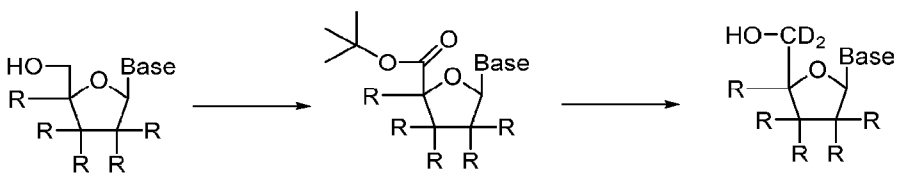


382

To a solution of 2-hexadecylpropane-1,3-diol (7.04 g, 23.43 mmol) in 100 ml of DCM was added dropwise phosphorous trichloride (3.59 g, 23.43 mmol) dissolved in 20 ml of DCM followed by triethylamine (6.53 ml, 46.9 mmol). The reaction was refluxed for one hour. TLC analysis showed that the starting material was consumed and two new spots formed. The mixture was concentrated to dryness, dissolved in dry diethyl ether and filtered. The filtrate was concentrated to yield the crude product (8.85 g) that was used in the next step without further purification.

Example 124.

Synthesis of 5'-Deuterated Nucleoside Analogs



The nucleoside was suspended in methylene chloride (40 mL, partially soluble). After stirring at rt for 30 min the mixture was treated sequentially with PDC, acetic anhydride and then tert-butanol. The mixture continued to stir at room temperature. TLC (5% methanol in DCM) and LCMS indicated only a small amount of remaining starting material

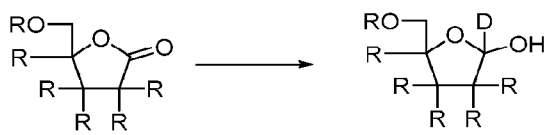
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at 4 hours. The mixture was filtered through a pad of silica gel that was loaded into a 150 mL fritted funnel. The silica was eluted with ethyl acetate. The collected filtrate was concentrated by under reduced pressure. The crude dark oil was purified by chromatography over silica gel (25 mm x 175 mm) with 2:1 hexanes:ethyl acetate to ethyl acetate gradient. The pure fractions were collected and concentrated to give of a white gum. The material was placed under high vacuum for 2 days and was used in the next step without further purification.

The 5'-protected nucleoside was dissolved in 200 proof ethanol and was then treated with solid sodium borodeuteride. The mixture became homogeneous and was then heated to 80°C. After 12h, a white/pale yellow precipitate formed. The mixture was allowed to cool to rt. TLC (5% methanol in methylene chloride) indicates complete conversion of starting material. The mixture was cooled to 0°C with an ice-bath and then slowly quenched with acetic acid (approximately 1 mL). The clear solution was warmed to rt and then partitioned between ethyl acetate (30 mL) and brine (3 mL). The organic phase was concentrated and then purified by chromatography over silica gel (19 mm x 180 mm) using a mobile phase of 5% methanol in methylene chloride.

Example 125.

Synthesis of 1'-Deuterated Nucleoside Analogs



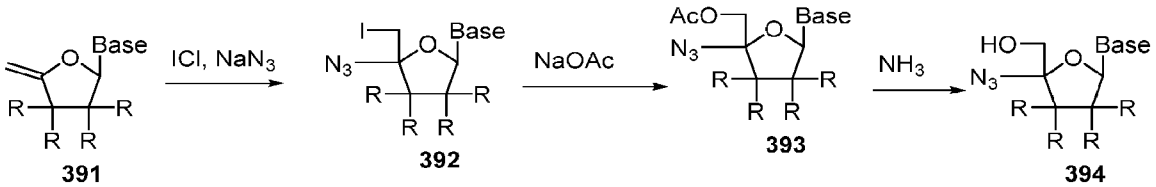
389 390

The lactone (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 room temperature. 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.

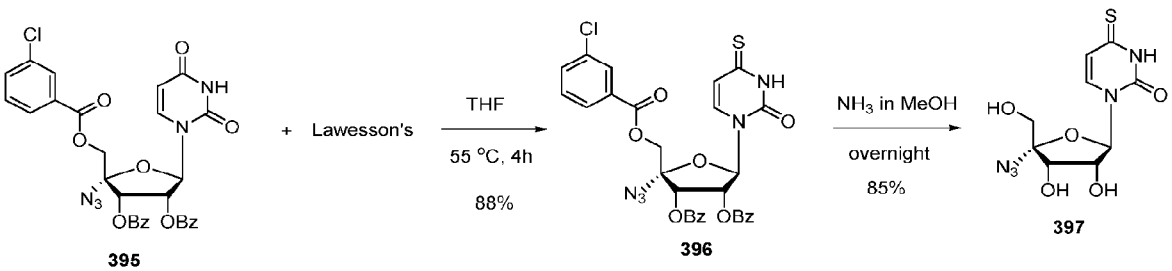
Example 126.

Synthesis of 4'-Substituted Nucleoside Analogs

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Example 127.



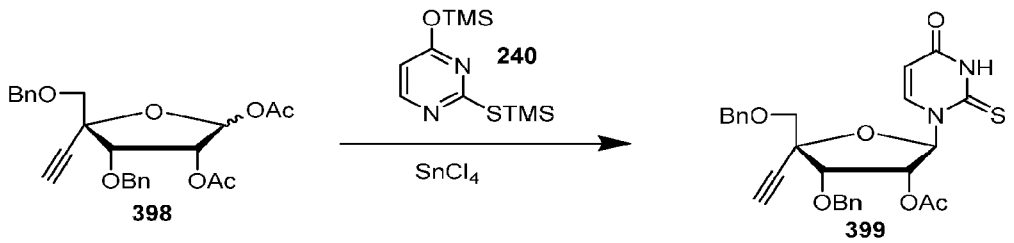
1-(4'-Azido-5'-*O*-(3-chloro)benzoyl-2',3'-*O*-dibenzoyl-□-D-ribofuranosyl)4-thiouracil (396): A pear-shaped flask was charged under nitrogen atmosphere with 1-(4'-azido-5'-*O*-(3-chloro)benzoyl-2',3'-*O*-dibenzoyl-□-D-ribofuranosyl)uracil (1.08 g, 1.709 mmol), Lawesson's reagent (0.76 g, 1.88 mmol), THF (40 mL), and placed into a 55 °C oil bath. The reaction, monitored by TLC, was completed after ~4 h. Then the mixture was concentrated by rotary evaporation to give an oil which was purified by silica gel chromatography 20-25% EtOAc in hexanes to provide 1-(4'-azido-5'-*O*-(3-chloro)benzoyl-2',3'-*O*-dibenzoyl-□-D-ribofuranosyl)4-thiouracil (1.04 g, 94%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$); δ 9.51 (br s, 1 H), 8.04-7.91 (m, 5H), 7.59-7.51 (m, 3H), 7.41-7.30 (m, 6H), 7.06 (d, J = 7.6 Hz, 1H), 6.40 (d, J = 7.6 Hz, 1H), 6.25 (d, J = 7.6 Hz, 1H), 5.97 (dd, J = 2.4, 7.6 Hz, 1H), 5.86 (d, J = 2.4 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H).

1-(4'-Azido-□ -D-ribofuranosyl)4-thiouracil (397): To a stirred solution of 1-(4'-azido-5'-*O*-(3-chloro)benzoyl-2',3'-*O*-dibenzoyl-□-D-ribofuranosyl)4-thiouracil (1.04 g, 1.605 mmol) in methanol (32 ml) at 0 °C, was added methanolic ammonia (7 mL, 7 M in MeOH). The mixture was allowed to warm to room temperature and stirred at room temperature for overnight. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (5-8%) in methylene chloride] to give pure 1-(4'-azido-□ -D-ribofuranosyl)4-thiouracil (410 mg, 85%) as yellow solid. ^{1}H NMR (400 MHz, CD_3OD); δ 7.71 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 5.2 Hz, 1H), 4.38 (t, J = 5.2 Hz, 1H), 4.30 (d, J = 5.2 Hz, 1H), 3.67 (d, J = 12.0 Hz, 1H), 3.58 (d, J = 12.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD); δ 192.4, 149.8, 136.6, 114.7, 100.8,

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92.1, 74.6, 73.3, 64.9. HRMS (ESI) Calcd. for $C_9H_{11}O_5N_5NaS$ $[M+Na]^+$: 324.0373. Found: 324.0372.

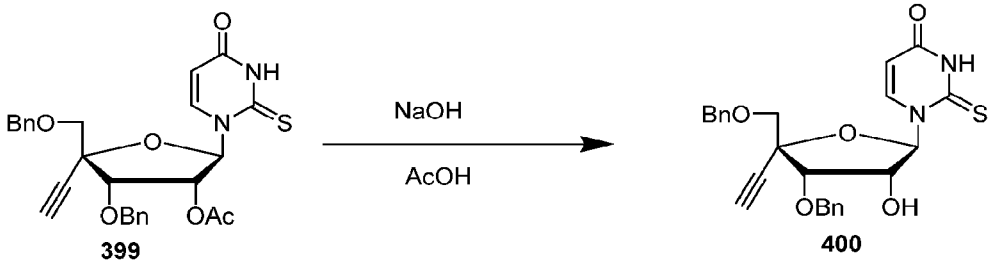
Example 128.



A round bottom flask was charged with 2-thiouracil (1.28 g, 10.0 mmol), $(NH_4)_2SO_4$ (66 mg, 0.50 mmol), and bis(trimethylsilyl)amine (21 mL, 100 mmol) under nitrogen. The mixture was refluxed with stirring overnight (16 h) until a blue-green solution formed. The mixture was cooled to room temperature and volatiles were removed by rotary evaporation, followed by high vacuum, to give persilylated 2-thiouracil as a light blue liquid. Quantitative yield was assumed, and this compound was used immediately in the next step.

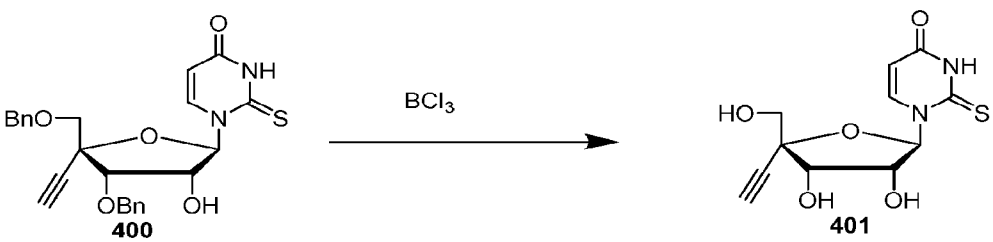
A solution of **398** (2.19 g, 5.00 mmol) in 1,2-dichloroethane (50 mL) was added to the freshly prepared **240** under nitrogen, and the resulting cloudy mixture was cooled to 0°C with stirring. Tin (IV) chloride (1.17 mL, 10.0 mmol) was added to the stirred mixture via syringe over one minute, and the mixture was allowed to warm to room temperature. After stirring for 20 h, the mixture was diluted with 75 mL DCM, and solid $NaHCO_3$ and Celite (2.0 g each) were carefully added to the vigorously stirred reaction mixture. The mixture was cooled to 0°C, and sat. aq. $NaHCO_3$ (1.2 mL) was added dropwise to the vigorously stirred mixture. The mixture was warmed to room temperature and stirred 2 h. The mixture was filtered through a Celite pad, which was rinsed with DCM (30 mL). The combined filtrates were concentrated by rotary evaporation to yield ~5 g of a crude orange oil. The crude was taken up in DCM, and automated flash chromatography on a Combiflash (80 g column, 5 to 50% EtOAc in hexanes gradient) yielded **399** (2.21 g, 83%) as a white flaky solid in 95% purity. ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.17 (br s, 1H), 7.96 (d, 1H), 7.40-7.30 (m, 8H), 7.14-7.06 (m, 2H), 6.75 (d, J = 1.9 Hz, 1H), 5.45 (dd, J = 5.4 IIz, 2.0 IIz, 1II), 5.27 (dd, J = 8.3 IIz, 2.5 IIz, 1II), 4.76 (d, J = 12.4 IIz, 1II), 4.50 (d, J = 12.4 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 4.25-4.20 (m, 2H), 3.92 (d, J = 10.7 Hz, 1H), 3.61 (d, J = 10.7 Hz, 1H), 2.72 (s, 1H), 2.20 (s, 3 H). ESI-MS: *m/z* 379.1 ([M – thiouridine]$^+$).

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399 400

To a stirred solution of **399** (2.21 g, 4.36 mmol) in 1,4-dioxane (227 mL) and water (38 mL) at room temperature, was added 1.0 M aqueous NaOH (38 mL, 38 mmol) all at once. The mixture was stirred at room temperature for 16 h, and was neutralized by dropwise addition of AcOH (2.17 mL, 38 mmol). The mixture was stirred for 30 min and was then concentrated by rotary evaporation. The residue was partitioned between EtOAc and water (100 mL each). The organic layer was removed and the aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give 2.5 g of crude material. The crude was taken up in DCM, and automated flash chromatography on a Combiflash (80 g column, 5 to 50% EtOAc in hexanes gradient) provided **400** (1.57 g, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.21 (br s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.45-7.30 (m, 8H), 7.20-7.15 (m, 2H), 6.72 (d, J = 2.5 Hz, 1H), 5.37 (dd, J = 8.2 Hz, 2.3 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 10.8 Hz, 1H), 4.41 (d, J = 10.8 Hz, 1H), 4.28 (td, J = 5.6 Hz, 2.6 Hz, 1H), 4.21 (d, J = 5.6 Hz, 1H), 3.95 (d, J = 10.6 Hz, 1H), 3.71 (d, J = 10.7 Hz, 1H), 3.08 (d, J = 5.7 Hz, 1H), 2.77 (s, 1H). ESI-MS: m/z 465.1 ([M + H]$^+$).



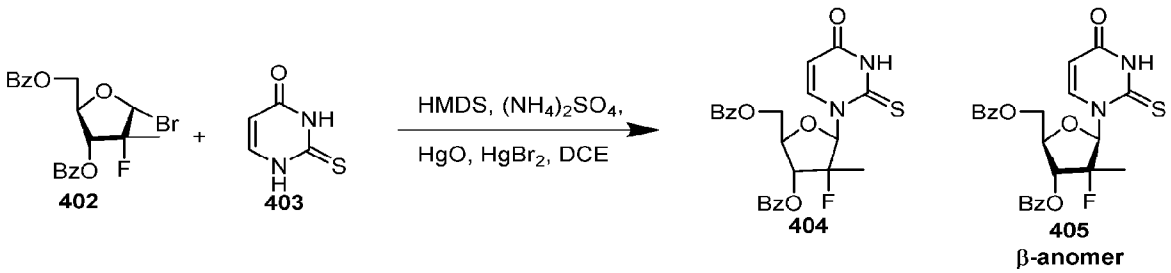
400 401

To a stirred solution of **400** (1.57 g, 3.38 mmol) in DCM (68 mL) under nitrogen at -78°C, was added dropwise via syringe a 1.0 M solution of BCl_3 in DCM (16.9 mL, 16.9 mmol). The mixture was stirred at -78°C for 3 h, then quenched by slow dropwise addition of a 7:10 v/v pyridine/MeOH mixture (68 mL). The mixture was warmed to room temperature with stirring, and concentrated by rotary evaporation to give 11 g of crude oil. The crude was

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taken up in 9:1 DCM:MeOH, and automated flash chromatography on a Combiflash (120 g column, 10 to 25% MeOH in DCM gradient) removed bulk impurities. Fractions containing the desired product were collected and concentrated to give 2 g of semipure product. This crude was taken up in MeOH and immobilized on Celite. A second automated flash chromatography on a Combiflash (40 g column, 2.5 to 25% MeOH in DCM gradient) provided **401** (0.622 g, 65%) as a powdery white solid. ^{1}H NMR (400 MHz, CD_3OD) □ 8.19 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 5.95 (d, J = 8.1 Hz, 1H), 4.26 (d, J = 6.0 Hz, 1H), 4.23 (dd, J = 5.9 Hz, 3.4 Hz, 1H), 3.85 (d, J = 12.2 Hz, 1H), 3.77 (d, J = 12.2 Hz, 1H), 3.08 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) □ 178.2, 162.3, 142.7, 106.9, 94.7, 85.6, 80.6, 79.2, 76.4, 71.0, 65.8. ESI-MS: m/z 285.0 ($[M + H]^+$).

Example 129.



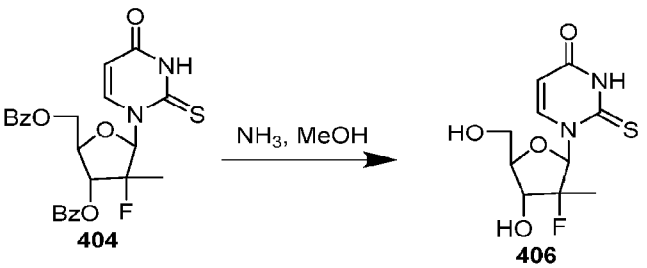
A stirred suspension of thiouracil (3.48g, 27.2mmol, 2.2eq) in HMDS (25.9mL, 1M) with 10mg of ammonium sulfate was heated to reflux under argon. After 2h the clear solution that resulted was cooled and concentrated to a white paste. A solution of bromosugar (5.4g, 12.35mmol, 1eq) in DCE (40mL) was then added to the thiouracil flask via cannula with 2x10mL DCE washes. The reaction was charged with mercury oxide (3.48g, 16mmol, 1.3eq), mercury bromide (3.56g, 9.88mmol, .8eq) was added and the reaction was fitted with a reflux condenser and refluxed. After 16h was cooled, and quenched with 100mL of a 3:1 mix of methanol and water. After 30 min of stirring reaction was diluted in 300mL water and extracted with dichloromethane (3x100mL). The combined organics were dried with sodium sulfate, filtered and concentrated in vacuo. Crude reaction was purified by silica gel chromatography (2-10% methanol in dichloromethane) to provide 2.5g of nucleoside as a mixture of two compounds bearing the correct mass. Further silica gel chromatography (20-70% ethyl acetate in hexanes) afforded 785mg of compound **404** (13%) and 805mg of compound **405** (13%).

Compound 404 ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, J = 34.2, 7.8 Hz, 4H), 7.86 (d, J = 6.6 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.57 – 7.32 (m, 4H), 6.48 (d, J = 21.7 Hz, 1H),

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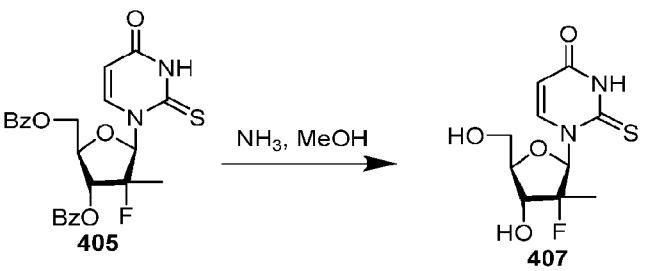
6.30 (d, J = 6.6 Hz, 1H), 5.50 (dd, J = 16.6, 8.1 Hz, 1H), 4.87 – 4.48 (m, 4H), 1.71 (d, J = 21.5 Hz, 3H).

Compound 405 ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 (dd, J = 26.3, 8.0 Hz, 5H), 7.86 (d, J = 6.7 Hz, 1H), 7.71 – 7.33 (m, 7H), 6.43 (d, J = 17.5 Hz, 1H), 6.29 (d, J = 6.7 Hz, 1H), 5.69 (dd, J = 21.8, 8.5 Hz, 1H), 4.94 – 4.35 (m, 5H), 1.66 (d, J = 22.1 Hz, 3H).



404 406

A suspension of the compound 404 (785mg, 1.62mmol) in 7M ammonia in methanol (16mL, .1M) was prepared. After 16h, reaction was concentrated and purified by silica gel chromatography (5-20% methanol in dcm) provided 220mg of diol (49%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, J = 6.6 Hz, 1H), 6.38 (d, J = 28.2 Hz, 1H), 6.19 (t, J = 5.4 Hz, 1H), 4.13 – 3.91 (m, 2H), 3.85 (dd, J = 12.6, 1.9 Hz, 1H), 3.64 (dd, J = 12.5, 3.7 Hz, 1H), 1.62 – 1.42 (m, 3H). LCMS calculated for $C_{10}H_{13}FN_2O_4S$ 276.06 found 277.00 M+1; 274.90 M-1

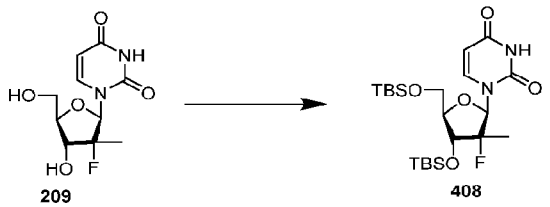


405 407

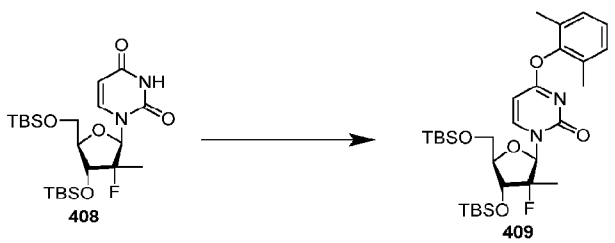
A suspension of the compound 405 (805mg, 1.62mmol) in 7M ammonia in methanol (16mL, .1M) was prepared. After 16h, reaction was concentrated and purified by silica gel chromatography (5-20% methanol in dcm) provided 210mg of diol (46%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (d, J = 6.6 Hz, 1H), 6.43 (d, J = 18.3 Hz, 1H), 6.19 (d, J = 6.6 Hz, 1H), 4.02 – 3.88 (m, 1H), 3.81 (dd, J = 12.5, 2.1 Hz, 1H), 3.72 – 3.53 (m, 1H), 3.39 – 3.23 (m, 1H), 1.56 (d, J = 22.3 Hz, 3H). LCMS calculated for $C_{10}H_{13}FN_2O_4S$ 276.06 found 274.90 M-1. The phosphoramidate prodrug of compound **236** can be synthesized using the general procedure in Example 93, and the triphosphate of compound **236** can be synthesized using the general procedure in Example 98.

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Example 130.

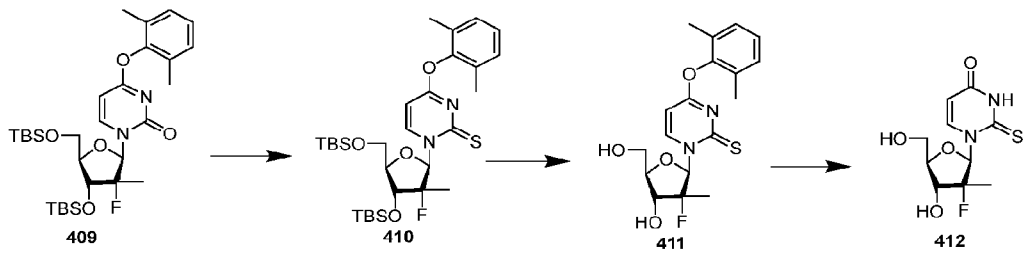


A stirred suspension of nucleoside (190mg, 0.73mmol) in dichloromethane (14.6mL, .05M) was charged sequentially with DMAP (89mg, 0.73mmol), imidazole (124mg, 1.83mmol), and TBSCl (242mg, 1.61mmol) and was stirred overnight. After 18h reaction was concentrated, diluted in ether and filtered. The liqueur was concentrated and purified by silica gel chromatography 5-50% ethyl acetate in hexanes to provide 200mg (57%) of desired bis TBS nucleoside. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 17.8 Hz, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 4.17 – 3.90 (m, 3H), 3.87 – 3.64 (m, 1H), 1.31 (d, *J* = 21.7 Hz, 3H), 0.90 (d, *J* = 10.2 Hz, 18H), 0.10 (s, 12H).



A stirred solution of **408** (200mg, 0.409 mmol) in DCM (4mL) was charged with DMAP (100 mg, 0.818 mmol) and triethylamine (120 µl, 0.859 mmol). The clear solution was cooled to 0 °C and then charged with 2,4,6-triisopropylbenzene-1-sulfonyl chloride (248 mg, 0.818 mmol). Reaction was stirred 18h then cooled back to 0°C. A 0°C solution 2,6-dimethylphenol (150 mg, 1.228 mmol), DABCO (9.18 mg, 0.082 mmol) and triethylamine (171 µl, 1.228 mmol) in DCM (4mL) was prepared and added to the reaction dropwise. Reaction was stirred 3h then was quenched with cold 50 mL sat $NaHCO_3$ and 100mL DCM. The separated organic layer was washed with once with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Resulting oil was purified 5-50% EtOAc in hexanes to provide 234mg of phenol ether as a glass. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 7.4 Hz, 1H), 7.04 (s, 3H), 6.33 (d, *J* = 17.8 Hz, 1H), 6.08 (d, *J* = 7.4 Hz, 1H), 4.30 – 3.94 (m, 3H), 3.84 (d, *J* = 12.0 Hz, 1H), 2.13 (s, 6H), 1.32 (d, *J* = 21.8 Hz, 3H), 0.95 (d, *J* = 27.3 Hz, 18H), 0.15 (d, *J* = 15.3 Hz, 12H).

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A stirred solution of **409** (200mg, 0.338mmol) in toluene (6.6mL, 0.05M) was charged with lawesson's reagent (204mg, 0.506mmol) and heated to 110°C. After 3h, the reaction was cooled, concentrated onto 1g of celite, and was purified by silica gel chromatography 1-20% EtOAc/hexanes to provide a total of 200mg of material containing a minor amount of phosphorus impurity which was carried on. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 18.2 Hz, 1H), 7.03 (s, 3H), 6.28 (d, *J* = 7.4 Hz, 1H), 4.34 – 3.95 (m, 4H), 2.11 (s, 6H), 1.44 (d, *J* = 21.6 Hz, 3H), 1.06 – 0.82 (m, 18H), 0.14 (dd, *J* = 9.0, 1.1 Hz, 12H).

A stirred solution of **410** (200mg, ~0.338mmol) in THF (6.6mL, 0.5M) was charged TBAF (821uL 1M in THF, 0.821mmol). The reaction was stirred for 18h, was concentrated on 1g of celite, and then was purified via silica gel chromatography 2-7% methanol in DCM to provide 100mg (~80% 2 steps) of material containing a minor amount of tetrabutylammonium salt. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.75 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.35 (dd, *J* = 18.2, 1.7 Hz, 1H), 7.22 – 6.96 (m, 3H), 6.60 – 6.41 (m, 1H), 4.13 – 3.91 (m, 3H), 3.91 – 3.73 (m, 2H), 2.11 (s, 6H), 1.42 (dd, *J* = 22.2, 1.6 Hz, 3H).

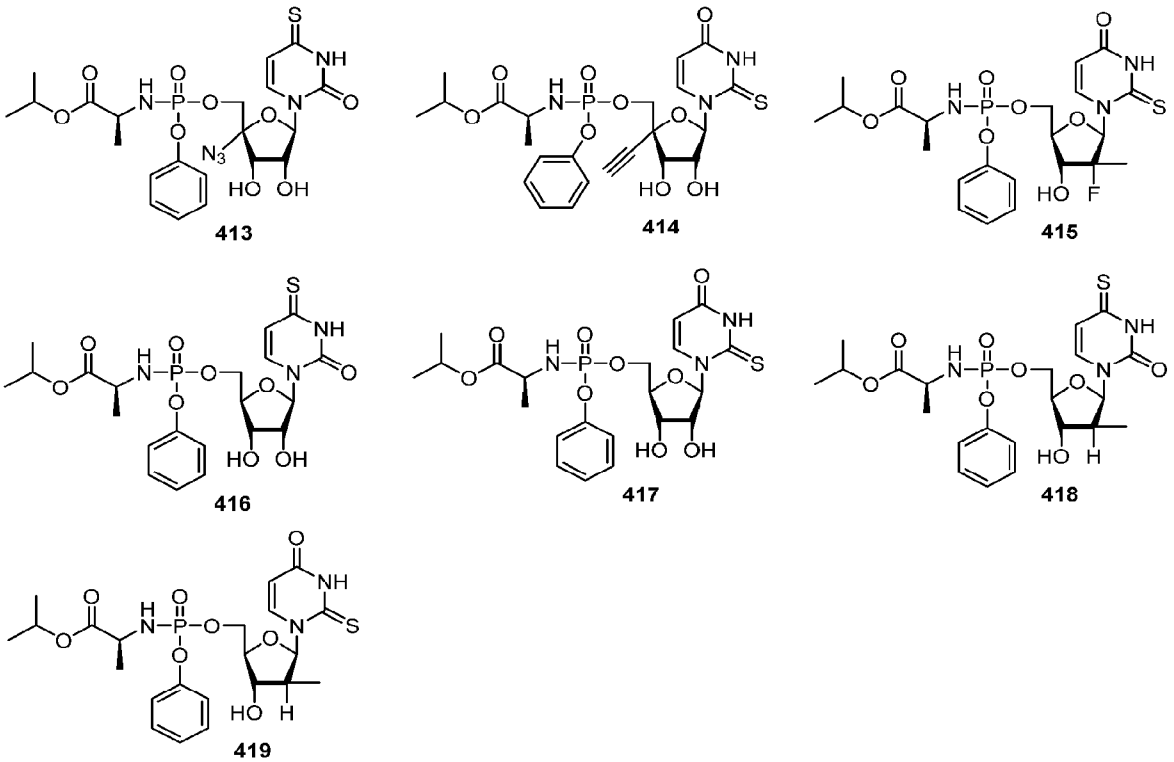
A solution of syn-o-nitrobenzaldoxime (131 mg, 0.789 mmol) in acetonitrile(2.6mL) was charged with 1,1,3,3-tetramethylguanidine (99 µl, 0.789 mmol) to give an orange solution. After 15 minutes, the resulting solution was added dropwise to a stirred solution of **411** (100mg, 0.63mmol) in acetonitrile (2.6mL). After 3h, the reaction was concentrated onto 500mg of celite and was purified by silica gel chromatography 2-20% methanol in DCM to provide 45mg of **412** 62%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 18.7 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 4.09 – 3.87 (m, 3H), 3.80 (dd, *J* = 12.5, 1.9 Hz, 1H), 1.43 (d, *J* = 22.2 Hz, 3H). MS $C_{10}H_{13}FN_2O_4S$ [M-H$^+$]; calculated: 277.1, found: 277.0.

The triphosphate of compound 412 has activity against dengue virus infection.

Example 131.

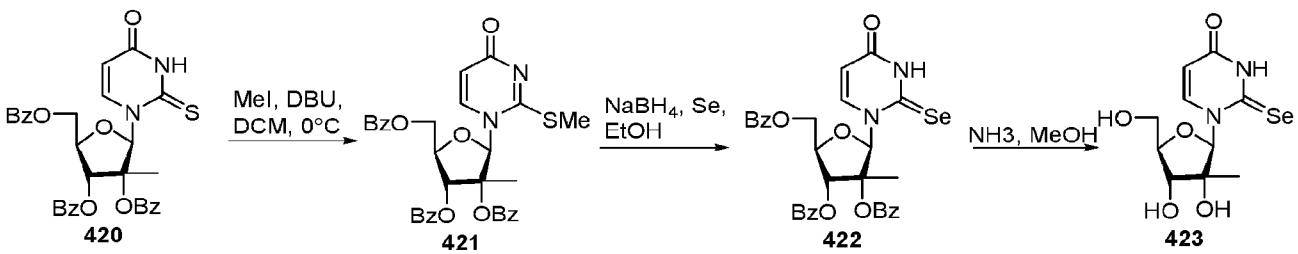
5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:

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Example 132.

Synthesis of 2'-methyl-2-selenouridine:



Synthesis of 421. To a stirred solution of (2R,3R,5R)-5-((benzoyloxy)methyl)-3-methyl-2-(4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl dibenzoate **420** (2.899 g, 4.94 mmol) in anhydrous CH_2Cl_2 (35 ml) was added iodomethane (3.08 ml, 49.4 mmol) and cooled to 0 °C. DBU (1.106 ml, 7.41 mmol) was then added dropwise and stirred at 0°C for 1 h. The reaction was quenched by the addition of 15 mL of water and extracted with CH_2Cl_2. The aqueous layer was separated and organic layer was washed with water (2X15 mL) and the aqueous layer was back extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give an oil, which was purified over silica gel column chromatography using linear gradient of 0-50% EtOAC in

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Hexanes to get pure **421** as a white solid (2.678 g, 90% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 - 7.98 (m, 4H), 7.83 - 7.79 (m, 2H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.65 - 7.53 (m, 2H), 7.53 - 7.32 (m, 5H), 7.32 - 7.16 (m, 2H), 6.63 (s, 1H), 5.95 (dd, *J* = 7.8, 0.6 Hz, 1H), 5.64 (d, *J* = 6.0 Hz, 1H), 5.00 - 4.63 (m, 3H), 2.63 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.2, 165.5, 165.3, 162.9, 138.5, 134.0, 133.9, 130.1, 129.9, 129.8, 129.6, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 109.6, 91.21, 85.5, 80.5, 77.5, 77.2, 76.9, 74.7, 62.6, 19.4, 15.4.

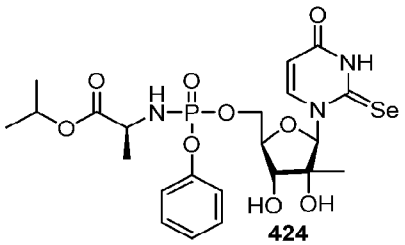
Synthesis of 422. Anhydrous Ethanol (10 ml) was cooled at 0 °C and deoxygenated by passing argon for 15 min and this solution was added to a mixture of gray powder selenium (0.263 g, 3.33 mmol) and sodium tetrahydroborate (0.132 g, 3.50 mmol) cooled in an ice bath. After being stirred for 30 min, this solution was carefully added to deoxygenated neat solid of **421** (1.000 g, 1.665 mmol) at 0 °C and stirred for 10 min at 0 °C, then allowed to warm to RT overnight. TLC (5% MeOH: CH_2Cl_2) showed product R_f=0.71. The mixture was bubbled with argon to remove H_2Se for an hour, diluted with EtOAC (30 mL) and washed with water (15 mL) followed by brine (15 mL). The aqueous layer was reextracted with EtOAC (30 mL). Combined organic layers were dried (Na_2S0_4), filtered and concentrated to get crude solid which was purified by silica column chromatography using 0-10% linear gradient of methanol in dichloromathane to obtain **422** as a pale yellow solid. The solid was repurified by column chromatography using EtOAC and hexanes to remove minor impurities and obtained pure **422** in 99% yield. ^{1}H NMR (300 MHz, Chloroform-d) δ 10.25 (s, 1H), 8.07 (t, *J* = 8.4 Hz, 4H), 7.81 (d, *J* = 6.0 Hz, 2H), 7.77 (s, 1H), 7.71 (d, *J* = 6.0 Hz, 1H), 7.67 - 7.36 (m, 7H), 7.30 - 7.19 (m, 2H), 5.96 (d, *J* = 8.3 Hz, 1H), 5.61 (d, *J* = 6.0 Hz, 1H), 5.01 - 4.59 (m, 3H), 1.77 (s, 3H).

Synthesis of 423. A solution of **422** (0.950 g, 1.500 mmol) in 7 N NH_3 in methanol (10 mL) was heated in a sealed tube at 40°C overnight. TLC (10% MeOH:CH_2Cl_2) showed complete conversion with product R_f=0.2, while starting material R_f=0.7. The reaction mixture was concentrated and the resulting crude mixture was purified by silica gel column chromatography and eluted with 0-20% linear gradient of methanol in CH_2Cl_2 to obtain **423** as a pale yellow solid (0.350 g, 72.7% yield). ^{1}H NMR (300 MHz, Methanol-d4) δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.10 (s, 1H), 6.08 (d, *J* = 8.1 Hz, 1H), 4.62 (s, 1H), 4.08 - 3.69 (m, 4H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, DMSO): 179.3, 161.76, 143.8, 111.1, 100.5, 85.4, 81.8, 74.5, 61.4, 23.5; HRMS $[M+Na]^+$ for $C_{10}H_{14}N_2O_5NaSe$ cacld:344.99601, observed:344.99632.

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Example 133.

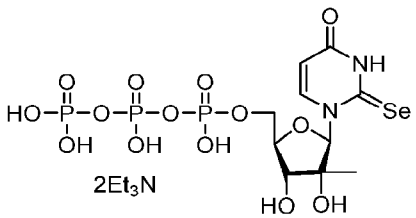
5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:



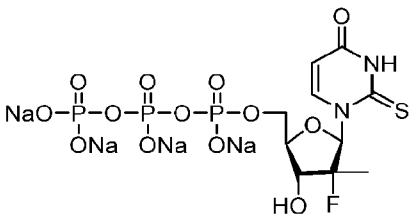
424

Example 134.

5'-Triphosphates synthesized utilizing the general procedure:



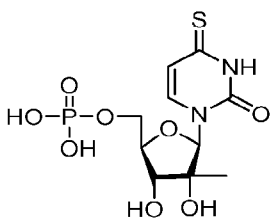
425



426

Example 135.

Synthesis of 2'-methyl-4-thiouridine-5'-monophosphate:



427

To a 10 mL flame-dried pear-shaped flas charged with 1-((2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-4-thioxo-3,4-dihydropyrimidin-2(1H)-one (0.205 g, 0.747 mmol) was added $PO(OMe)_3$ (1.868 ml) to give a bright yellow solution. This was cooled to 0 °C and then $POCl_3$ (0.139 ml, 1.495 mmol) was added dropwise to give still a bright yellow solution. After stirring at 0 °C for 4.5 h, TLC showed no SM. The crude mixture was poured into 30 mL cold DI water. After stirring for 5 min, it was transferred to a separation funnel and $CHCl_3$ (30 mL) was added. The aqueous layer was washed with $CHCl_3$ (30 mL) once again. Then the aqueous layer was neutralized to about pH = 7.2 by adding concentrated NH_4OH dropwise. The mixture was re-extracted with $CHCl_3$ (30 mL) once. The aqueous layer

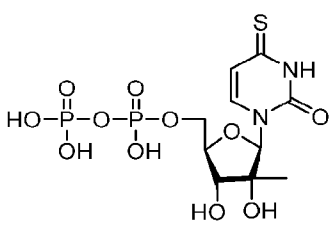
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was cocnetrated in vacuo to give a light yellow solid. The solids were stirred with MeOH (60 mL) for 1 h and then it was filterted through a sinsterted glass. The filtrate was treated with celite and concentrated in vacuo. The crude material was purified by SiO_2 column chromatography eluting from 100% DCM to 100% IPA to IPA/NH_4OH/H_2O = 8/1/1 to 7/2/1 to afford the product and some other inorganics (white). Then the material was diluted with MeOH and celite was added. The crude material was concentrated in vacuo and was purified by 100% IPA to IPA/NH_4OH/H_2O = 9/1/1 to 8/1/1 to 7/2/1. The fractions containing prodcut was pulled together and concentrated in vacuo and co-evaporated with MeOH to afford an yellow oil, which was dissolved in water and lyophilized overnight to afford **427** (25 mg) as an yellow solid.

^{1}H NMR (400 MHz, CD_3OD); δ 7.99 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.93 (s, 1H), 4.29-4.25 (m, 1H), 4.14-4.09 (m, 1H), 4.03-3.94 (m, 2H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD); δ 192.3, 150.2, 136.7, 114.8, 93.2, 83.1, 80.3, 73.0, 63.3, 20.3. ^{31}P NMR (400 MHz, CD_3OD); δ 1.27. HRMS (ESI) Calcd. for $C_{10}H_{14}O_8N_2PS$ $[M-H]^+$: 353.0214. Found: 353.0213.

Example 136.

Synthesis of 2'-methyl-4-thiouridine-5'-diphosphate:



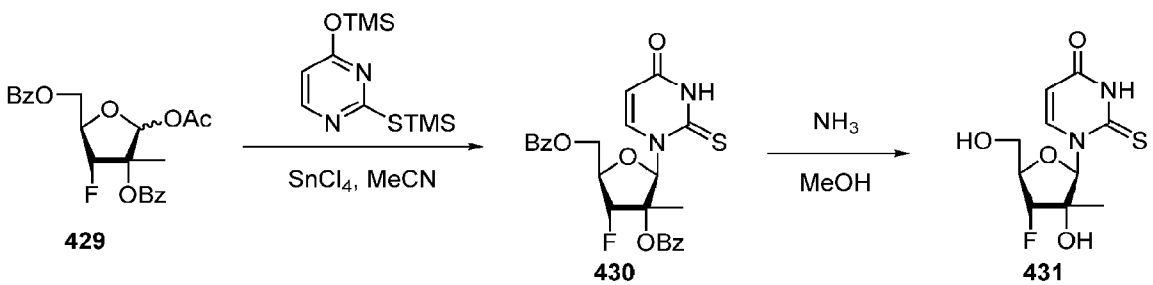
428

A stirred solution of **427** (39mg, 110umol) in DMF (1.1mL, 0.1M) was charged with tributyl amine (262uL, 1.1mmol) . Reaction was stirred for 25 min then concentrated in vacuo. Resultant paste was redisolved in DMF (1.1mL, 0.1M) and charged with carbonyl diimidazole (89mg, 550umol) to give a clear solution. After stirring 24h methanol (150uL, 1.4mmol) wad added dropwise. After 2h reaction was charged with tributylammonium phosphate (12mL, 0.5M in DMF, 2.2mmol) to give a cloudy solution. Reaction was stirred 2d, solvent was then removed and crude paste was loaded onto a DEAE column eluting from 50-450mM TEAB to provide triethyl ammonium salt of diphosphate. Diphosphate was transformed to sodium salt eluting through a column of Na^+Dowex at 0°C to afford 28mg 51% yield of sodium salt of diphosphate.

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^{1}H NMR (400 MHz, D_2O) δ7.73 (d, J = 7.6 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 5.87 (s, 1H), 4.24 – 4.11 (m, 2H), 4.00 (d, J = 2.1 Hz, 2H), 1.08 (s, 3H). ^{32}P NMR (162 MHz, D_2O) -6.55 (d, J = 23.0 Hz), -11.02 (d, J = 22.9 Hz). HRMS $C_{10}H_{16}N_2O_{11}P_2S$ [M^-]; calculated:432.995, found: 432.988.

Example 137.



429 430 431

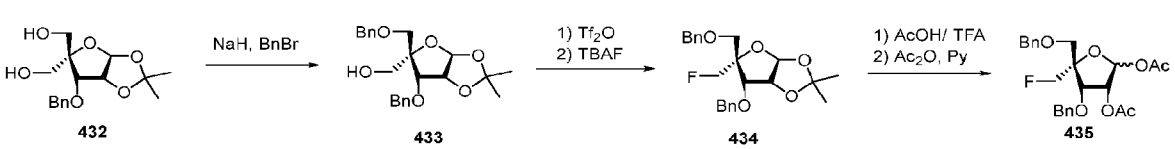
2-Thiouracil (1.025 g, 8.0 mmol) was persilylated by mixing with ammonium sulfate (0.053 g, 0.400 mmol) in hexamethyldisilazane (16.77 mL, 80.0 mmol) and heating the mixture to reflux for 16 h. The resulting light blue solution was cooled to room temperature, and volatiles were removed by rotary evaporation followed by high vacuum to give persilylated 2-thiouracil as a light blue liquid, which was >95% pure by ^{1}H NMR analysis. The entirety of this material was used immediately in the next step.

To a stirred solution of the crude, freshly prepared persilyl-2-thiouracil (8.0 mmol) in 1,2-dichloroethane (20.0 mL) under nitrogen at room temperature, was added a solution of **429** (1.666 g, 4.00 mmol) in 1,2-dichloroethane all at once. The stirred solution was cooled to 0°C, and $SnCl_4$ (0.94 mL, 8.00 mmol) was added dropwise via syringe. The mixture was warmed to rt and stirred overnight for 16 h. The mixture was then recooled to 0°C and quenched carefully with sat. aq. $NaHCO_3$ (40 mL). The mixture was warmed to rt and vigorously stirred 1 h. The mixture was extracted with EtOAc (2 x 150 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give 3.5 g crude residue. The crude residue was taken up in DCM, and automated flash chromatography on a Combiflash (80 g column, 5 to 50% EtOAc gradient in hexanes) gave **430** (0.708 g, 1.46 mmol, 37% yield) as a white flaky solid. ^{1}H NMR analysis showed ~95% purity; the entirety of the compound was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) □ 9.52 (br s, 1H), 8.18 (d, *J* = 7.0 Hz, 2H), 8.06 (d, *J* = 7.0 Hz, 2H), 7.67-7.57 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.55-7.45 (m, 5H), 5.96 (dd, *J* = 8.3 Hz, 2.1 Hz, 1H), 5.33 (dd, *J* = 52.0 Hz, 2.4 Hz, 1H), 4.84-4.68 (m, 3H), 1.65 (d, *J* = 2.0 Hz, 3H).

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A sealable pressure tube was charged with a stir bar, **430** (0.708 g, 1.461 mmol) and a 7 N ammonia solution in MeOH (20 mL, 140 mmol) at 0°C. The tube was sealed, warmed to room temperature, and stirred for 3 days at rt. The tube was then heated at 45°C for 5 h, recooled to rt, and concentrated by rotary evaporation to give 700 mg crude. The crude was dissolved in MeOH and immobilized on Celite. Automated flash chromatography on a Combiflash (24 g column, 0 to 10% MeOH gradient in DCM) gave approximately 450 mg of a partially deprotected 2'-monobenzoate product. This compound was placed into a sealable pressure tube with a stir bar and a 7 N ammonia solution in MeOH (20 mL, 140 mmol). The mixture was heated with stirring, gradually increasing heat, until the reaction was complete: 24 h at 45°C, 24 h at 55°C, and finally 24 h at 75°C. The mixture was cooled to rt and concentrated by rotary evaporation to give 500 mg of a brown oil. The crude was dissolved in MeOH and immobilized on Celite. Automated flash chromatography on a Combiflash (24 g column, 0 to 10% MeOH gradient in DCM) gave 160 mg of a mostly pure compound. This was again taken up in MeOH and immobilized on Celite. A second automated flash column on the Combiflash (12 g column, 0 to 7% MeOH gradient in DCM) gave 115 mg of a white solid with some solvent occluded. The solid was dissolved in water, frozen in a dry ice/acetone bath, and lyophilized to give **431** (0.102 g, 0.369 mmol, 9.2% yield over 2 steps) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) □ 12.70 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.5 Hz, 1H), 6.02 (d, J = 8.2 Hz, 1H), 5.86 (s, 1H), 5.47 (t, J = 4.9 Hz, 1H), 4.76 (dd, J = 52.9 Hz, 8.7 Hz, 1H), 4.20-4.10 (br m, 1H), 3.85 (ddd, J = 13.1 Hz, 5.4 Hz, 2.1 Hz, 1H), 3.66 (ddd, J = 12.8 Hz, 4.9 Hz, 2.5 Hz, 1H), 1.20 (s, 3H); ^{1}H NMR (400 MHz, D_2O) □ 7.94 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.17 (d, J = 8.2 Hz, 1H), 4.81 (dd, J = 52.4, 8.1 Hz, 1H), 4.38-4.27 (m, 1H), 4.04 (dd, J = 13.2 Hz, 2.7 Hz, 1H), 3.90 (dd, J = 13.2 Hz, 3.6 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, D_2O) □ 176.5, 162.2, 141.8, 106.9, 94.2 (d, J = 3.8 Hz), 91.3 (d, J = 190.6 Hz), 79.9 (d, J = 24.3 Hz), 78.6 (d, J = 14.2 Hz), 59.0, 19.5; ^{19}F NMR (376 MHz, D_2O) □ -212.37 (dd, J = 52.3 Hz, 14.3 Hz); HRMS calcd. for $C_{10}H_{13}FN_2O_4SNa$ [M + Na]$^+$: 299.04723, found: 299.04743.

Example 138.



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3,5-Di-*O*-benzyl-4-*C*-hydroxymethyl-l,2-*O*-isopropylidene-□-D-ribofuranose: To a solution of 3-*O*-benzyl-4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-□-D-ribofuranose (10.0 g, 32.2 mmol) in anhydrous DMF (50 mL) at -5 °C was added a suspension of NaH (60% in mineral oil (w/w), two portions during 30 main, total 1.48 g, 37.1 mmol). Benzyl bromide (4.4 mL, 37.1 mmol) was added dropwise and stirring at room temperature was continued for 3 h whereupon ice-cold water (50 mL) was added. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic phase was dried (Na_2SO_4). After evaporation, the residue was purified by silica gel column chromatography eluting with 15-20% EtOAc in Hexanes (v/v) to yield the product, **433** (8.84 g, 69%) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.37-7.25 (m, 10H), 5.79 (d, J = 4.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.65 (t, J = 4.8 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 4.8 Hz, 1H), 3.93 (d, J = 12.0 Hz, 1H), 3.83 (d, J = 12.0 Hz, 1H), 3.61 (d, J = 12.0 Hz, 1H), 3.54 (d, J = 12.0 Hz, 1H), 2.26 (br s, 1H), 1.64 (s, 3H), 1.35 (s, 3H).

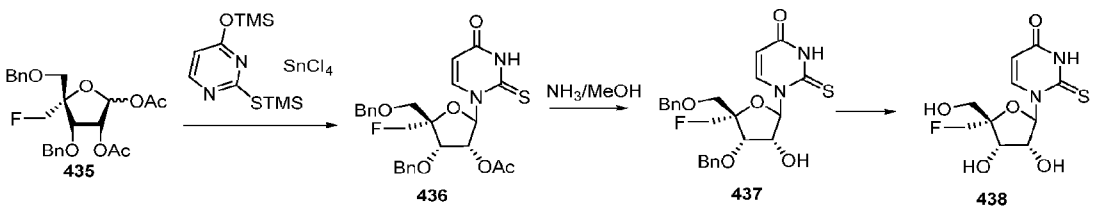
3,5-Di-*O*-benzyl-4-*C*-fluoromethyl-l,2-*O*-isopropylidene-□-D-ribofuranose: To a stirred solution of **433** (7.87 g, 19.65 mmol) in CH_2C1_2 (190 mL) was added successively pyridine (2.37 mL, 29.5 mmol) and trifluoromethanesulfonic anhydride (3.64 mL, 21.62 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for ~45 min. and then TLC indicated completion of reaction to a single, faster moving compound. After which, the mixture was wahed with water and brine. The combined aqueous layers were back extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), concentrated under reduced pressure to give a light brown solid.

The solid obtained from previous step was dissolved in acetonitrile (100 ml). A 1M solution of tetrabutylammonium fluoride in THF (78 mL, 78.0 mmol) was added and the reaction mixture was stirred at ~50 °C for overnight. Removal of the solvent under reduced pressure and silica gel chromatography of the dark oily residue |10-15% EtOAc in Hexanes| gave **434** (4.3 g, 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.34-7.26 (m, 10H), 5.77 (d, J = 3.6 Hz, 1H), 4.87 (dd, J = 10.0, 48.8 Hz, 1H), 4.73 (d, J = 10 Hz, 1H), 4.63-4.47 (m, 5H), 4.26 (dd, J = 1.6, 4.8 Hz, 1H), 3.61 (dd, J = 1.6, 10.4 Hz, 1H), 3.55 (dd, J = 1.6, 10.4 Hz, 1H), 1.63 (s, 3H), 1.35 (s, 3H). ^{19}F NMR (400 MHz, $CDCl_3$); δ -28.46 (t, J = 48.8 Hz).

1,2-Di-*O*-acetyl-3,5-di-*O*-benzyl-4-*C*-fluoromethyl-D-ribofuranose: A stirred solution of **434** in 70% acetic acid (73 mL)was charged with TFA (7.3 mL), and heated to 40

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°C. After 4h reaction was concentrated and coevaporated with toluene. Paste was then dissolved in pyridine (27 mL) and charged with acetic anhydride (10.57 mL, 112 mmol). After stirring overnight reaction was concentrated and pulled up in ethyl acetate and was washed with water. The dried (Na_2SO_4) was filtered and concentrated to an oil which was purified by sillica gel chromatography 5-20% ethyl acetate in hexanes to provide **435** (3.54 g, 71%) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.35-7.25 (m, 10H), 6.18 (s, 1H), 5.35 (d, J = 5.2 Hz, 1H), 4.73-4.66 (m, 1H), 4.60-4.48 (m, 5H), 4.43 (d, J = 4.8 Hz, 1H), 3.68 (dd, J = 1.6, 10.4 Hz, 1H), 3.51 (dd, J = 1.6, 10.4 Hz, 1H), 2.11 (s, 3H), 1.90 (s, 3H).



1-(2'-*O*-Acetyl-3',5'-di-*O*-benzyl-4'-*C*-fluoromethyl-β-D-ribofuranosyl)2-thiouracil: A stirred mixture of 2-thiouracil (600 mg, 4.68 mmol) and ammonium sulfate (30 mg, 0.23 mmol) in hexamethyldisilazane (4.9 mL, 23.41 mmol) and chlorobenzene (10 mL) was heated to reflux under nitrogen 3-4 h. until all solids dissolved and a light blue solution was formed. The mixture was cooled to rt and concentrated by rotary evaporation, followed by hi-vac, to give a blue liquid with some white solid in it. The entirety of the crude was taken on to the next step immediately.

To a stirred cloudy solution of **435** (950 mg, 2.13 mmol) and bis-silylated 2-thiouracil in 1,2-DCE (10.0 ml) at 0°C under nitrogen, was added tin(IV) chloride (0.5 ml, 4.26 mmol). The mixture immediately turned yellow, and the mixture became less cloudy. The mixture was warmed to rt and stirred overnight. After stirring 15h at rt, the mixture was diluted with 25 mL DCM, and 1.0 g each of solid $NaHCO_3$ and Celite were carefully added to the vigorously stirred reaction mixture. The mixture was cooled to 0° C, and sat. aq. $NaHCO_3$ (2 mL) was added dropwise with vigorous stirring. The mixture was warmed to rt and stirred 2 h. The mixture was filtered through a small Celite pad which was then rinsed with DCM (20 mL). The combined filtrates were concentrated to an oil which was purified by sillica gel chromatography 30-35% ethyl acetate in hexanes to provide **436** (890 mg, 81%) as colorless foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$); δ 10.11 (br s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.40-

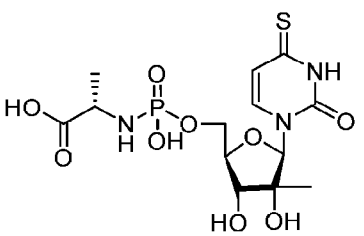
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7.19 (m, 10H), 6.81 (d, J = 2.8 Hz, 1H), 5.49 (dd, J = 3.2, 4.8 Hz, 1H), 5.38 (d, J = 8.0 Hz, 1H), 4.73-4.59 (m, 3H), 4.50-4.35 (m, 4H), 3.95 (d, J = 10.0 Hz, 1H), 3.57 (d, J = 10.4 Hz, 1H), 2.15 (s, 3H). ^{19}F NMR (400 MHz, $CDCl_3$); δ -28.22 (t, J = 50.8 Hz).

1-(3',5'-Di-*O*-benzyl-4'-*C*-fluoromethyl-*β*-D-ribofuranosyl)2-thiouracil: To a stirred solution of **436** (890 mg, 1.73 mmol) in methanol (29 ml) at 0 °C, was added methanolic ammonia (6.2 mL, 7 M in MeOH). The mixture was allowed to warm 40 °C and stirred for overnight. The solvent was evaporated under reduced pressure and then purified by sillica gel chromatography 25-30% ethyl acetate in hexanes to provide **437** (800 mg, 89%) as colorless foamy solid.

1-(4'-*β*-Fluoromethyl-β-D-ribopentofuranosyl)2-thiouracil: In a 50 mL pear-shaped flask charged with **437** (800 mg, 1.693 mmol) was added dry DCM (20.0 mL) under N_2. This was cooled to -78 °C and then BCl_3 (11.8 mL, 11.8 mmol, 1.0M in DCM) was added dropwise. The reaction was allowed to stir at -78 °C for 15 min, and then warm up slowly to -40 °C, TLC showed no SM, then MeOH (5 mL) was added dropwise and stirred at -40 °C for. After which, solvent was removed in vacuo and the crude material was purified by SiO_2 column chromatography eluting 5-7% MeOH in DCM to provide **438** (340 mg, 69%) as white solid. ^{1}H NMR (400 MHz, CD_3OD); δ 8.21 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 5.6 Hz, 1H), 5.98 (d, J = 8.0 Hz, 1H), 4.67 (d, J = 0.8 Hz, 1H), 4.56 (d, J = 2.0 Hz, 1H), 4.34-4.30 (m, 2H), 3.81-3.78 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD); δ 178.9, 162.4, 143.0, 107.3, 93.3, 88.9, 88.8, 85.3, 83.6, 76.7, 72.3, 63.5. ^{19}F NMR (400 MHz, $CDCl_3$); δ -30.18 (t, J = 50.8 Hz). HRMS (ESI) Calcd. for $C_{10}H_{13}O_5N_2FNaS$ $[M+Na]^+$: 315.0421. Found: 315.0424.

Example 139.



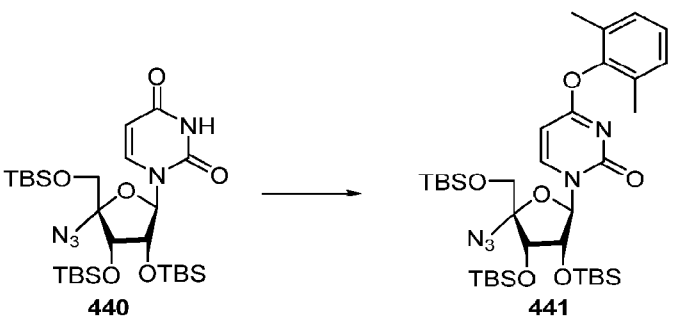
439

To a 100 mL pear-shaped flask charged with **260** (300 mg, 0.552 mmol) was added H_2O (8.00 ml) and Et_3N (8 ml). This was heated to 35 °C (oil-bath temp). Start at 4:50pm and stop at 9am. After overnight stirring, TLC showed no SM. Then solvent was removed in vacuo and then Celite was added and the mixture was concentrated in vacuo. The crude

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material was purified by SiO_2 column chromatography eluting from iPrOH (3CV) to iPrOH/NH4OH/H2O = 8/1/1 to afford **439** (0.18 g, 77% yield) as a yellow solid. ^1H NMR (400 MHz, D_2O); δ 7.91 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.98 (s, 1H), 4.23-4.11 (m, 2H), 4.03-3.96 (m, 2H), 3.62-3.55 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, D_2O); δ 190.4, 180.4, 149.0, 136.2, 113.7, 91.7, 80.7, 79.0, 71.6, 61.9, 51.0, 20.4, 18.8. ^{31}P NMR (400 MHz, D2O); δ 7.67. HRMS (ESI) Calcd. for $C_{13}H_{19}O_9N_3PS$ $[M-H]^+$: 424.0585. Found: 424.0584.

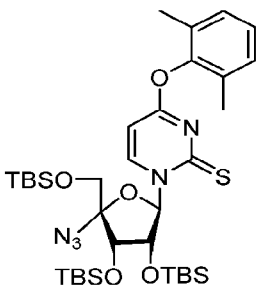
Example 140.



To a 250 mL pear-shaped flask charged with 1-((2R,3R,4S,5R)-5-azido-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (6.4 g, 10.19 mmol) was added dry DCM (85 ml) to give a colorless solution under argon. This was treated with N,N-dimethylpyridin-4-amine (2.490 g, 20.38 mmol) and triethylamine (2.98 ml, 21.40 mmol) to give a still colorless solution. The flask was cooled to 0 °C and then 2,4,6-triisopropylbenzene-1-sulfonyl chloride (6.17 g, 20.38 mmol) was added. After 1 h, ice-water bath was removed. After stirring for 17 h, the reacion became a brownish solution. It was cooled to 0 °C and then a dry DCM (21.23 ml) solution of 2,6-dimethylphenol (3.73 g, 30.6 mmol), DABCO (0.229 g, 2.038 mmol) and triethylamine (4.26 ml, 30.6 mmol) was added dropwisely. After addition, ice-water bath was removed. After stirring for 5 h, it was quenched with 50 mL NaHCO3, the organic layer was separated, washed again with 50 mL water once, 50 mL brine once, dried (Na2SO4), filterted and concentrated in vacuo. The crude material was dissolved in DCM and was purified by ISCO column chromatography (120 g, 50 mL each) eluting from 100% to 20% EtOAc in hexanes in 30 min (product came out ~4.5% EtOAc in hexanes) to afford the product, which was triturated with hexanes to afford **441** (4.7 g, 6.42 mmol, 63.0 % yield) as a white solid.

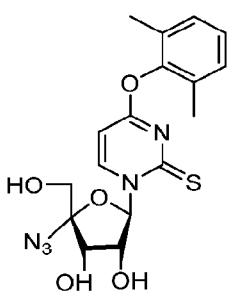
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^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 1.6 Hz, 3H), 6.14 (d, J = 3.7 Hz, 1H), 6.10 (d, J = 7.4 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.26 (d, J = 4.7 Hz, 1H), 3.86 (d, J = 11.3 Hz, 1H), 3.64 (d, J = 11.3 Hz, 1H), 2.14 (s, 6H), 0.99 (s, 8H), 0.96 (s, 8H), 0.92 (s, 8H), 0.18 (d, J = 7.1 Hz, 6H), 0.14 (d, J = 3.1 Hz, 6H), 0.08 (d, J = 0.5 Hz, 5H).



442

To a 500 mL rbf charged with **441** (12.7 g, 17.35 mmol) was added dry toluene (173 ml) under argon. Then 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (10.52 g, 26.0 mmol) was added. This mixture was heated to 110 °C for 5 hours, the crude material was concentrated in vacuo and the crude material was purified by SiO_2 column chromatography eluting from 100% hexanes to 5% EtOAc in hexanes to 10% EtOAc in hexanes to afford **442** (10 g, 13.37 mmol, 77 % yield) as a glassy solid, which contains some impurity but used for the next step directly.



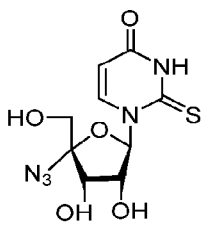
443

To a 200 mL pear-shaped flask charged with **442** (0.14 g, 0.187 mmol) (yellow solid) was added dry THF (1.871 ml) to give a yellow solution. This was vacuumed and charged with argon. The flask was cooled to 0 °C and then TBAF (0.599 ml, 0.599 mmol) was added dropwisely, followed by glacial AcOH (0.034 ml, 0.599 mmol). After 3 min, ice-water bath was removed. After 1.5 h, TLC showed no SM. Then the crude mixture was diluted with

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$CHCl_3$, which was poured into a separation funnel. Then sat $NaHCO_3$ was added. The aqueous layer was re-extracted with CHCl3 once, the combined organic layer was washed with brine once. Again, the aqueous layer was re-extracted with DCM. The combined organic layer was dried (Na_2SO_4), filterted and concentrated in vacuo. The crude material was purified by SiO_2 column chromatography eluting from 100% DCM (75 mL, 3CV) to 1% MeOH in DCM (100 mL) to 2% MeOH in DCM (200 mL) to afford **443** (70 mg, 0.173 mmol, 92 % yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 7.2 Hz, 1H), 7.9 (s, 3H), 6.60 (s, 1H), 6.39 (d, J = 7.6 Hz, 1H), 4.39 – 4.26 (m, 3H), 4.05-3.90 (m, 2H), 3.16 (d, J = 8.8 Hz, 1H), 2.14 (s, 6H).



444

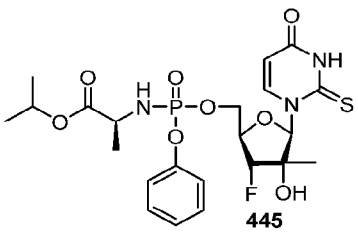
To a 10 mL pear-shaped flask charged with **443** (70 mg, 0.173 mmol) was added dry CH_3CN (1.7 mL) to give a light yellow solution. Then to another 10 mL flask charged with syn-o-nitrobenzaldoxime (86 mg, 0.518 mmol) was added dry CH_3CN (1.7 mL), followed by 1,1,3,3-tetramethylguanidine (0.065 mL, 0.518 mmol) to give an orange solution. This was added dropwise to the previous flask to give an orange solution at the end. After stirring at rt for 2 h, TLC showed no SM. Then silica gel was added and the crude material was concentrated in vacuo. The crude material was purified by SiO_2 column chromatography eluting from 5% MeOH in DCM to 7.5% MeOH in DCM to afford **444** (38 mg, 73% yield) as an off-white solid.

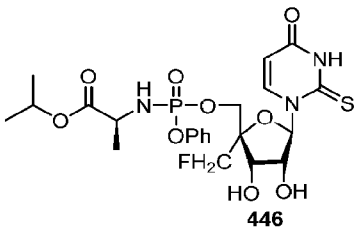
^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 4.0 Hz, 1H),5.97 (d, J = 8.4 Hz, 1H), 4.34-4.27 (m, 2H), 3.68 (dd, J = 38.4, 12.0 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD); δ 178.5, 162.4, 142.4, 107.3, 101.1, 95.2, 75.8, 72.4, 64.2. HRMS (ESI) Calcd. for $C_9H_{11}O_5N_5NaS$ $[M+Na]^+$: 324.0373. Found: 324.0370.

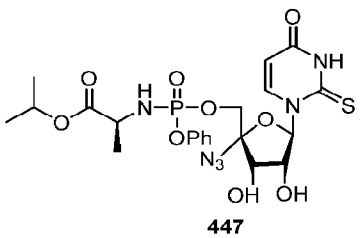
Example 141.

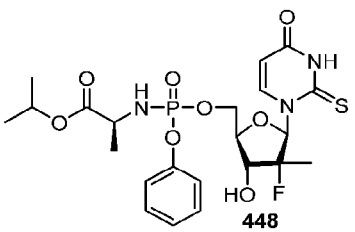
5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:

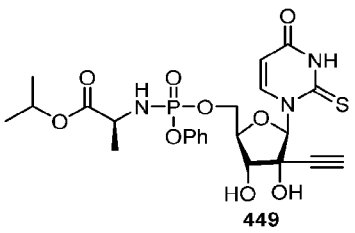
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445


446

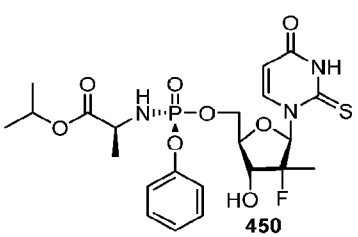

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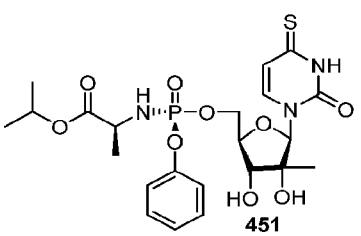

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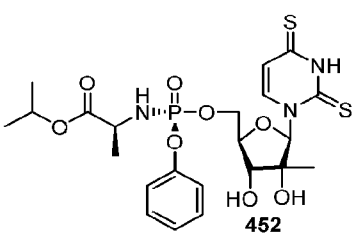

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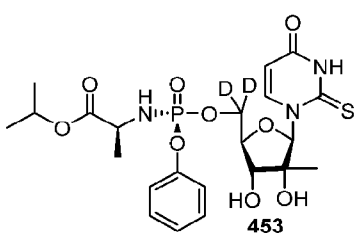
Example 142.

(S, S) 5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:


450


451

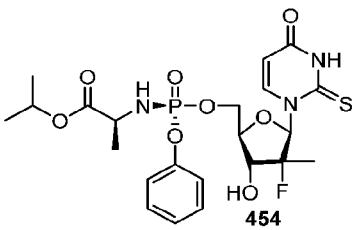

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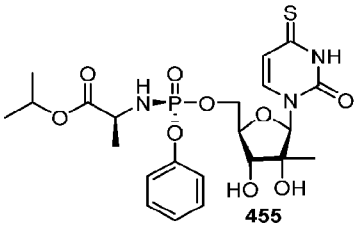

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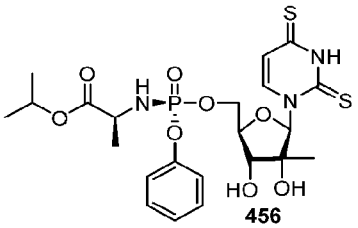
Example 143.

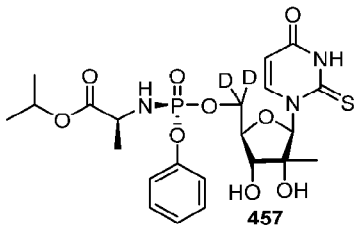
(S, R) 5'-Phosphoramidate prodrugs synthesized utilizing the general procedure:

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454

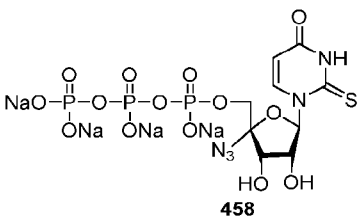

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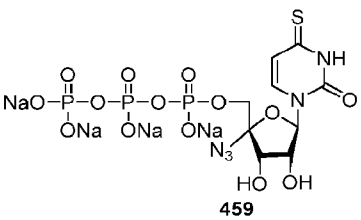

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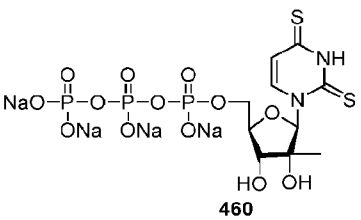

457

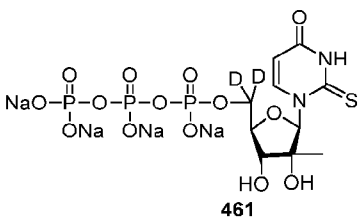
Example 144.

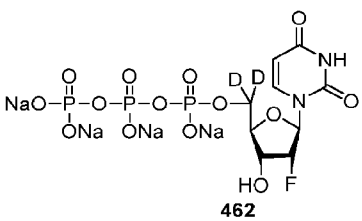
5'-Triphosphates synthesized utilizing the general procedure:


458


459

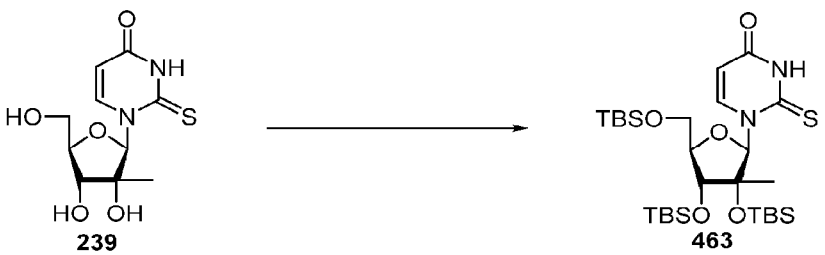

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Example 145.

Synthesis of 2'-Methyl-2,4-dithiouridine

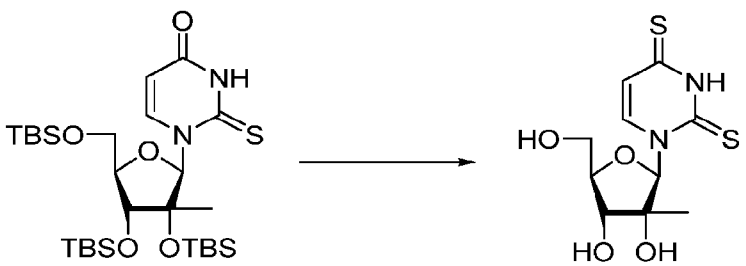

239 463

A stirred suspension of 2'methyl-2-thiouridine (1.18g, 4.3mmol) in DCM (43mL, .1M) was charged sequentially with imidazole (1.75g, 25.8mmol, 6eq), DMAP (526mg,

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4.3mmol, 1eq), and TBSCl (2.59g, 17.21mmol, 4eq.). After 18 hours an additional equivalent of TBSCl (640mg, 4.3mmol, 1eq) was added. The reaction mixture was then allowed to stir for 4 hours. The reaction mixture was then concentrated onto celite (2g), which was then loaded onto a silica gel column. The product was eluted using 10-50% ethyl acetate in hexanes to afford a mix of mono and bis silyated material.

Mixture of mono and bis silyl nucleosides were dissolved in DCM (8.6mL 0.5M) and cooled to -78°C. The reaction vessel was then charged with 2,6-lutidine (2mL, 17.2mmol, 4eq) followed by the dropwise addition of TBSOTf (1.95mL, 8.6mmol, 2eq). The reaction mixture was then allowed to warm from -78°C to room temperature over 2 hours. The reaction mixture was then allowd to stir for a further 18 hours. An additional aliquot of TBSOTf (1mL, 4.3mmol, 1eq) was added to the reaction mixture at 0°C. The reaction mixture was then allowed to stir for an additional 28 hours. The reaction was quenched with saturated aqueous ammonium chloride (100mL) and extracted with ethyl acetate (3x75mL). The pooled organic extracts were washed with saturated aqueous sodium bicarbonate (100mL) and brine (50mL). The dried (sodium sulfate) organic layer was filtered and concentrated to an oil *in vacuo*. The product was purified by silica gel chromatography eluting with 10-35% ethyl acetate in hexanes to provide the sillylate nucleoside (1.7g, 2.75mmol, 64%).



464 **465**

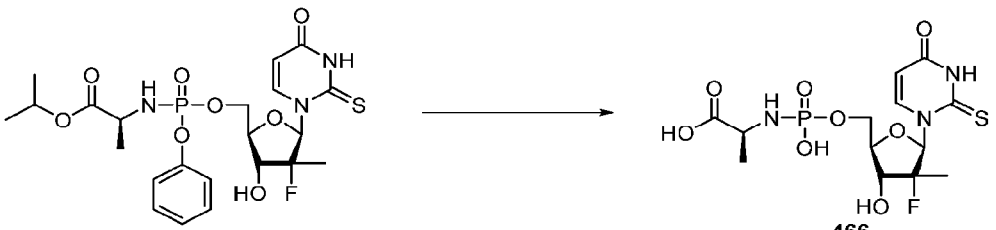
To stirred solution of silylated nucleoside (1.7g, 2.75mmol) in toluene (55mL, .01M) was added Lawesson's reagent (1.67g, 4.13mmol, 1.5eq). The reaction mixture was heated to 110°C for 1 hour and then was cooled. The reaction mixture was then concentrated onto 1 gram of celite, which was then loaded onto a silica gel column. The product was eluted in 1-20% ethyl acetate in hexanes to afford protected 2'-methyl-2,4-dithiouridine with a minor amount of aryl byproduct.

To a stirred solution of protected 2'-methyl-2,4-thiouridine (2.75mmol) in THF (55mL, .01M) was added TBAF (9.62mL, 9.62mmol, 3.5 eq 1M in THF). The reaction was

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stirred overnight and concentrated onto 1 gram of celite, which was then loaded onto a silica gel column. The product was eluted in 1-20% methanol in DCM to provide 2'-methyl-2,4-dithiouridine (650mg, 81% 2 steps).

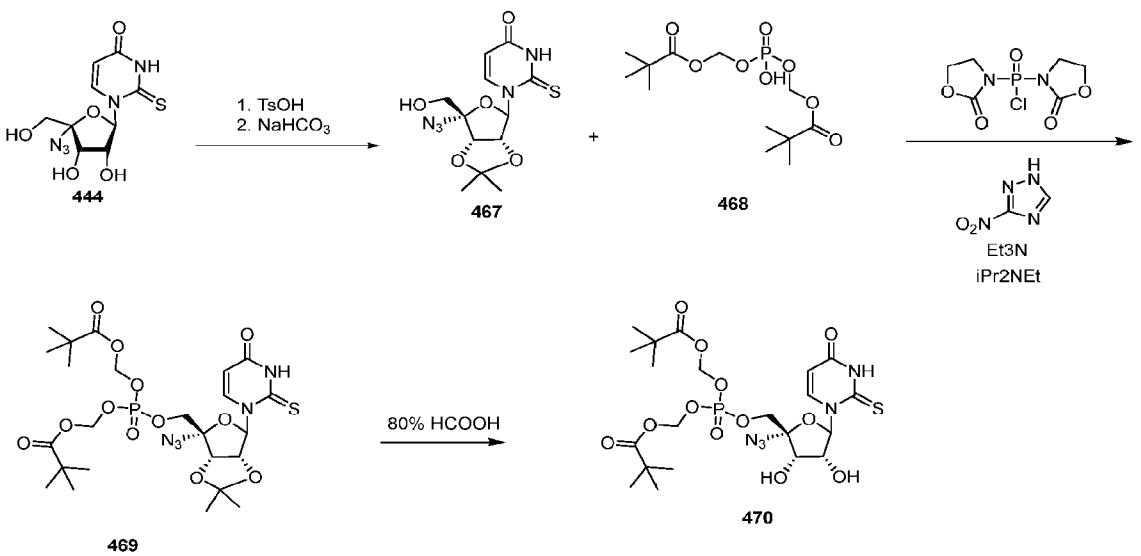
Example 146.



A solution of phosphoramidate (52mg, 95umol) in water and triethylamine (2.7mL, 1:1, .035M) was heated at 35°C for 20 hours. The reaction was then concentrated to a paste which was dissolved in 40mL of water and washed with 40mL of DCM. The aqueous layer was concentrated onto 500mg of celite. The product was purified by silica gel chromatography eluting from isopropanol (100%) to an 8:1:1 mixture of isopropanol/water/ammonium hydroxide to provide the desired product (18mg, 42umol, 42%).

Example 147.

Synthesis of 4'-azido-2-thiouridine-bis-POM-5'-monophosphate



To a 25 mL pear-shaped flask charged with 1-((2R,3R,4S,5R)-5-azido-3,4-dihydroxy-

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5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.15 g, 0.498 mmol) (light yellow solid, containing a little Et3N salt) was added molecular sieve dried acetone (3.11 ml) resulting in a suspension. A vacuum was pulled on the flask,a nd the flask was then charged with argon. Next, 2,2-dimethoxypropane (3.11 ml) was added to give a yellow suspension. The reaction mixture was then treated with Ts-OH (0.028 g, 0.149 mmol) immediately resulting in a yellow solution. The reaction mixture was allowed to stir at room temperature. After overnight stirring (22 h), solid SODIUM BICARBONATE (0.013 g, 0.149 mmol) was added. After stirring at room temperature for 30 min, the crude material was concentrated in vacuo. The crude material was treated with EtOAc and water. The organic layer was separated, dried (Na2SO4), filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (12 g column) eluting from 100% DCM to 5% MeOH in DCM to afford the product, which had an impurity. This material was dissolved in DCM and purified by ISCO column chromatography (12 g column) eluting from 100% hexanes to 80% EtOAc in hexanes to afford the product (0.12 g) as a white solid, which is still including a little impurity, but was used for the next reaction.

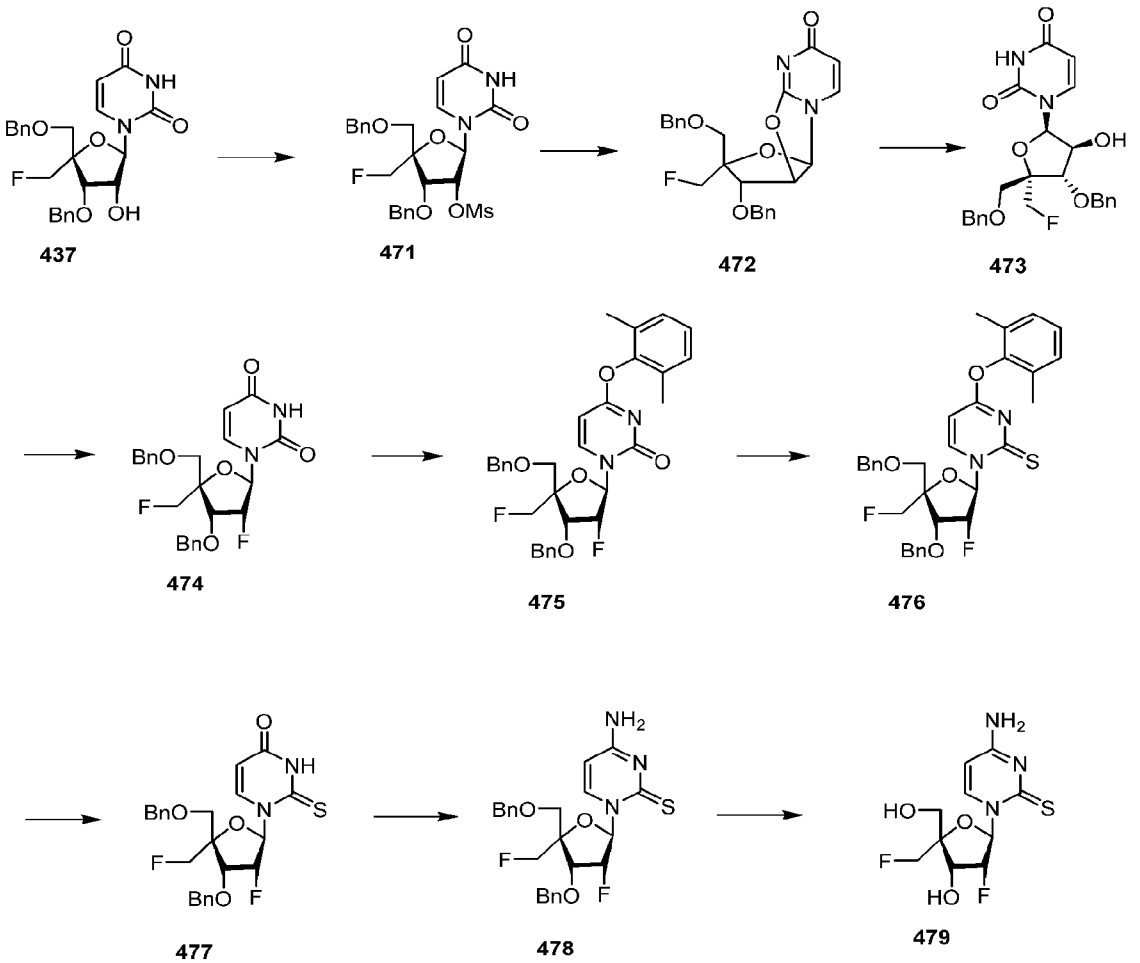
To a 50 mL pear-shaped flask charged with ((hydroxyphosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (0.229 g, 0.703 mmol) was added dry THF (4 mL) to give a colorless solution. The falsk was evacuated and charged with argon. Next, triethylamine (0.108 ml, 0.773 mmol) was added dropwise. After stirring at room temperature for 30 min, 1-((3aR,6R,6aS)-6-azido-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.12 g, 0.352 mmol) was added. The reaction mixture was cooled to 0°C and then N-ethyl-N-isopropylpropan-2-amine (0.245 ml, 1.406 mmol), bis(2-oxooxazolidin-3-yl)phosphinic chloride (0.224 g, 0.879 mmol) and 3-nitro-1H-1,2,4-triazole (0.100 g, 0.879 mmol) were added. The reaction mixture was allowed to stir overnight gradually warming to room temperature. The reaction was then diluted with EtOAc and quenched with sat $NaHCO_3$. The organic layer was separated, dried (Na2SO4), filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (12 g column) eluting from 100% DCM to 5% MeOH in DCM to afford a semi-pure product. The product was futher purified by loading the crude celite solid onto ISCO (12 g column) eluting from 10% EtOAc in hexanes to 80% EtOAc in hexanes to afford the desired product (25 mg, 11% yield) as a yellow solid.

To a 10 mL pear-shaped flask charged with **467** (25 mg, 0.038 mmol) was added 80% formic acid (1 mL) at room temperature. After 22.5 hours, the solvent was removed in vacuo

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and DCM was added to co-evaporate resulting in a yellow solid. The crude material was purified by ISCO column chromatography eluting from 100% DCM to 5% MeOH in DCM over 20 min (4 g column) to afford the desired nucleoside (14 mg, 60% yield) as a white solid.

Example 148.



To a solution of 1-((2R,3R,4S,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-5-(fluoromethyl)-3-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (3.6 g, 7.89 mmol) in pyridine (35.0 ml), methane sulfonyl chloride (0.671 ml, 8.68 mmol) was added at 0°C. The reaction mixture was allowed to slowly attain room temperature and stir for 2 hours. The reaction mixture was diluted with ethylacetate (150.0 ml). The organic layer was washed

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with water (50 ml), saturated aqueous $NaHCO_3$ (50 ml). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated resulting in the crude product.

DBU (1.060 ml, 7.10 mmol) was added to a solution of (2R,3R,4S,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-(fluoromethyl)tetrahydrofuran-3-yl methanesulfonate (3.3 g, 6.17 mmol) in acetonitrile (31.0 ml) at room temperature. The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then neutralized with acetic acid (0.406 ml, 1.0 mmol). The reaction mixture was cocnentrated and purified by column chromatorgraphy (DCM/Methanol) to give (2R,3S,3aR,9aR)-3-(benzyloxy)-2-((benzyloxy)methyl)-2-(fluoromethyl)-3,3a-dihydro-2H-furo[2',3':4,5]oxazolo[3,2-a]pyrimidin-6(9aH)-one (2.5 g, 92 %) as pale yellow solid.

To a solution of (2R,3S,3aS,9aR)-3-(benzyloxy)-2-((benzyloxy)methyl)-2-(fluoromethyl)-3,3a-dihydro-2H-furo[2',3':4,5]oxazolo[3,2-a]pyrimidin-6(9aH)-one (2.50 g, 5.7 mmol) in ethanol (35 ml) was added 1M NaOH (5.7 ml, 5.70 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 48 h. The reaction mixture was then neutralized with 1M HCl (5.70 ml) followed by the addition of ethyl acetate (100.0 ml). The organic layer was separated and washed with brine (50.0 ml), dried over anhydrous sodium sulfate, filtered and concentrated to get white crude product. The product was purified by silica gel column chromatography (Hexanes/Ethyl acetate) resulting in a white solid (1.8 g, 69.2 %).

To a solution of 1-((2R,3S,4S,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-5-(fluoromethyl)-3-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (50 mg, 0.11 mmol) in dichloromethane (2.0 ml) was added pyridine (0.018 ml, 0.219 mol) followed by DAST (0.087 ml, 0.657 mmol). The reaction mixutre was stirred at room temperature for 24 hours. The reaction mixture was then diluted with dichloromethane, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The product was purified by column chromatography.

To a 25 mL pear-shaped flask charged with 1-((2R,3R,4R,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-5-(fluoromethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (0.5 g, 1.091 mmol) was added dry DCM (Volume: 8.72 ml, Ratio: 4) to give a colorless solution. The reaction vessel was evacuated and then charged with argon. Next, N,N-dimethylpyridin-4-amine (0.266 g, 2.181 mmol) and triethylamine (0.232 g, 2.290 mmol) were added. The clear solution was cooled to 0°C followed by the addition of 2,4,6-triisopropylbenzene-1-sulfonyl chloride (0.661 g, 2.181 mmol). After ovenight stirring (18.5

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h), TLC showed no starting material. A dry DCM (Volume: 2.181 ml, Ratio: 1) solution of 2,6-dimethylphenol (0.400 g, 3.27 mmol), 1,4-diazabicyclo[2.2.2]octane (0.024 g, 0.218 mmol) and triethylamine (0.331 g, 3.27 mmol) was then added at 0°C. After addition was complete the ice batch was removed. After stirring for 3 hours and 20 minutes, TLC showed the reaction to be complete. Next, the crude reaction mixture was treated with saturated aqueous $NaHCO_3$ and DCM. The separated organic layer was washed once with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (24 g column) eluting from 100% hexanes to 20% EtOAc in hexanes over 40 min to afford the product (0.54 g, 88% yield) as a white solid.

To a 35 mL pear-shaped flask charged with 1-((2R,3R,4R,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-5-(fluoromethyl)tetrahydrofuran-2-yl)-4-(2,6-dimethylphenoxy)pyrimidin-2(1H)-one (0.15 g, 0.267 mmol) (white solid) was added dry toluene (5.33 ml) to give a white suspension. The reaction vessel was evacuated and then charged with argon. Lawesson's Reagent (0.200 g, 0.493 mmol) was added. The reaction mixture was heated to 115°C and the light yellow suspension became a yellow solution after refluxing. After 2hours, the reaction mixture was allowed to cool resulting in a yellow suspension that was filtered through a sinstered glass. The solids were washed with EtOAc. The filtrate was treated with silica gel and concentrated in vacuo. The crude material was purified by SiO2 column chromatography eluting from 5% EtOAc to 10% to 20% to afford the product with some Lawesson's byproduct, which was used directly for the next step.

To a 10 mL pear-shaped flask charged with 1-((2R,3R,4R,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-5-(fluoromethyl)tetrahydrofuran-2-yl)-4-(2,6-dimethylphenoxy)pyrimidine-2(1H)-thione (0.57 g, 0.985 mmol) was added dry CH_3CN (1.7 mL) under argon. A separate flask was charged with syn-o-nitrobenzaldoxime (0.491 g, 2.96 mmol) followed by dry CH_3CN (1.700 mL) and 1,1,3,3-tetramethylguanidine (0.371 mL, 2.96 mmol) to give an orange solution. This solution was then added dropwise to the previous flask. After stirring for 3.5 h, TLC showed the starting material was consumed. Silica gel was added to the reaction mixture and the mixture was concentrated in vacuo. The material was purified by ISCO column chromatography (24 g column) eluting from 100% DCM to 10% MeOH in DCM over 17 min to afford the product (0.21 g, 45% yield) as an off-white solid.

To a 25 mL pear-shaped flask charged with 1-((2R,3R,4R,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-5-(fluoromethyl)tetrahydrofuran-2-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (0.224 g, 0.472 mmol) was added dry DCM (Volume: 4.72 ml)

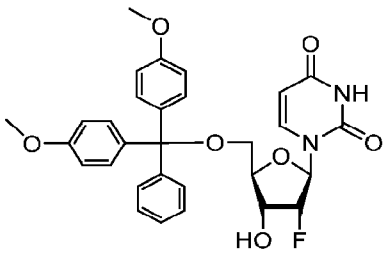
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under argon to give a pale yellow solution. Then N,N-dimethylpyridin-4-amine (0.115 g, 0.944 mmol) was added followed by triethylamine (0.138 ml, 0.991 mmol). The reaction was cooled to 0°C and then 2,4,6-triisopropylbenzene-1-sulfonyl chloride (0.286 g, 0.944 mmol) was added resulting in a bright yellow solution. After stirring at 0°C for 1hour and 45minutes, the reaction mixture was treated with 10 mL 28% aqueous ammonia hydroxide at room temperature. After stirring at room temperature for 1hour and 35 minutes, TLC showed the starting material to be consumed. Next the organic layer was separated and washed once with bine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (24 g column) eluting from 100% DCM to 10% MeOH in DCM over 20 minutes to afford semi-pure product. This material was resubjected to ISCO column chromatography (12 g column) eluting from 100% DCM to 5% MeOH in DCM over 15 minutes to afford the product (0.18 g, 81% yield) as a white solid.

To a 25 mL pear-shaped flask charged with 4-amino-1-((2R,3R,4R,5R)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluoro-5-(fluoromethyl)tetrahydrofuran-2-yl)pyrimidine-2(1H)-thione (0.18 g, 0.380 mmol) was added dry DCM (7.60 ml) to give a colorless solution. The reaction vessel was evacuated and then charged with argon. The flask was cooled to -78°C and then BORON TRICHLORIDE (3.04 ml, 3.04 mmol) was added dropwise. After stirring at -78°C for 35 minutes, the dry-ice acetone bath was replaced by an ice-water bath. After stirring for an additional 4 hours, the reaction was quenched by the addition of dry MeOH dropwise. Next, silica gel was added and the crude material was concentrated in vacuo. The crude material was purified by SiO_2 column chromatography eluting with 5% - 15% MeOH in DCM to give semi-pure product. The product was repurified by ISCO column chromatography eluting from 5% MeOH in DCM to 20% MeOH in DCM (12 g column). However, the product was still contaminated with 10% impurity. The material was again repurified by ISCO column chromatography (12 g column) eluting with a gradient of DCM and 30% MeOH in DCM (4% ammonia hydroxide) to afford the final product (39 mg, 35% yield) as a white solid.

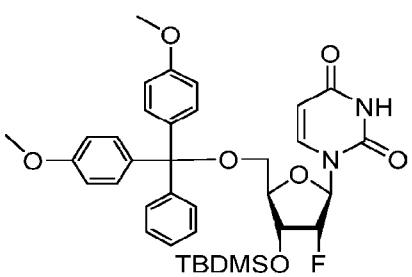
Example 149.

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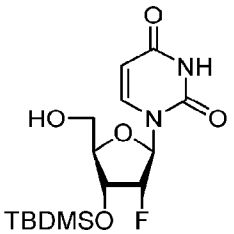
A solution of 2'-deoxy-2'-fluorouridine (6g, 24.37 mmol) and 4,4'-(chloro(phenyl) methylene)-bis(methoxybenzene) (9.91 g, 29.2 mmol) in pyridine (48.7 ml) was stirred at rt for 16 hours. The mixture was treated with MeOH (20 mL), concentrated to dryness and was partitioned between water (50 mL) and EtOAc (250 mL). The aqueous phase was back extracted with EtOAc (50 mL) and the combined organic layers were washed with water (50 mL) and dried over Na_2SO_4. The solution was concentrated to give 2'-deoxy-2'-fluoro-5'-(4',4'-dimethoxytrityl)uridine (14g, quant.) which was used without further purification.



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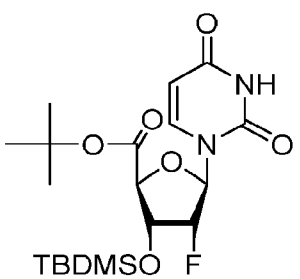
To a solution of 2'-deoxy-2'-fluoro-5'-(4',4'-dimethoxytrityl)uridine (13.37 g, 24.37 mmol) in methylene chloride (30 mL) were added 1*H*-imidazole (2.48 g, 36.6 mmol) and *tert*-butylchlorodimethylsilane (5.51 g, 36.6 mmol). The reaction was stirred for 16 hours and then was diluted with EtOAc (250 mL). The mixture was washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give 2'-Deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)-5'-(4',4'-dimethoxytrityl)uridine (16 g, 99%). This product was used in the next step without further purification.

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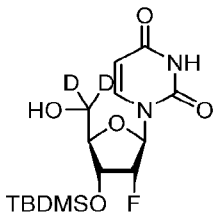
To a solution of 2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)-5'-(4',4'-dimethoxytrityl) uridine (13.37 g, 20.17 mmol) in DCM (10 mL) were added acetic acid (20.19 ml, 353 mmol) and water (5 ml). The reaction was stirred at room temperature for 20 hours, diluted with EtOAc (250 mL), washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried (sodium sulfate), filtered and concentrated. The residue was purified by column chromatography over silica gel (1% MeOH in DCM, 2% MeOH in DCM) to afford 2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)uridine (6.73 g, 93 % yield) as a yellow solid.



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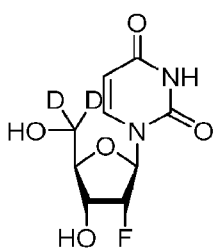
To a suspension of PDC (14.05 g, 37.3 mmol) in anhydrous DCM (37.3 ml)/DMF (9.34 ml) were added sequentially 2-methylpropan-2-ol (35.7 ml, 373 mmol), 2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)uridine (6.73 g, 18.67 mmol) and acetic anhydride (17.62 ml, 187 mmol). After 18 hours, the mixture was quenched with absolute EtOH (5 mL), diluted with EtOAc (15 mL), dried over Na_2SO_4, filtered through Celite and concentrated. The crude residue was purified by column chromatography over silica gel using 1% MeOH in DCM to give (2S,3R,4R,5R)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluorotetrahydrofuran-2-carboxylate (6.72 g, 83%)

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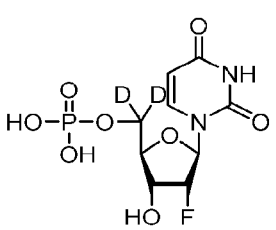
484

To a solution of (2S,3R,4R,5R)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluorotetrahydrofuran-2-carboxylate (3.29 g, 7.64 mmol) was added sodium borodeuteride (1.422 g, 30.6 mmol) in one portion. The reaction was stirred at 80°C for 20 hours in a sealed tube. The mixture was cooled to room temperture and then quenched with acetic acid (6.99 ml, 122 mmol). The mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with EtOAc. After concentrating, the resulting residue was purified by column chromatography over silica gel (Rf = 0.5 hexane EtOAc 1:1) to give [5'-$^{2}H_2$]-2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)uridine (1g, 36%).



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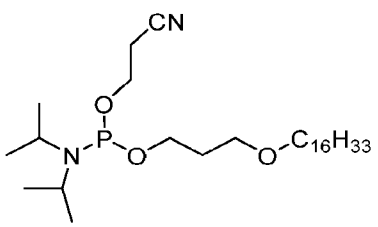
To a solution of [5'-$^{2}H_2$]-2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)uridine (200mg, 0.552 mmol) in MeOH (6 mL) was added Dowex 50WX8 (H+ form) (6 g) in one portion. The mixture was stirred for 72 h, filtered and concentrated to give [5'-$^{2}H_2$]-2'-deoxy-2'-fluorouridine (150 mg, quant.).



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To a solution of phosphoryl trichloride (1.69 mL, 18.13 mmol) in trimethyl phosphate (2 mL) at 5°C, under N_2, was added [5'-$^2H_2$]-2'-deoxy-2'-fluorouridine (100 mg, 0.403 mmol) in small portions. The solution was stirred vigorously for 2h at 5°C and then was quenched by dropwise addition of DI water (8 mL). The reaction mixture was extracted with chloroform (2 x 10 mL), and the aqueous phase was treated with concentrated with NH_4OH to pH 6.5, while keeping the solution below 30 °C. The aqueous layer was extracted once more with chloroform (10 mL) and then concentrated to dryness. The residue was suspended in MeOH (15 mL), filtered, and concentrated. The resulting solid was purified by column chromatography over silica gel (7:2:1 iPrOH/conc. NH4OH, H_2O, Rf = 0.2). The product was further purified by column chromatography over DEAE using methanol followed by a mobile phase gradient from 0 to 100 mM aqueous ammonium bicarbonate. Fractions were concentrated to dryness, dissolved in water and lyophilized to give [5'-$^2H_2$]-2'-deoxy-2'-fluorouridine-5'-monophosphate (27 mg, 20%) as an amorphous white solid.



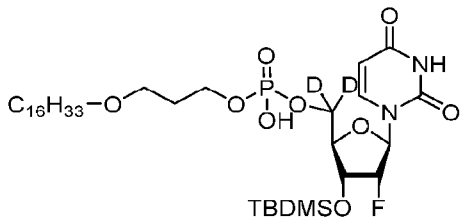
487

A suspension of 3-hexadecyloxypropan-1-ol (2.02 g, 6.72 mmol) and DIPEA (4.7 mL, 26.9mmol) in anhydrous methylene chloride (45 mL) was treated dropwise over a 10 minute period with 3-((chloro(diisopropylamino)phosphino)oxy)propanenitrile (3 mL, 13.45 mmol). After 18hours at room temperature, the mixture was quenched with saturated sodium bicarbonate solution (15 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic phases were concentrated to dryness, and the resulting crude residue purified by chromatography over silica gel (25 mm x 140 mm) using a solvent gradient from 10 to 20% ethyl acetate in hexanes to give hexadecyloxypropyl-(2-cyanoethyl) diisopropylphosphoramidite (2.1 g, 65%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.89 – 3.54 (m, 6H), 3.49 (t, *J* = 6.3 Hz, 2H), 3.39 (t, *J* = 6.7 Hz, 2H), 2.64 (t, *J* = 6.6 Hz, 2H), 1.87 (p, *J* = 6.3 Hz, 2H), 1.57 (p, *J* = 6.3 Hz, 2H), 1.25 (s, 26H), 1.18 (dd, *J* = 6.8, 3.5 Hz, 12H), 0.87 (t, *J* = 6.6 Hz, 3H).

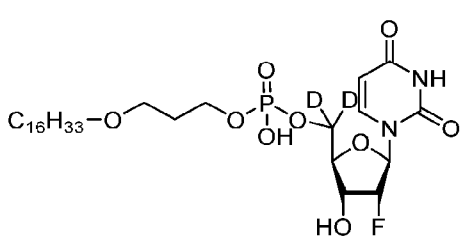
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^{31}P NMR (162 MHz, Chloroform-*d*) δ 147.40.



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A solution of [5'-$^{2}H_2$]-2'-deoxy-2-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)uridine (600 mg, 1.65 mmol) and hexadecyloxypropyl-(2-cyanoethyl) diisopropylphosphoramidite (1.65 g, 3.31 mmol) in anhydrous THF (22 mL) was treated dropwise with 1-*H*-tetrazole (14.7 mL of 0.45 M solution in acetonitrile, 6.62 mmol). After 16hours at room temperature, the mixture was treated dropwise with *tert*-butyl hydroperoxide (1.5 mL of a 5.5 M solution in nonane, 8.28 mmol) and stirred at room temperature for 1hour and then quenched with 1.0 M aqueous solution of sodium thiosulfate (40 mL). After 30 min, the mixture was extracted with ethyl acetate (2 x 80mL). Combined organic phases were washed with brine (40 mL) and dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by column chromatography over silica gel (40g) with a mobile phase gradient from 1% to 5% methanol in methylene chloride to give the cyanoethyl phosphate intermediate which without further purification was dissolved in methanol (30 mL) and treated with concentrated ammonium hydroxide (5 mL, 128 mmol). After 4hours at room temperature, the mixture was concentrated to dryness. The resulting residue was purified by column chromatography over silica gel using a CombiFlash instrument equipped with a 40 g silica cartridge eluting with a solvent gradient from 5 to 25% methanol in methylene chloride to give [5'-$^{2}H_2$]-2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)-5'-((hexadecyloxypropyl) phospho)uridine (1 g, 82%) as a white foam.



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A solution of [5'-$^{2}H_2$]-2'-deoxy-2'-fluoro-3'-*O*-(*tert*-butyldimethylsilyl)-5'-((hexadecyloxypropyl) phospho)uridine (1 g, 1.38 mmol) in THF (15 mL) was treated with acetic acid (0.5 g, 8.28 mmol) and triethylammonium fluoride (1.2 g, 5.52 mmol). After 36hours, the mixture was concentrated and the resulting residue eluted through a short column (11 mm x 90 mm) of Dowex 50WX8 (H+ form) using methanol (120 mL) as the mobile phase. The product was further purified by column chromatography over silica gel (24 g) using a mobile phase gradient from 0 to 25% methanol in methylene chloride with 2.5% (v/v) ammonium hydroxide. Pure fractions were pooled and concentrated. The resulting solid was co-evaporated with methylene chloride (2 x 75 mL) and then dried under high vacuum for 19hours to give [5'-$^{2}H_2$]-2'-deoxy-2'-fluoro-5'-((hexadecyloxypropyl)phospho)- uridine (455 mg, 54%) as a white solid.

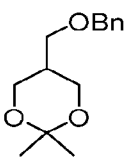
^{1}H NMR (400 MHz, Chloroform-d4/Methanol-d_4) δ 7.75 (d, *J* = 8.1 Hz, 1H), 5.95 (dd, *J* = 17.9, 1.6 Hz, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 5.01 (ddd, *J* = 52.8, 4.6, 1.7 Hz, 1H), 4.30 (ddd, *J* = 20.7, 8.1, 4.5 Hz, 1H), 4.16 - 4.07 (m, 3H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.41 (t, *J* = 6.7 Hz, 2H), 1.92 (p, *J* = 7.6 Hz, 2H), 1.53 (p, *J* = 7.6 Hz, 2H), 1.25 (s, 26H), 0.87 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d4/Methanol-d4) δ 164.31, 150.24, 140.33, 102.11, 94.19, 92.32, 88.88, 88.53, 80.83, 80.75, 71.18, 67.62, 67.45, 66.50, 66.40, 64.83, 64.77, 63.81, 31.81, 30.37, 30.29, 29.59, 29.57, 29.54, 29.51, 29.47, 29.41, 29.25, 26.00, 25.96, 22.57, 13.96.

^{31}P NMR (162 MHz, Chloroform-d4/Methanol-d4) δ -0.87.

HRMS $C_{28}H_{49}D_2FN_2O_9P$ [M+H^+]; calculated: 611.34359, found: 611.34363.

Example 150.

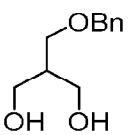


490

To a solution of acetonide (2,2-dimethyl-1,3-dioxan-5-yl)methanol (3.0 g, 20.52 mmol) and tetrabutyl ammonium iodide (7.58 g, 20.52 mmol) in anhydrous THF (100 mL)

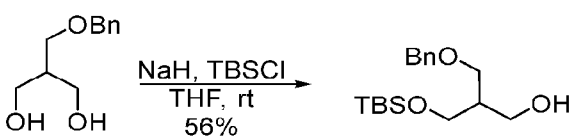
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was added sodium hydride (1.108 g, 27.7 mmol) in 3 portions. The mixture was allowed to stir at room temperature for 1 hour and then treated with benzyl bromide (2.93 ml, 24.63 mmol) over 3 minutes. The mixture was allowed to stir overnight at room temperature (18 hours). The mixture was analyzed by tlc (2:1 hexanes:ethyl acetate) and 1H NMR which showed complete consumption of starting material. The mixture was quenched with saturated ammonium chloride solution (75 mL) and extracted with ethyl acetate (200 mL and 100 mL). Combined organic phases were dried over sodium sulfate and then concentrated to dryness. The crude material was then purified by column chromatography over silica gel eluting with 0-30% EtOAc/hexanes to obtain MD-02-130 as colorless oil. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35 - 7.24 (m, 5H), 4.50 (s, 2H), 3.96 (dd, J = 12.0, 4.2 Hz, 1H), 3.77 (dd, J = 11.8, 6.4 Hz, 1H), 3.51 (d, J = 6.7 Hz, 2H), 2.04 - 1.97 (m, 1H), 1.41 (s, 3H), 1.38 (s, 3H).



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To a solution of 5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxane (4.1 g, 17.35 mmol) in MeOH (30 ml) was added *p*-toluenesulfonic acid (150 mg) and stirred at room temperature overnight. The reaction mixture was then quenched with 0.5 mL Et_3N, concentrated, diluted with EtOAC and washed with water followed by brine. The organic layer was concentrated and subjected to silica chromatography eluting with 10-100% EtOAC/hexanes to obtain the product as a colorless liquid (2.7 g, 13.76 mmol, 79%).

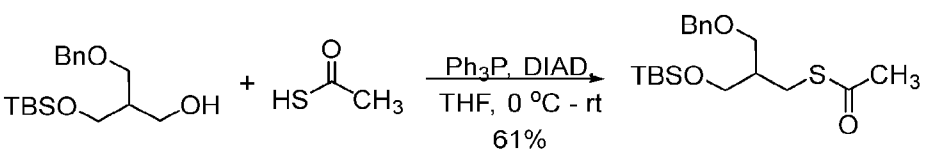


491 **492**

Sodium hydride (0.228 g, 5.71 mmol) was suspended in anhydrous THF (15 mL) and then treated dropwise with an anhydrous THF (10 mL) solution of intermediate 2-((benzyloxy)methyl)propane-1,3-diol (1.12 g, 5.71 mmol) at room temperature. The mixture

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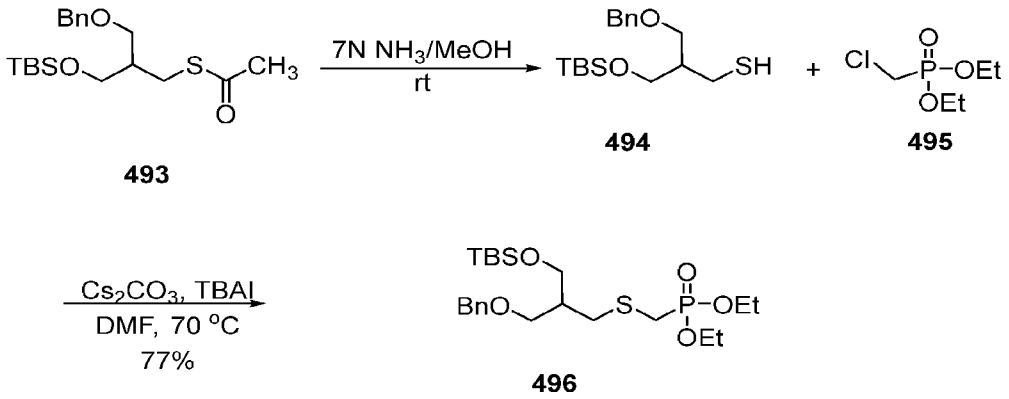
was allowed to stir for 45 minutes and then treated with TBDMSCl (0.860 g, 5.71 mmol). The mixture was allowed to stir at room temperature for 1 h and quenched with 10% K_2CO_3 solution and extracted with ethyl acetate (2 x 50 mL). Combined organic phases were dried over sodium sulfate, filtered and concentrated. The crude mixture was purified by silica chromatography eluting with 0-100% of ethyl acetate/hexanes to obtain **492** (0.99 g, 3.19 mmol, 56%) as a colorless oil. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35 - 7.26 (m, 5H), 4.49 (s, 2H), 3.79 - 3.73 (m, 2H), 3.66 - 3.47 (m, 2H), 2.77 (t, J = 5.7 Hz, 2H), 2.04 - 1.99 (m, 1H), 0.86 (s, 9H), 0.03 (s, 6H).



492 **493**

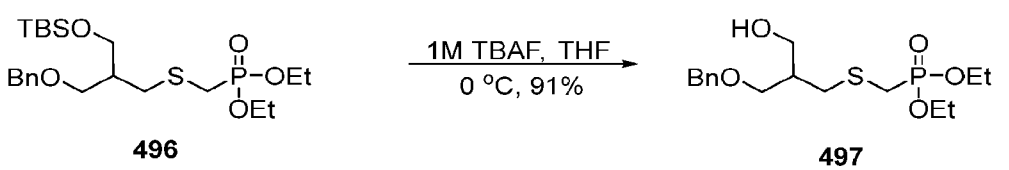
To a solution of triphenylphosphine (4.24 g, 16.15 mmol) in anhydrous THF (25 mL) was added (*E*)-diisopropyl diazene-1,2-dicarboxylate (3.18 mL, 16.15 mmol) at 0°C (pale yellow cake formed during addition). After 30 min, a solution of 3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy) methyl)propan-1-ol (2.280 g, 7.34 mmol) in anhydrous THF (10 mL) was added and stirred for 10 minutes and then thioacetic acid (1.139 mL, 16.15 mmol) in anhydrous THF (5 mL) was added drop wise. After stirring at 0°C for 1hour, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then heated to reflux at 75°C for 1h. The reaction mixture was allowed to cool to room temperature and concentrated and purified on silica chromatography eluting with linear gradient of 0-10% EtOAc/hexanes to obtain **493** (1.65 g, 4.49 mmol, 61%) as a liquid. ^{1}H NMR (400 MHz, chloroform-d) δ 7.19 - 7.05 (m, 5H), 4.29 (s, 2H), 3.48 - 3.42 (m, 2H), 3.33 - 3.23 (m, 2H), 2.80 - 2.75 (m, 2H), 2.12 (s, 3H), 1.85 - 1.76 (m, 1H), 0.67 (s, 9H), -0.17 (s, 6H).

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A solution of S-(3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)propyl) ethanethioate (1.654 g, 4.49 mmol) in anhydrous methanol (10.00 ml) was thoroughly flushed with argon and cooled to 0°C. To this solution, 7N NH_3 in MeOH (2.5 mL) was added drop wise and allowed to warm to room tempeature and stirred for 5hours. The reaction mixture was concentrated and vacuum dried to obtain crude thiol **494**, which was used immediately for the next reaction without further purification.

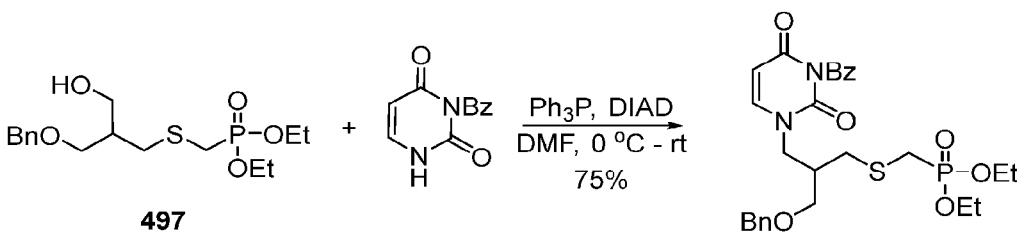
A mixture of 3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)propane-1-thiol (1.465 g, 4.49 mmol), cesium carbonate (1.608 g, 4.93 mmol), tetrabutylammonium iodide (4.14 g, 11.22 mmol) and diethyl (chloromethyl)phosphonate (0.767 ml, 4.93 mmol) in anhydrous DMF (20 mL) was heated at 70°C overnight. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc and washed with water, brine. The organic layer was concentrated and purified by silica chromatography eluting with linear gradient of 10-35% EtOAc/hexanes, followed by isocratic 35% EtOAc/hexanes to obtain **496** (1.64 g, 3.45 mmol, 77%) as a colorless oil. ^{1}H NMR (400 MHz, chloroform-d) δ 7.33 - 7.26 (m, 5H), 4.47 (s, 2H), 4.17 - 4.09 (m, 4H), 3.71 - 3.64 (m, 2H), 3.55 - 3.46 (m, 2H), 2.76 (d, J = 6.7 Hz, 2H), 2.72 (d, J = 13.6 Hz, 2H), 2.02 - 1.92 (m, 1H), 1.31 (t, J = 7.0 Hz, 6H), 0.85 (s, 9H), 0.02 (s, 6H). ^{31}P NMR (121 MHz, chloroform-d) δ 24.55.



To a solution of diethyl(((3-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)propyl)thio) methyl)phosphonate (1.5 g, 3.15 mmol) in

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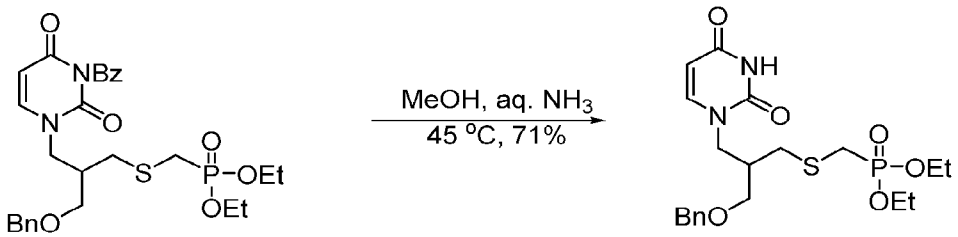
anhydrous THF (25 mL) at 0°C was added tetrabutylammonium fluoride (3.78 mL, 3.78 mmol) drop wise and stirred for 1.5 hours at 0°C. TLC (60% EtOAc/hexanes) indicated complete conversion. The reaction mixture was concentrated and purified on silica chromatography (24g, 30-100% EtOAc/hexanes followed by 100% EtOAc) to obtain **497** (1.03 g, 2.86 mmol, 91%) as a colorless liquid.^{1}H NMR (400 MHz, chloroform-d) δ 7.30-7.20 (m, 5H), 4.44 (s, 2H), 4.19 - 3.97 (m, 4H), 3.71 (t, *J* = 5.0 Hz, 2H), 3.51 (d, *J* = 6.5 Hz, 2H), 2.82 (d, *J* = 6.6 Hz, 2H), 2.65 (d, *J* = 12.7 Hz, 2H), 2.03-1.97 (m, 1H),1.27 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, chloroform-d) δ 137.9, 128.3, 127.6, 127.5, 73.2, 71.1, 62.8, 62.7, 62.7, 62.7, 62.6, 41.0, 32.3, 26.3, 24.9, 16.4; ^{31}P NMR (162 MHz, chloroform-d) δ 24.46.



497 **498**

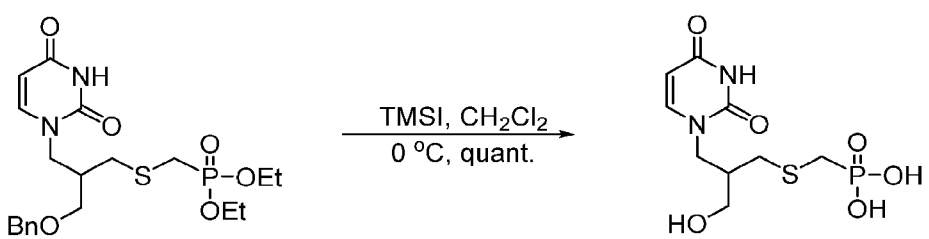
To a solution of diethyl (((3-(benzyloxy)-2-(hydroxymethyl)propyl)thio)methyl)phosphonate (1.0 g, 2.76 mmol) and 3-benzoylpyrimidine-2,4(1H,3H)-dione (1.491 g, 6.90 mmol) in DMF (20 mL) at 0°C was added triphenylphosphine (1.809 g, 6.90 mmol) followed by (E)-diisopropyl diazene-1,2-dicarboxylate (1.358 ml, 6.90 mmol) drop wise and stirred at room temperature overnight. The reaction mixture was concentrated and purified on silica chromatography eluting with isocratic solvents mixture EtOAc/CH_2Cl_2/hexanes (5:3:2) until all impurities eluted and then the solvent was changed to a linear gradient of 0-20% MeOH/CH_2Cl_2 to obtain **498** (1.16 g, 2.06 mmol, 75%) as a colorless liquid. ^{1}H NMR (300 MHz, chloroform-d) δ 7.90 (d, *J* = 9.8 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.39 - 7.30 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 1H), 5.65 (d, *J* = 8.0 Hz, 1H), 4.49 (q, *J* = 11.8 Hz, 2H), 4.18 - 4.04 (m, 5H), 3.69 (dd, *J* = 13.8, 8.8 Hz, 1H), 3.63 - 3.41 (m, 2H), 2.81 - 2.55 (m, 4H), 2.42 - 2.33 (m, 1H), 1.31 (td, *J* = 6.9, 3.2 Hz, 6H). ^{31}P NMR (162 MHz, chloroform-d) δ 23.89.

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498 **499**

To a solution of diethyl(((3-(3-benzoyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((benzyloxy) methyl)propyl)thio)methyl)phosphonate (1.153 g, 2.057 mmol) in MeOH (12 mL) was added NH_4OH (6 mL) at room temperature and then heated to 45°C for 5hours. TLC (5% MeOH/CH_2Cl_2, product Rf = 0.2) indicated complete conversion. The reaction mixture was concentrated, co-evaporated with MeOH (x2) and purified by silica chromatography eluting with linear gradient of 0-5% MeOH/CH_2Cl_2 followed by isocratic 5% MeOH/CH_2Cl_2 to get **499** (0.66 g, 1.45 mmol, 71%) as a colorless gummy liquid. ^{1}H NMR (300 MHz, chloroform-d) δ 9.45 (s, 1H), 7.37 - 7.25 (m, 5H), 7.11 (d, *J* = 7.9 Hz, 1H), 5.53 (d, *J* = 7.9 Hz, 1H), 4.45 (q, *J* = 11.8 Hz, 2H), 4.19 - 4.09 (m, 4H), 3.99 (dd, *J* = 13.7, 5.4 Hz, 1H), 3.65 (dd, *J* = 13.7, 8.7 Hz, 1H), 3.48 (ddd, *J* = 32.7, 9.8, 4.1 Hz, 2H), 2.88 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.84 - 2.59 (m, 3H), 2.31 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, chloroform-d) δ 163.9, 151.0, 145.4, 137.5, 128.5, 127.9, 127.9, 101.6, 77.4, 77.0, 76.6, 73.3, 68.2, 62.7 (t, *J* = 6.8 Hz), 49.3, 37.7, 33.1 (d, *J* = 2.9 Hz), 25.2 (d, *J* = 150.1 Hz), 16.4 (d, *J* = 6.0 Hz).



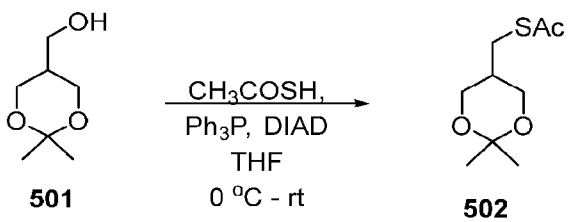
499 **500**

A solution of diethyl (((3-(benzyloxy)-2-((2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl) propyl)thio)methyl)phosphonate (0.283g, 0.620 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0°C was thoroughly flushed with argon gas and iodotrimethylsilane (0.886 mL, 6.20 mmol) was added drop wise and stirred at 0°C for 3hours. The reaction flask was covered with aluminum foil to avoid exposure to light and stored in the refrigerator overnight. The

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reaction mixture was taken out from refrigerator and allowed to warm to room temperature under argon. The reaction mixture was then quenched with anhydrous methanol (6 mL) and concentrated under vacuum. The resulting orange crude mixture was dissolved in DI water (15 mL) and neutralized with 1M TEAB (triethyl ammonium bicarbonate, ~6 mL) to pH =~8.0. The resulting mixture was extracted with ether (3x10 mL). The aqueous layer was collected, concentrated, and co-evaporated with ethanol to remove excess TEAB salts. ^{1}H NMR and ^{31}P NMR showed pure product with excess TEAB salts. The solid was redissolved in DI water and loaded onto a prewashed Dowex-H^{+} resin column and eluted with DI water and collected in 5 mL volume fractions. UV active fractions were collected and concentrated to obtain **500** in quantitative yield as a pale yellow solid. ^{1}H NMR (300 MHz, methanol-d^{4}) δ 7.60 (d, J = 7.9 Hz, 1H), 5.65 (d, J = 7.8 Hz, 1H), 4.00 - 3.72 (m, 4H), 3.71 - 3.53 (m, 2H), 2.77 (m, 4H), 2.23 - 2.19 (m, 1H). ^{31}P NMR (121 MHz, methanol-d^{4}) δ 22.75.

Example 151.

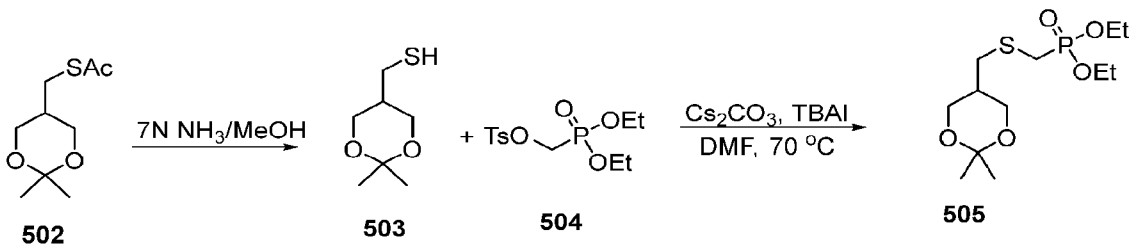


501 **502**

To a solution of triphenylphosphine (19.74 g, 75 mmol) in anhydrous THF (150 mL) was added (*E*)-diisopropyl diazene-1,2-dicarboxylate (14.82 mL, 75 mmol) at 0°C (pale yellow cake formed during addition). After 20 min, a solution of (2,2-dimethyl-1,3-dioxan-5-yl)methanol (5.0 g, 34.2 mmol) in anhydrous THF (5 mL) was added and stirred for 10 minutes followed by the addition of neat ethanethioic S-acid (5.30 ml, 75 mmol) drop wise . The reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 4 hours. TLC (40% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was filtered to remove solid precipitates, which were rinsed with EtOAc. The filtrate was concentrated and purified on silica chromatography eluting with linear gradient of 0-30% EtOAc/hexanes. The product was obtained as a mixture containing a nonpolar impurity. The product fractions were concentrated and precipitated in hexanes. The precipitated solid was removed by filtration, and the filtrate was concentrated (1H-NMR

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analysis indicated presence of minor impurity) and re subjected to silica chromatography eluting with 1:1 Hexanes/CH_2Cl_2 to obtain MD-02-171 (6.2 g, 30.3 mmol, 89%) as a liquid. Product Rf = 0.26 (10% EtOAc/hexanes), UV active, PMA stain. ^{1}H NMR (300 MHz, chloroform-d) δ 3.95 (dd, *J* = 11.9, 4.0 Hz, 2H), 3.66 (dd, *J* = 11.9, 6.5 Hz, 2H), 2.94 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.88-1.82 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H).

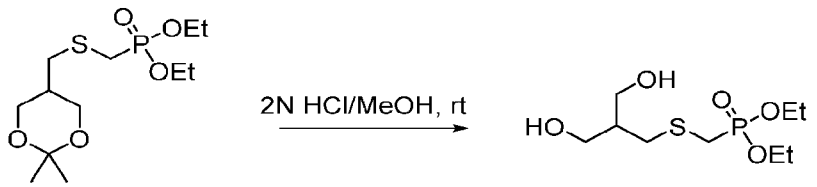


502 **503** **504** **505**

A solution of *S*-((2,2-dimethyl-1,3-dioxan-5-yl)methyl) ethanethioate (3.4 g, 16.64 mmol) in anhydorus MeOH (40 ml) was thoroughly flushed with argon and cooled to 0°C. 7N NH_3 in MeOH (20.00 mL) was added and the reaction mixture was then allowed to warm to room temperature. After 3 hours, the reaction mixture was concentrated and vacuum dried to give a crude thiol **503**. ^{1}H-NMR spectrum of crude mixture showed product and acetamide by-product. Without further purification, crude product **503** was used in the next reaction.

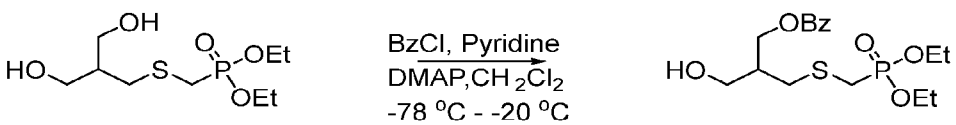
A suspension of (2,2-dimethyl-1,3-dioxan-5-yl)methanethiol (2.7g, 16.64 mmol), cesium carbonate (5.96 g, 18.31 mmol), (diethoxyphosphoryl)methyl 4-methylbenzenesulfonate (5.90 g, 18.31 mmol), and tetrabutylammonium iodide (15.37 g, 41.6 mmol) in anhydrous DMF (65 mL) was purged with argon and heated at 70°C overnight. The reaction mixture was then allowed to cool to room temperature and concentrated to a gummy solid. The solid was resuspended in EtOAC and filtered to remove solid precipitates. The filtrate was concentrated and purified on silica chromatography eluting with 40-100% EtOAc/hexanes to obtain **505** (5.3 g, 16.97 mmol, quantitative yield) as colorless oil. ^{1}H NMR (300 MHz, chloroform-d) δ 4.25 - 4.07 (m, 4H), 3.99 (dd, *J* = 11.9, 4.2 Hz, 2H), 3.68 (dd, *J* = 11.9, 6.7 Hz, 2H), 2.78 (d, *J* = 7.3 Hz, 2H), 2.68 (d, *J* = 13.6 Hz, 2H), 1.93 - 1.86 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H). ^{31}P NMR (121 MHz, chloroform-d) δ 24.04.

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505 **506**

To a solution of diethyl ((((2,2-dimethyl-1,3-dioxan-5-yl)methyl)thio)methyl)phosphonate (5.8 g, 18.57 mmol) in methanol (70 mL) was added 2 M HCl (7.00 mL) at room temperature and stirred for 3hours. TLC (5% MeOH/CH2Cl2) indicated complete conversion as visualized by $KMnO_4$ stain. The solvents were evaporated and the residue was purified on silica chromatography eluting woth 0-10% MeOH/DCM. The product eluted in 8-10% solvent gradient to obtain **506** (3.6 g,13.46 mmol, 72%) as a colorless liquid . ^{1}H NMR (399 MHz, chloroform-d) δ 4.24 - 4.05 (m, 4H), 3.83 (d, J = 4.1 Hz, 4H), 3.44 (brs, OH), 2.96 (d, J = 7.2 Hz, 2H), 2.69 (d, J = 12.6 Hz, 2H), 1.68 (m, 2H), 1.33 (t, J = 7.1 Hz, 6H). ^{31}P NMR (162 MHz, chloroform-d) δ 24.61.

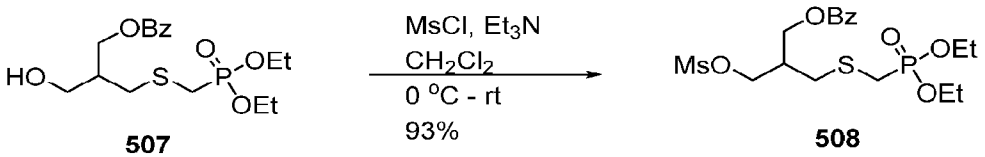


506 **507**

To a solution of diethyl (((3-hydroxy-2-(hydroxymethyl)propyl)thio)methyl)phosphonate **506** (1.256 g, 4.61 mmol) in anhydrous dichloromethane (40 mL) was added pyridine (0.372 mL, 4.61 mmol) and N,N-dimethylpyridin-4-amine (0.056 g, 0.461 mmol) followed by cooling the reaction vessel to -78°C. Benzoyl chloride (0.536 mL, 4.61 mmol) was then added drop wise and the allowed mixture was gradually allowed to warm to -15°C (ice+salt mixture) followed by stirring at this temperature for 5hours. The reaction mixture was quenched with DI water and extracted with dicholomethane. The organic phase was rewashed with 1N HCl (x2), followed by $NaHCO_3$. The organic layer was concentrated and purified on silica chromatography eluting linear gradient of 30-100% EtOAc/hexanes to obtain **507** (0.83 g, 2.12 mmol, 48%) as colorless liquid. ^{1}H NMR (300 MHz, chloroform-d) δ 8.03 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.40 (d, J = 6.2 Hz, 2H), 4.27 - 4.05 (m, 4H), 3.92 -

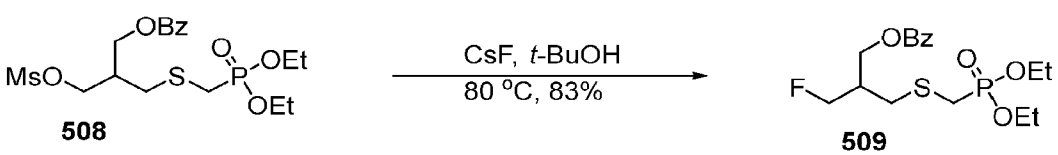
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3.68 (m, 2H), 3.56 (s, OH), 2.97 (d, J = 6.7 Hz, 2H), 2.72 (d, J = 12.3 Hz, 2H), 2.36 - 2.09 (m, 1H), 1.34 (t, J = 7.1 Hz, 6H). ^{31}P NMR (121 MHz, chloroform-d) δ 24.33.



507 **508**

To a solution of 3-(((diethoxyphosphoryl)methyl)thio)-2-(hydroxymethyl)propyl benzoate (0.2 g, 0.531 mmol) in anhydrous (5 mL) at 0°C was added triethylamine (0.089 mL, 0.638 mmol) followed by methanesulfonyl chloride (0.049 mL, 0.638 mmol). The reaction mxture was allowed to warm to room temperature and stir overnight (Note: product and starting material has close Rf, with product being slightly non-polar). The reaction mixture was concentrated and purified on silica chromatography eluting with 40-100% EtOAc/hexanes to obtain **508** (0.225 g, 0.495 mmol, 93%) as colorless liquid.^{1}H NMR (300 MHz, chloroform-d) δ 8.03 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.53 - 4.38 (m, 4H), 4.19 - 4.10 (m, 4H), 3.04 (s, 3H), 2.94 (d, J = 7.0 Hz, 2H), 2.74 (d, J = 13.0 Hz, 2H), 2.58 - 2.52 (m, 1H), 1.33 (t, J = 7.0 Hz, 6H). 31P NMR (121 MHz, chloroform-d) δ 23.62.

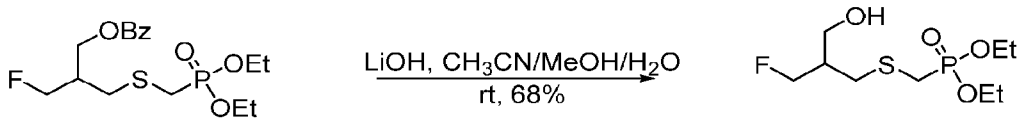


508 **509**

To a suspension of 3-(((diethoxyphosphoryl)methyl)thio)-2-(((methylsulfonyl)oxy)methyl)propyl benzoate (2.1 g, 4.62 mmol) and cesium fluoride (2.106 g, 13.86 mmol) was added anhydrous t-BuOH (22 mL) under argon. The reaction mixture was heated at 80°C overnight. TLC analysis (60% EtOAc/hexanes) indicated complete conversion. The reaction mixture was concentrated and purified on silica chromatography (dry loading) eluting with 30-100% EtOAc/hexanes to obtain **509** (1.450 g, 3.83 mmol, 83%) as colorless liquid. . ^{1}H NMR (300 MHz, chloroform-d) δ 8.07 - 7.98 (m, 2H), 7.62 - 7.54 (m, 1H), 7.50 - 7.36 (m, 2H), 4.72 (t, J = 4.4 Hz, 1H), 4.57 (t, J = 4.5 Hz, 1H), 4.52 - 4.35 (m, 2H), 4.26 - 4.03 (m, 4H), 2.93 (dt, J = 6.9, 1.1 Hz, 2H), 2.75 (d, J = 13.1 Hz, 2H), 2.49 - 2.37 (m, 1H), 1.34 (t,

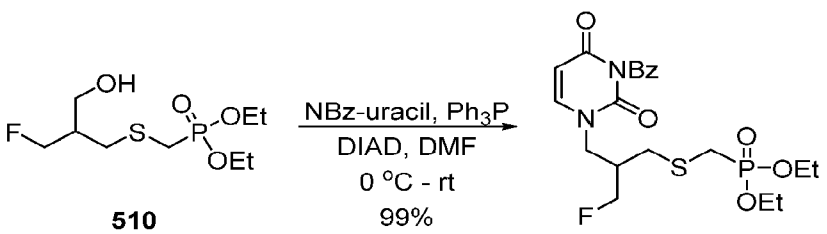
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J = 7.0 Hz, 6H). ^{19}F NMR (282 MHz, chloroform-d) δ 0.47 (td, J = 47.0, 23.7 Hz). ^{31}P NMR (121 MHz, chloroform-d) δ 23.85 .



509 **510**

A solution of 3-(((diethoxyphosphoryl)methyl)thio)-2-(fluoromethyl)propyl benzoate (1.450 g, 3.83 mmol) in anhydrous acetonitrile (10 mL) was treated with lithium hydroxide (0.138 g, 5.75 mmol) dissolved in 4 mL of water and 10 mL of MeOH. The reaction mixture was stirred at room temperature for 1 hour and then neutralized with acetic acid. The solvent was removed under vacuum and purified by silica chromatography (dry loading) eluting with 0-10% MeOH/CH_2Cl_2 to obtain **510** (0.72g, 2.62 mmol, 68%) as colorless liquid. ^{1}H NMR (300 MHz, chloroform-d) δ 4.67 - 4.51 (m, 1H), 4.50 - 4.35 (m, 1H), 4.25 - 4.09 (m, 4H), 3.84 (ddd, J = 11.4, 4.9, 1.6 Hz, 1H), 3.73 (dd, J = 11.4, 5.2 Hz, 1H), 2.89 (d, J = 6.6 Hz, 2H), 2.71 (d, J = 12.4 Hz, 2H), 2.22 - 1.94 (m, 1H), 1.34 (t, J = 7.1 Hz, 6H). ^{19}F NMR (282 MHz, Chloroform-d) δ 2.55 (td, J = 47.3, 46.3, 21.4 Hz). ^{31}P NMR (121 MHz, chloroform-d) δ 24.35.

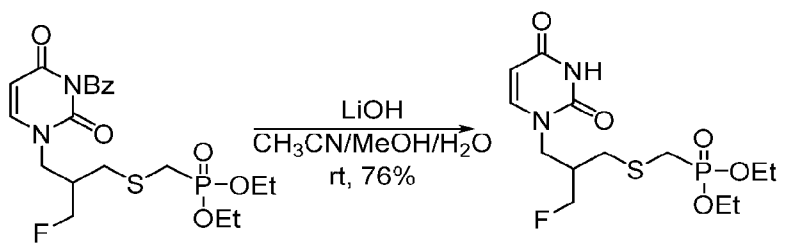


510 **511**

To a solution of diethyl (((3-fluoro-2-(hydroxymethyl)propyl)thio)methyl)phosphonate (0.650 g, 2.370 mmol) and 3-benzoylpyrimidine-2,4(1H,3H)-dione (1.281 g, 5.92 mmol) in DMF at 0°C was added triphenylphosphine (1.554 g, 5.92 mmol) followed by (*E*)-diisopropyl diazene-1,2-dicarboxylate (1.166 ml, 5.92 mmol) drop wise. The reaction mixture was stirred at room temperature overnight. TLC (EtOAc/CH_2Cl_2/hexanes (5:3:2) indicated product spot in the

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base line. The reaction mixture was concentrated, co-evaporated with toluene (2x5 mL) and purified by silica chromatography eluting with isocratic EtOAc/CH_2Cl_2/hexanes (5:3:2) until all the unreacted NBz- uracil has eluted, and then the solvent system was changed to a linear gradient of 0-20% MeOH:CH_2Cl_2 to elute the product. ^{1}H-NMR indicated product and trace amount of DMF solvent. The product was redissolved in DCM and washed with brine solution (x3). The organic phase was concentrated and vacuum dried to get **511** (1.11 g, 2.34 mmol, 99%) as a pale brownish yellow gummy liquid. ^{1}H NMR (600 MHz, chloroform-d) δ 7.91 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 4-61 - 4.43 (m, 2H), 4.17 - 4.09 (m, 4H), 4.07 (dd, J = 14.2, 5.5 Hz, 1H), 3.80 - 3.71 (m, 1H), 2.91 (dd, J = 13.7, 6.9 Hz, 1H), 2.78 - 2.62 (m, 3H), 2.48 - 2.43 (m, 1H), 1.30 (q, J = 6.8 Hz, 6H). ^{13}C NMR (151 MHz, chloroform-d) δ 168.6, 162.3, 150.0, 144.8 (d, J = 8.6 Hz), 135.1, 131.3, 130.4, 129.1, 102.2 (d, J = 6.6 Hz), 82.6 (d, J = 170.2 Hz), 77.2, 77.0, 76.8, 63.2 - 62.1 (m), 49.3, 38.3 (d, J = 18.7 Hz), 31.9, 25.1(d, J = 150.4 Hz), 16.4. ^{19}F NMR (282 MHz, chloroform-d) δ 0.23 (td, J = 48.3, 16.7 Hz). ^{31}P NMR (121 MHz, chloroform-d) δ 23.55.

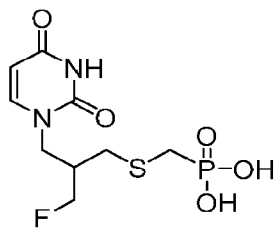


511 **512**

A solution of diethyl (((3-(3-benzoyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(fluoromethyl) propyl)thio)methyl)phosphonate (1.0 g, 2.117 mmol) in anhydrous acetonitrile (5 mL) was treated with a solution of lithium hydroxide (0.076 g, 3.17 mmol) in 2 mL of water and 5 mL of MeOH. The reaction was stirred at room temperature overnight. TLC (5% MeOH/CH_2Cl_2) indicated complete conversion. The reaction mixture was then neutralized with acetic acid (5 mL). The solvents were removed under vacuum and co-evaporated with toluene to remove trace amount of acetic acid. The product was purified by silica chromatography (dry loading) eluting with 0-10% MeOH/CH_2Cl_2 to obtain **512** (0.59 g, 1.602 mmol, 76%) as a gummy liquid. ^{1}H NMR (300 MHz, chloroform-d) δ 9.90 (s, 1H),

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7.28 (d, J = 7.9 Hz, 1H), 5.69 (d, J = 8.8 Hz, 1H), 4.65 (dd, J = 9.9, 3.6 Hz, 0.5H), 4.56 - 4.45 (m, 1H), 4.35 (dd, J = 9.9, 3.7 Hz, 0.5H), 4.14 (p, J = 7.1 Hz, 4H), 4.00 (dd, J = 14.0, 5.7 Hz, 1H), 3.69 (dd, J = 13.9, 8.6 Hz, 1H), 2.96 - 2.61 (m, 4H), 2.54 - 2.29 (m, 1H), 1.31 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 163.9, 151.1, 145.1, 102.3, 82.3 (d, J = 170.0 Hz), 77.3, 77.0, 76.7, 62.7 (t, J = 6.1 Hz), 48.7 (d, J = 4.7 Hz), 38.4 (d, J = 18.7 Hz), 31.9 (d, J = 4.3 Hz), 25.2 (d, J = 150.6 Hz), 16.4 (d, J = 5.9 Hz). ^{19}F NMR (282 MHz, chloroform-d) δ -0.59 (td, J = 47.2, 28.6 Hz). ^{31}P NMR (121 MHz, chloroform-d) δ 23.77.



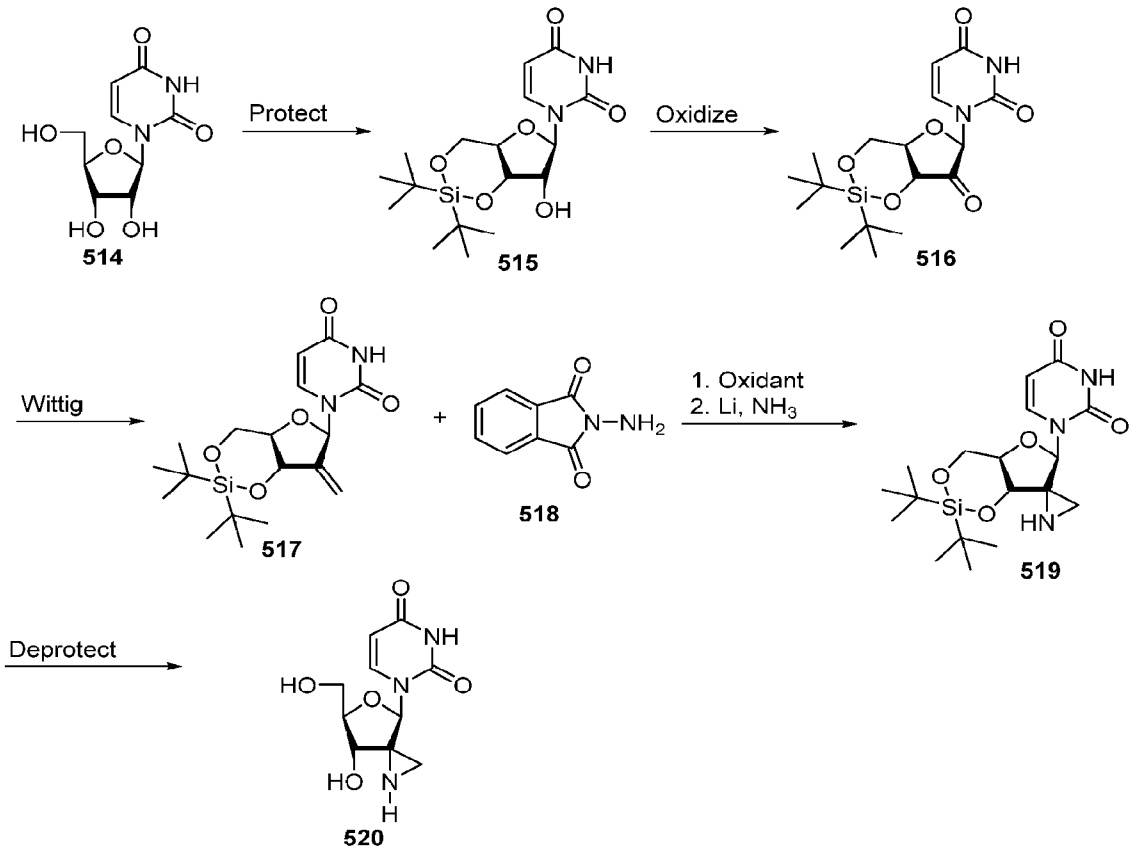
513

To a solution of diethyl (((3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(fluoromethyl)propyl)thio)methyl)phosphonate (0.577 g, 1.566 mmol) in acetonitrile (15 ml) was added bromotrimethylsilane (2.067 ml, 15.66 mmol) drop wise at room temperature. The reaction mixture was allowed to stir overnight. The reaction was quenched with anhydrous methanol (4 mL), concentrated, co-evaporated with acetonitrile, and vaccum dried. The resulting bright orange gummy liquid was dissolved in DI water (10 mL) and neutralized with 1M TEAB (8 mL). The resulting aqueous solution was extracted with ether (x3). The aqueous layer was collected, concentrated, and co-evaporated with methanol to obtain a solid. ^{1}H-NMR showed product+excess triethylammonium salt. The solid was subjected to deionization by passing through DOWEX-H+ (prewashed thoroughly with methanol followed by DI water) column eluting with DI water. The fractions containing UV absorption on TLC were pooled and lyophilized to obtain a light brown solid. The product was further purified using amberchrom resin eluting with DI water to obtain **513** as a white fluffy solid.

Example 152.

Synthesis of Aziridine Analog.

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Example 153

Crystallization Methods: various methods for crystallizing the nucleoside or nucleotide compounds or the second antiviral compounds are provided below.

Method 1: The compounds described herein are crystallized by dissolving in a suitable solvent or solvent system to prepare a nearly saturated solution. The container is then covered but not too tightly to allow slow evaporation of the solvent. The method is repeated with more concentrated solutions if needed to promote crystal formation.

Method 2: The compounds described herein are crystallized by mixing in a solvent or solvent system in which they are moderately soluble. The mixture is then heated to or a few degrees below the solvent's boiling point to provide a saturated solution. The container is then covered and allowed to cool slowly to allow slow evaporation of the solvent. The method is repeated using more compound to obtain a more concentrated solution if needed to promote crystal formation.

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Method 3: The compounds described herein are crystallized by dissolving in a solvent to form a saturated or nearly saturated solution. A suitable precipitant (i.e., a solvent the compound is insoluble in), is added slowly to the saturated solution and layered on the solution. The precipitant should be less dense and miscible with the solvent. The method is repeated with more concentrated solutions if needed to promote crystal formation.

Example 154.

Assay Protocols

(1) Screening Assays for EV68, EV71, COXV, PV, HRV, 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 may 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)

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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 may be prepared and the plate may 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 155.

(2) 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

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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% CO2 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% CO2 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 room temperature. 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 (EC50, virus-inhibitory) concentrations are then calculated by linear regression analysis.

Example 156.

(3) 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

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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 room temperature. 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.

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Example 157.

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 □g/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 x 10^3 (5 x 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 □L. The plates were incubated at 37°C/5%$C0_2$ 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 room temperature 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 □g/mL streptomycin) such that the amount of virus added to each well in a volume of 100 □L 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% $C0_2$ 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

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in the dark at -20°C. XTT/PMS stock was prepared immediately before use by adding 40 □L 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 158.

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 □g/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 □L. The plates were incubated at 37°C/5% $C0_2$ 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 room temperature 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 □g/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 □L 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 159.

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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 □g/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 □L. The plates were incubated at 37°C/5% $C0_2$ 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 room temperature 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 □g/mL streptomycin, 1 mM sodium pyruvate, 0.1 mM NEAA, and 1 □g/ml TPCK-treated trypsin) such that the amount of virus added to each well in a volume of 100 □L 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 160.

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, 2mM glutamine, penicillin (100 □U/mL)/streptomycin (100 □g/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

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□g/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% $C0_2$ 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%$C0_2$ 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 room temperature, the britelite plus reagent was added to the 96 well plates at 100 □L per well. The plates were sealed with adhesive film and incubated at room temperature 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 1450Microbeta 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 161.

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 10^4cells per well in tissue culture medium and added to flat bottom microtiter plates in a volume of 100 □L. The plates were incubated at 37°C/5% $C0_2$ overnight to allow for cell adherence.

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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 room temperature 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% $C0_2$ 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 1mg/mL in RPMI1640. 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 □L 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 3 7°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 162.

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

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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 □Ci of [□-^{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 [□-^{32}P] GTP was measured using a liquid scintillation counter (Micro beta).

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 Micro Beta 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 163.

HCV Polymerase Inhibition Assay:

Activity of compounds for inhibition of HCV polymerase was evaluated using methods previously described (Lam *eta!.* 2010. Antimicrobial Agents and Chemotherapy 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 NS5B□22 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

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(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 Micro beta cassette along with scintillation fluid and the CPM in each reaction was counted on a Micro beta 1450. CPM data were imported into a custom Excel spreadsheet for determination of compound IC_{50}s.

Example 164.

NS5B RNA-dependent RNA polymerase reaction conditions

Compounds were assayed for inhibition of NS5B-□21 from HCV GT-1b Con-1. Reactions included purified recombinant enzyme, 1 u/µL negative-strand HCV IRES RNA template, and 1µM 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 165.

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),

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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 uL volume per sample: 20mM 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 uCi [^{32}P]-alpha-dGTP (800 Ci/mmol), 20 ug 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 (Microbeta).

Example 166.

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 50ml conical centrifuge tube. These tubes were centrifuged for 30 min at 600g. 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 ug/mL PHA-P, 100 U/mL penicillin and 100 ug/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 uL/well. Then, 100 uL of 2X concentrations of compound-containing medium was transferred to the 96-well plate containing cells in 50 uL of the medium. AZT was employed as an internal assay standard.

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Following addition of test compound to the wells, 50 uL 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 uL 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 uL of 1 mol/L EGTA, 125 uL of dH_2O, 125 uL of 20% Triton X-100, 50 uL of 1 mol/L Tris (pH 7.4), 50 uL of 1 mol/L DTT, and 40 uL of 1 mol/L $MgCl_2$. For each reaction, 1 uL of TTP, 4 uL of dH_2O, 2.5 uL of rAdT, and 2.5 uL of reaction buffer were mixed. Ten microliters of this reaction mixture was placed in a round bottom microtiter plate and 15 uL 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 uL 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 167.

HBV :

HepG2.2.15 cells (100µL) 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

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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 (40μg/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 □L) 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'), HBV-AD38-qR1 (5'-AGT CCA AGA GTY CTC TTA TRY AAG ACC TT-3'), and HBV-AD38-qP1 (5'-FAM CCG TGT GCA /ZEN/CTT CGC TTC ACC TCT GC-3'BHQ1) at a final concentration of 0.2 □M for each primer in a total reaction volume of 15 □L. 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 □L 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 168.

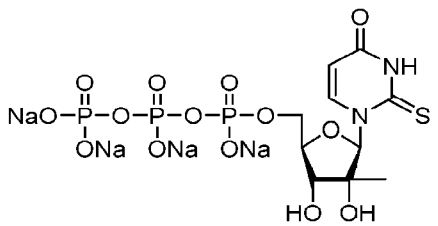
Dengue RNA-dependent RNA polymerase reaction conditions

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

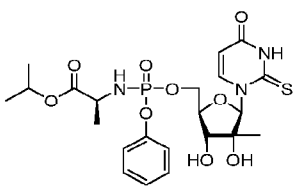
Example 169.

Human DNA polymerase inhibition data:

Structure and ID	Human DNA pol α (IC50 uM)	Human DNA pol β (IC50 uM)	Human DNA pol γ (IC50 uM)
 ENUC-01992-1	> 1000	588.2	> 1000

Example 170.

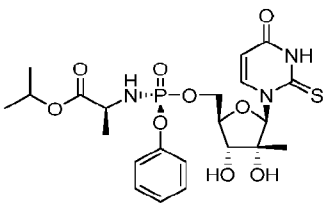
Inhibition of DNA Virus Replication

Structure and I.D.	HBV (EC50 uM)	HepG2 Cells (CC50 uM)	Adenovirus (EC50 uM)	Huh-7 Cells (CC50 uM)	HSV-1 (EC50 uM)	Huh-7 Cells (CC50 uM)
 ENUC-01911	> 100	> 100	> 100	> 100	> 100	> 100
	HIV (EC50 uM)	PBM Cells (CC50 uM)	HCMV (EC50 uM)	MRC-5 Cells (CC50 uM)	VZV (EC50 uM)	MRC-5 Cells (CC50 uM)
	> 100	> 100	> 100	> 100	> 100	> 100

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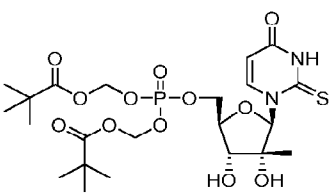
Example 171.

Enterovirus results for EIDD-2023:

Compound ID	Structure	Virus	Strain	Cell Line	EC_{50} (μM)	CC_{50} (μM)
EIDD-2023		EV68	US/KY/14-18953	RD	5.5	> 100
		COXV B3	HA 201933	Huh7	5.9	72
		COXV A18	G13	Huh7	2.64	> 100
		COXV A7	WP Parker	Huh7	4.34	> 100
		COXV B1	Conn5	Huh7	27.4	> 100
		COXV B2	Ohio 1	Huh7	51.3	> 100
		COXV B3	Nancy	Huh7	85.6	> 100
		COXV B4	JVB	Huh7	40.6	> 100
		EV70	J670/71	Huh7	3.28	> 100
		EV71	H	MRC-5	1.93	> 100
		PV	Mahoney	Huh7	5.9	> 100
		HRV-B	5560	Huh7	2.79	> 100

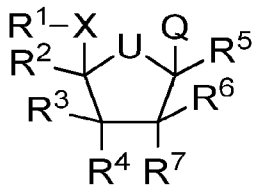
Example 172.

Enterovirus results for EIDD-2523:

Compound ID	Structure	Virus	Strain	Cell Line	EC_{50} (μM)	CC_{50} (μM)
EIDD-2523		EV68	US/KY/14-18953	RD	0.38	91
		EV71	Tainan/4643/98	RD	5.3	50
		COXV B3	HA 201933	Huh7	9.3	46
		COXV A18	G13	Huh7	2.69	32
		COXV A7	WP Parker	Huh7	3.37	30
		COXV B1	Conn5	Huh7	> 31	31
		COXV B2	Ohio 1	Huh7	2.65	34
		COXV B3	Nancy	Huh7	0.38	32
		COXV B4	JVB	Huh7	> 16	16
		EV70	J670/71	Huh7	0.07	31
		EV71	H	MRC-5	1.71	32
		HRV	26	HeLa	0.43	> 100
		HRV	1059	HeLa	0.72	> 100

CLAIMS

1. A composition comprising a compound (β-D or β-L) of the following formula:



Formula Ia

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

R^1 is OH, monophosphate, diphosphate, or triphosphate;

R^2, R^3, R^4, R^6 and R^7 are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

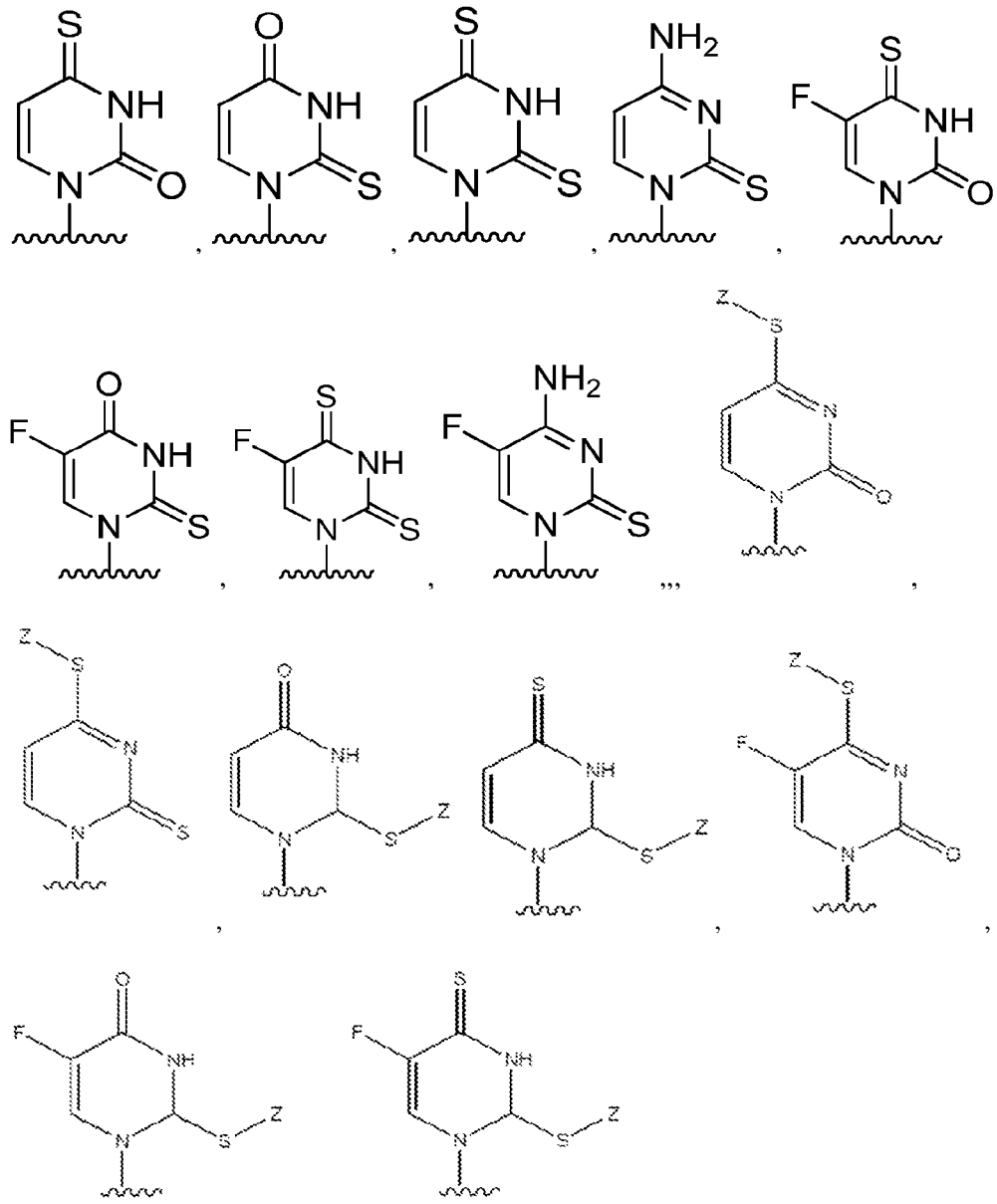
R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is H or D; and

Q is one of the following bases:

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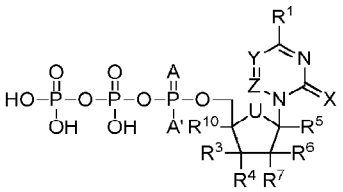
or

wherein Z is OH, alkoxide, methoxide, ethoxide, halogen, thiol, alkylthio, alkyl, lipid, or geranyl, and

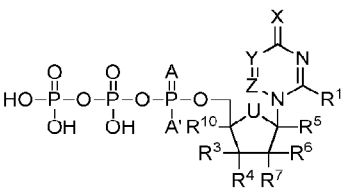
a second antiviral agent.

2. A composition comprising a compound (β-D or β-L) of one of the following formulae:

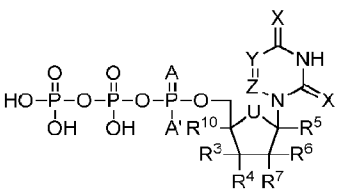
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Formula Ic



Formula Id



Formula Ie

or a pharmaceutically acceptable salt thereof, wherein

A is O or S;

A' is OH or $BH_3^-M^+$;

R^5 is H or D;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^1 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ic and Id, either X is S or R^1 is SR^8, or both X is S and R^1 is SR^8;

wherein in Formula Ie, at least one X is S;

Y is CH, N, or CR^2;

Z is CH, N, or CR^2;

R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9;

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^9; and

R^8 is methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^9;

each R^9 is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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R^2 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^9, and

a second antiviral agent.

3. The composition of claim 2, wherein the compound or a pharmaceutically acceptable salt thereof is defined as follow,

A is O;

A' is OH;

U is O;

R^5 is H;

Y and Z are CH; and

R^3, R^4, R^6, R^7 and R^{10} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

4. The composition of claim 2 or 3, wherein the compound is represented by Formula Ie, or a pharmaceutically acceptable salt thereof, wherein

one X is S and the other X is O;

R^3 is H;

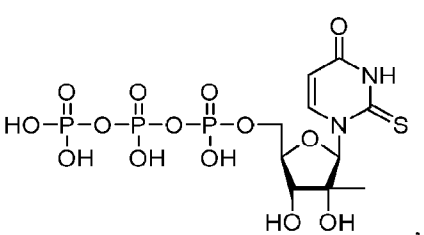
R^4 is OH;

R^6 is CH_3;

R^7 is OH; and

R^{10} is H.

5. A composition comprising a compound having the following structure:

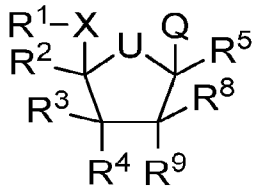


,

or a pharmaceutically acceptable salt thereof, and a second antiviral agent.

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6. A composition comprising a compound (β-D or β-L) of the following formula:



Formula If

or a pharmaceutically acceptable salt thereof, wherein

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

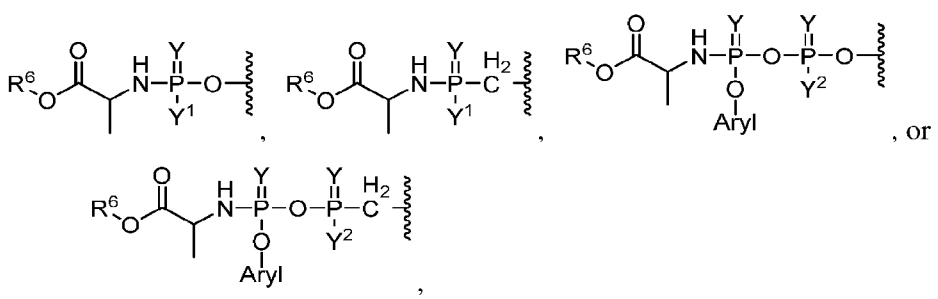
R^5 is H or D;

R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, $C_{1\text{-}22}$ alkyl, $C_{2\text{-}22}$ alkenyl, $C_{2\text{-}22}$ alkynyl, allyl, ethynyl, vinyl, $C_{1\text{-}22}$ alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or $C_{1\text{-}22}$ alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^6 and R^7 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

R^1 is one of the formula:



Y is O or S;

Y^1 is OAryl or $BH_3^-M^+$;

Y^2 is OH or $BH_3^-M^+$;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

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Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, cycloalkyl;

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10} and

a second antiviral agent.

7. The composition of claim 6, wherein

U is O;

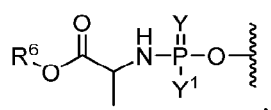
X is CH_2;

Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine;

R^5 is H; and

R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

8. The composition of claim 6 or 7, wherein

R^1 is ,

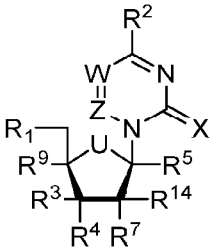
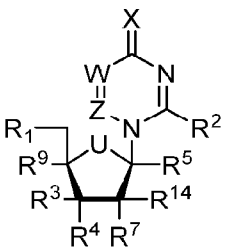
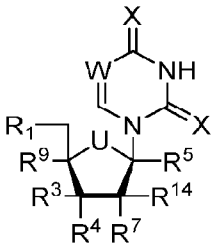
wherein Y is O,

Y^1 is phenoxy, and

R^6 is *iso*-propyl.

9. A composition comprising a compound of one of the following formulae:

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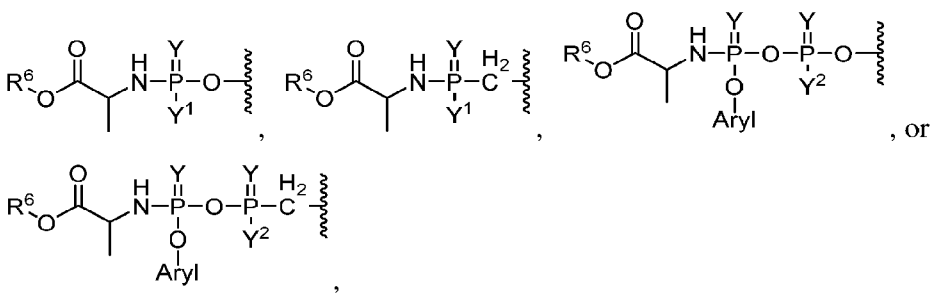
Formula Ig **Formula Ih** **Formula Ii**

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

R^5 is H or D;

R^1 is one of the formula:



Y is O or S;

Y^1 is OAryl or $BH_3^-M^+$

Y^2 is OH or $BH_3^-M^+$

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ig and Ih, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Ii, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

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R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

Aryl is phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-chlorophenyl, 4-bromophenyl;

R^8 is deutero, methyl, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^6 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^6 is optionally substituted with one or more, the same or different, R^{10}, and

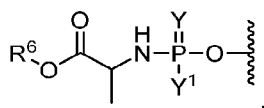
a second antiviral agent.

10. The composition of claim 9, wherein

U is O;

W and Z are CH;

R^5 is H;

R^1 is , wherein Y is O and Y^1 is phenoxy; and

R^6 is alkyl.

11. The compositionof claim 9 or 10,

wherein R^3, R^4, R^7, R^9 and R^{14} are each independently selected from H, CH_3, CD_3, CF_3, CF_2H, CFH_2, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F or I.

12. The composition of claim 11 having a structure represented by formula Ia or a pharmaceutically acceptable salt thereof,

wherein one X is O and the other X is S.

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13. The composition of claim 12, wherein R^6 is *iso*-propyl.

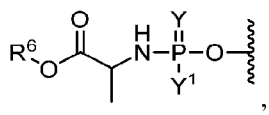
14. The composition of claim 9 or 10, or a pharmaceutically acceptable salt thereof, wherein R^5 is H,

R^3 is H,

R^4 is hydroxyl,

R^7 is hyroxyl,

R^{14} is methyl,

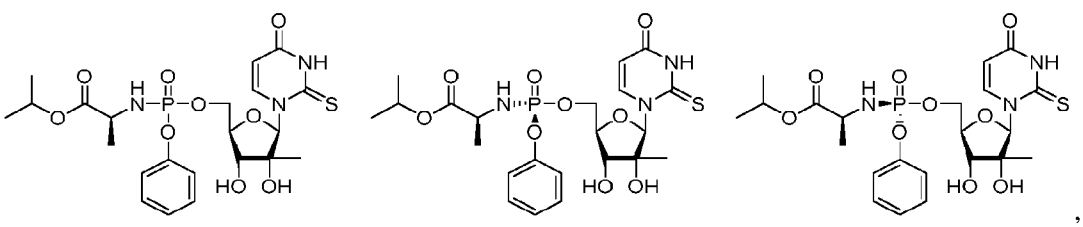
R^1 is ,

Y is O,

Y^1 is phenoxy, and

R^6 is *iso*-propyl.

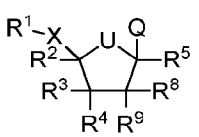
15. A composition comprising a compound having one of the following structures:



, and

a second antiviral agent.

16. A composition comprising a compound (β-D or β-L) of the following formula:



Formula Io

or a pharmaceutically acceptable salt thereof wherein,

U is NH, CH_2, CHF, CF_2, C=CH_2, C=CHF, C=CF_2, O or S;

X is O, CH_2, CHF, CF_2, or CD_2;

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R^5 is H or D;

Q is a heterocyclyl comprising two or more nitrogen heteroatoms substituted with at least one thione, thiol or thioether, wherein Q is optionally substituted with one or more, the same or different alkyl, halogen, or cycloalkyl;

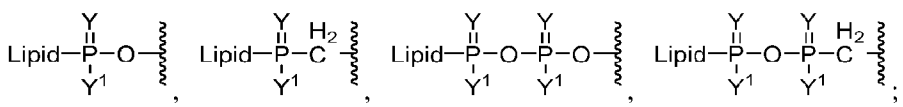
R^2, R^3, R^4, R^8 and R^9 are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^8 and R^9 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^1 is one of the formula:



Y is O or S;

Y^1 is OH or $BH_3^-M^+$; and

lipid is as described herein and

a second antiviral agent.

17. The composition of claim 16, wherein

U is O;

Q is a pyrimidine with at least one thione, thiol or thioether at the 2 and/or 4-position of said pyrimidine; and

R^5 is H.

18. The composition of claim 16 or 17, wherein the lipid is hexadecyloxypropyl.

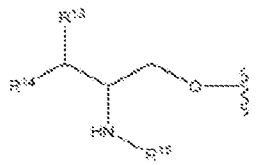
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19. The composition of claim 16 or 17, wherein the lipid is 2-aminohexadecyloxypropyl.

20. The composition of claim 16 or 17, wherein the lipid is 2-aminoarachidyl.

21. The composition of claim 16 or 17, wherein the lipid is chosen from the group consisting of lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, and lignoceryl.

22. The composition of claim 16 or 17, wherein the lipid is a sphingolipid of the formula:

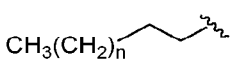
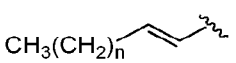
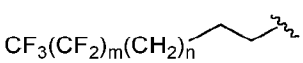
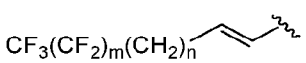


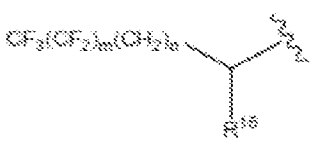
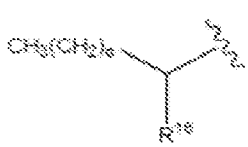
wherein,

R^{13} is hydrogen, fluoro, OR^{17}, $OC(=O)R^{17}$, $OC(=O)OR^{17}$, or $OC(=O)NHR^{17}$;

R^{15} is hydrogen, alkyl, $C(=O)R^{17}$, $C(=O)OR^{17}$, or $C(=O)NHR^{17}$;

R^{14} 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:

, , , ,

, and ;

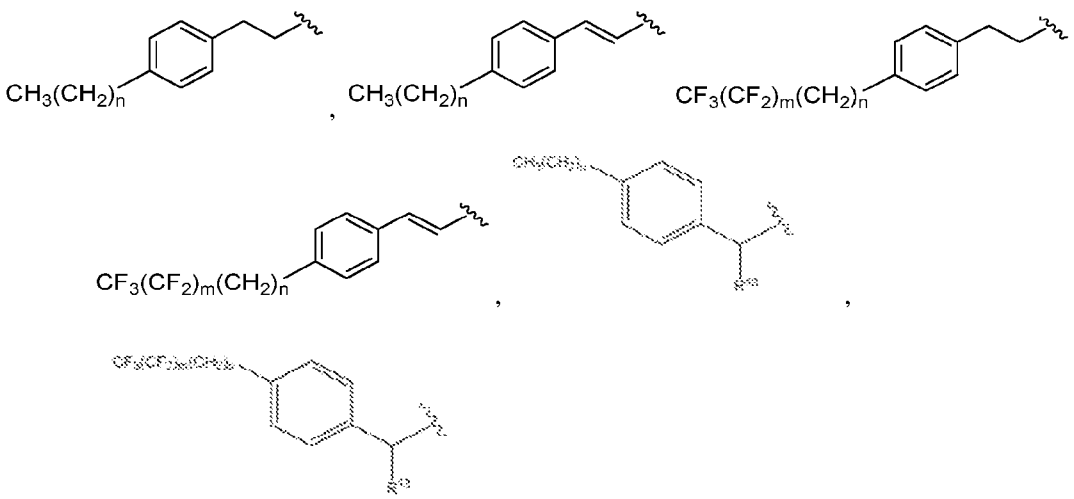
n is 8 to 14 or ≤ to 8 to ≤ 14;

o is 9 to 15 or ≤ 9 to ≤ 15;

the total or m and n is 8 to 14 or ≤ 8 to ≤ 14;

the total of m and o is 9 to 15 or ≤ 9 to ≤ 15; or

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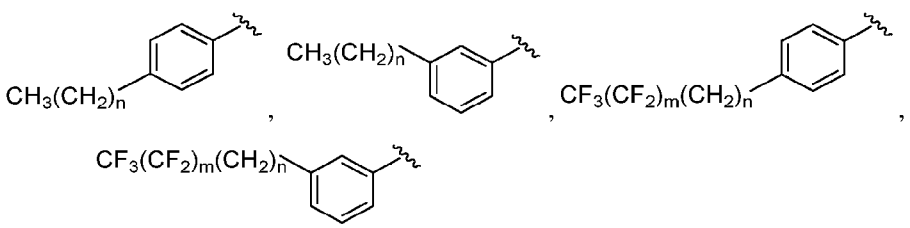


n is 4 to 10 or ≤ 4 to ≤ 10;

o is 5 to 11 or ≤ 5 to ≤ 11;

the total of m and n is 4 to 10 or ≤ 4 to ≤ 10;

and the total of m and o is 5 to 11 or ≤ 5 to ≤ 11; or



n is 6 to 12 or n is ≤ 6 to ≤ 12;

the total of m and n is 6 to 12 or n is ≤ 6 to ≤ 12;

R^{17} is hydrogen, a branched or straight chain C_{1-12} alkyl, C_{13-22} alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{11}; and

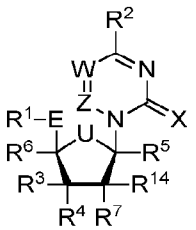
R^{11} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl,

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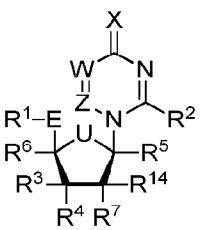
ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

23. The composition of claim 22, wherein the sphingolipid is optionally substituted a sphingosine, ceramide, or sphingomyelin, or 2-aminoalkyl optionally substituted with one or more substituents.

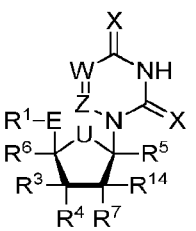
24. A composition cocmprising a compound of one of the following formulae:



Formala Ip



Formula Iq



Formula Ir

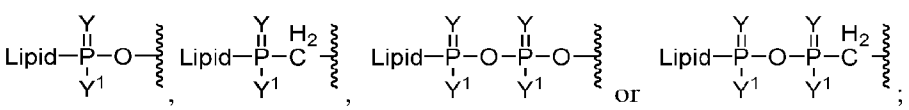
or a pharmaceutically acceptable salt thereof, wherein

R^5 is H or D;

U is NH, CH_2, CHF, CF_2, $C{=}CH_2$, C=CHF, $C{=}CF_2$, O or S;

E is CH_2 or CD_2;

R^1 is one of the formula:



Y is O or S;

Y^1 is OH or BH_3-M^+;

Lipid is as described herein;

each X is independently O, S, NH, NR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

R^2 is OH, SH, NH_2, OR^8, SR^8, NHR^8, NHOH, NR^8OH, $NHOR^8$, or NR^8OR^8;

wherein in Formula Ip and Iq, one of X is S or R^2 is SR^8, or both X is S and R^2 is SR^8;

wherein in Formula Ir, at least one X is S;

W is CH, N, or CR^8;

Z is CH, N, or CR^8;

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R^8 is deutero, methyl, trifluoromethyl, fluoro, iodo, alkenyl, alkynyl, vinyl, allyl, halogen, halogentated alkyl, hydroxyl alkyl, acyl, lipid, geranyl, C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3, R^4, R^6, R^7 and R^{14} are each independently selected from H, C_{1-22} alkyl, C_{2-22} alkenyl, C_{2-22} alkynyl, allyl, ethynyl, vinyl, C_{1-22} alkoxy, OH, SH, NH_2, N_3, CHO, CN, Cl, Br, F, I, or C_{1-22} alkyl optionally substituted with one or more, the same or different, R^{10};

R^3 and R^4 with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10};

R^7 and R^{14} with the carbon atom they are attached to can form a spirocycle containing carbon, oxygen, sulfur, or nitrogen and be optionally substituted with one or more, the same or different, R^{10}; and

each R^{10} is independently selected from alkyl, deutero, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, and

a second antiviral agent.

25. The composition of claim 24, wherein

E is CH_2;

U is O; and

Y and Z are CH.

26. The composition of claim 24 or 25, wherein the lipid is hexadecyloxypropyl.

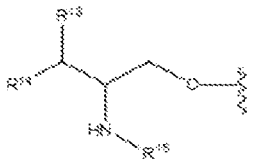
27. The composition of claim 24 or 25, wherein the lipid is 2-aminohexadecyloxypropyl.

28. The composition of claim 24 or 25, wherein the lipid is 2-aminoarachidyl.

29. The composition of claim 24 or 25, wherein the lipid is chosen from the group consisting of lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, and lignoceryl.

30. The composition of claim 24 or 25, wherein the lipid is a sphingolipid of the formula:

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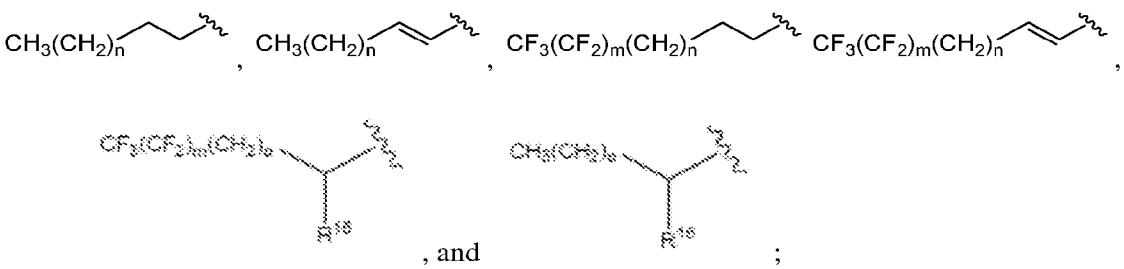


wherein,

R^{13} is hydrogen, fluoro, OR^{17}, $OC(=O)R^{17}$, $OC(=O)OR^{17}$, or $OC(=O)NHR^{17}$;

R^{15} is hydrogen, alkyl, $C(=O)R^{17}$, $C(=O)OR^{17}$, or $C(=O)NHR^{17}$;

R^{14} 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:



, and ;

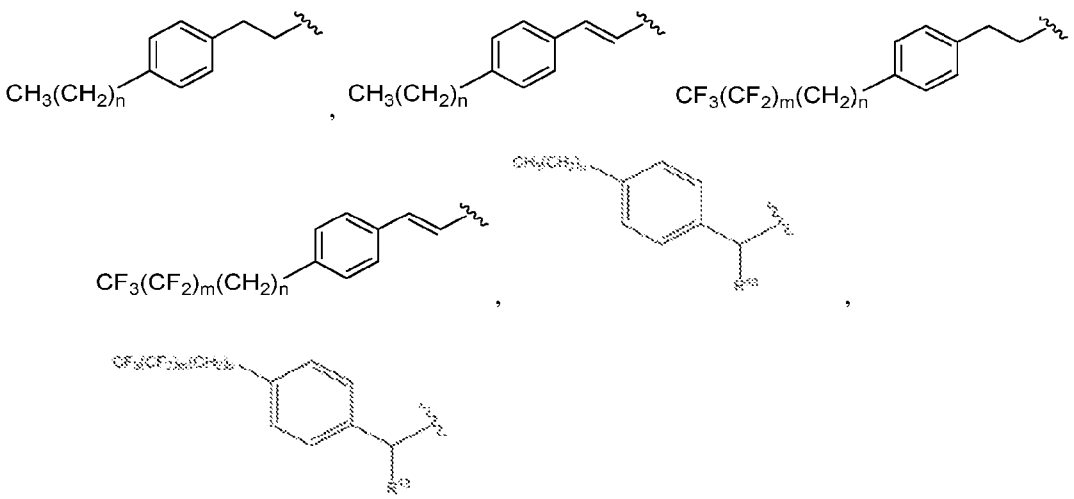
n is 8 to 14 or ≤ to 8 to ≤ 14;

o is 9 to 15 or ≤ 9 to ≤ 15;

the total or m and n is 8 to 14 or ≤ 8 to ≤ 14;

the total of m and o is 9 to 15 or ≤ 9 to ≤ 15; or

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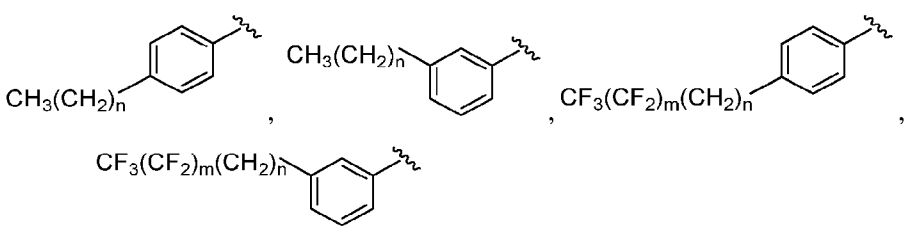


n is 4 to 10 or ≤ 4 to ≤ 10;

o is 5 to 11 or ≤ 5 to ≤ 11;

the total of m and n is 4 to 10 or ≤ 4 to ≤ 10;

and the total of m and o is 5 to 11 or ≤ 5 to ≤ 11; or



n is 6 to 12 or n is ≤ 6 to ≤ 12;

the total of m and n is 6 to 12 or n is ≤ 6 to ≤ 12;

R^{17} is hydrogen, a branched or straight chain C_{1-12} alkyl, C_{13-22} alkyl, cycloalkyl, or aryl selected from benzyl or phenyl, wherein the aryl is optionally substituted with one or more, the same or different R^{11}; and

R^{11} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl,

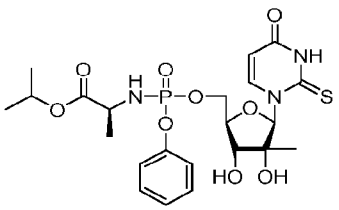
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ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

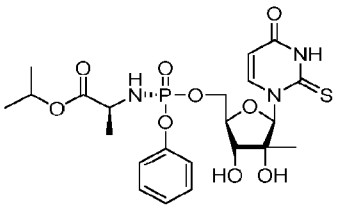
31. The composition of claim 30, wherein the sphingolipid is optionally substituted a sphingosine, ceramide, or sphingomyelin, or 2-aminoalkyl optionally substituted with one or more substituents.

32. The composition of any one of claims 1-31, wherein the second antiviral agent is selected from disoxaril, pleconaril, pirodavir, vapendavir pocapavir, or combinations thereof.

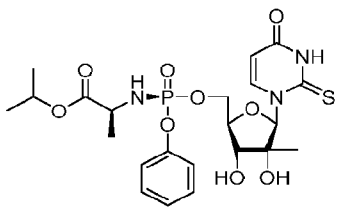
33. The composition of any one of claims 1-31, wherein the second antiviral agent is selected from disoxaril, pleconaril, pirodavir, vapendavir pocapavir, or combinations thereof, and the compound is selected from:



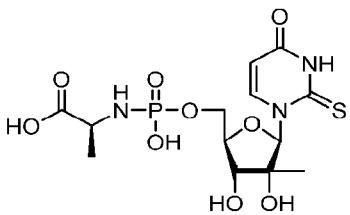
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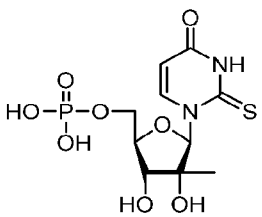


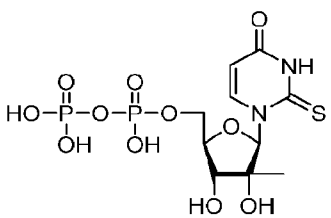
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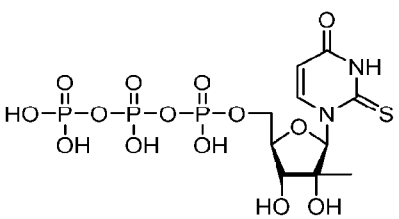


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34. A pharmaceutical composition for the treatment or prevention of a viral infection comprising a composition of any of claims 1-33, and a pharmaceutically acceptable carrier.

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35. The pharmaceutical composition of claim 34, wherein the viral infection is caused by an infectious agent comprising an RNA or DNA virus.

36. The pharmaceutical composition of claim 35 wherein the RNA or DNA virus comprises picornaviruses, cardioviruses, enteroviruses, coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, echovirus, erboviruses, hepatovirus, kobuviruses, parechoviruses, teschoviruses, caliciviruses, which include noroviruses, sapoviruses, lagoviruses, vesiviruses, astroviruses, togaviruses, flaviviruses, hepacivirus, coronaviruses, arteriviruses, rhabdoviruses, filoviruses, paramyxoviruses, orthomyxoviruses, hantaviruses, reoviruses, rotaviruses, birnaviruses, chrysoviruses, cystoviruses, hypoviruses partitiviruses, totoviruses, lentiviruses, polyomaviruses, papillomaviruses, adenoviruses, circoviruses ,parvoviruses, erythroviruses, betaparvoviruses, amdoviruses, densoviruses, iteraviruses, brevidensoviruses, pefudensoviruses, herpes viruses 1, 2, 3, 4, 5, 6, 7 and 8, poxviruses, or hepadnaviruses.

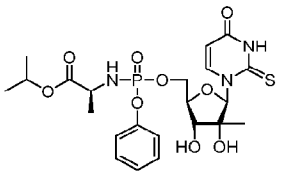
37. A liposomal composition comprising a composition of any of claims 1-33, and a pharmaceutically acceptable carrier.

38. A method of treating infections caused by RNA and DNA viruses comprising administering to a host in need an effective amount of a composition of any of claims 1-33.

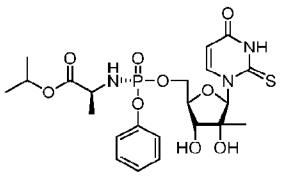
39. The method of claim 38, wherein the RNA and DNA virus comprises coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, echovirus, picornaviruses, cardioviruses, enteroviruses, erboviruses, hepatovirus, kobuviruses, parechoviruses, teschoviruses, caliciviruses, which include noroviruses, sapoviruses, lagoviruses, vesiviruses, astroviruses, togaviruses, flaviviruses, hepacivirus, coronaviruses, arteriviruses, rhabdoviruses, filoviruses, paramyxoviruses, orthomyxoviruses, hantaviruses, reoviruses, rotaviruses, birnaviruses, chrysoviruses, cystoviruses, hypoviruses partitiviruses, totoviruses, lentiviruses, polyomaviruses, papillomaviruses, adenoviruses, circoviruses ,parvoviruses, erythroviruses, betaparvoviruses, amdoviruses, densoviruses, iteraviruses, brevidensoviruses, pefudensoviruses, herpes viruses 1, 2, 3, 4, 5, 6, 7 and 8, poxviruses, or hepadnaviruses.

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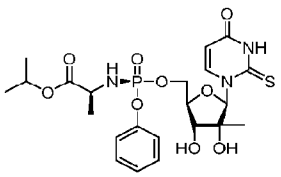
40. The method of claim 38 or 39, wherein the second antiviral agent selected from disoxaril, pleconaril, pirodavir, vapendavir and pocapavir, and combinations thereof is administered with one or more of the following compounds:



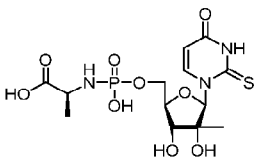
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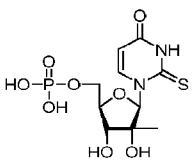


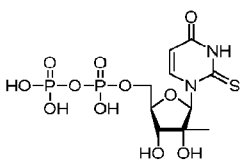
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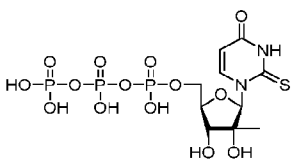


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41. The method of any one of claims 38-40, wherein the RNA and DNA virus is an enterovirus.

42. The method of claim 41, wherein the enterovirus infection is selected from the group consisting of coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, and echovirus.

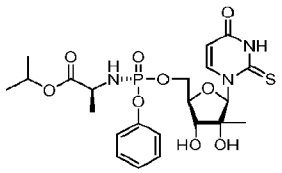
43. The method of claim 41, wherein the enterovirus infection is a coxsackie virus.

44. The method of claim 43, wherein the coxsackie virus is Coxsackie A16.

45. The method of any one of claims 38-44, wherein the host is immune suppressed.

46. A pharmaceutical formulation comprising

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2023 (EIDD-2023) or a pharmaceutically acceptable salt thereof, vapendavir, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

47. A method of treating or preventing an enterovirus infection comprising administering to a host in need an effective amount of the composition of claim 46, or a pharmaceutically acceptable salt thereof.

48. The method of claim 47, wherein the enterovirus infection is selected from the group consisting of coxsackie virus A, B and C, coxsackie A16, EV-D68, EV-A71, rhinovirus, poliovirus, and echovirus.

49. The method of claim 47, wherein the enterovirus infection is a coxsackie virus.

50. The method of claim 49, wherein the coxsackie virus is Coxsackie A16.

51. The method of any one of claims 46-50, wherein the host is immune suppressed.

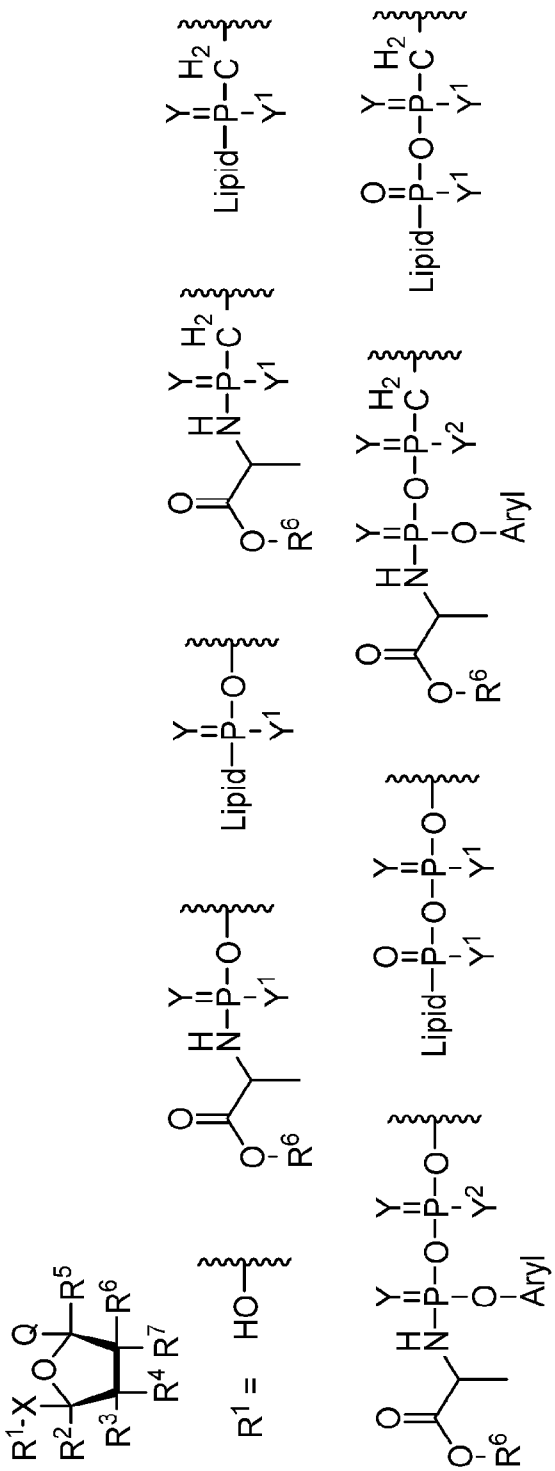


FIG. 1

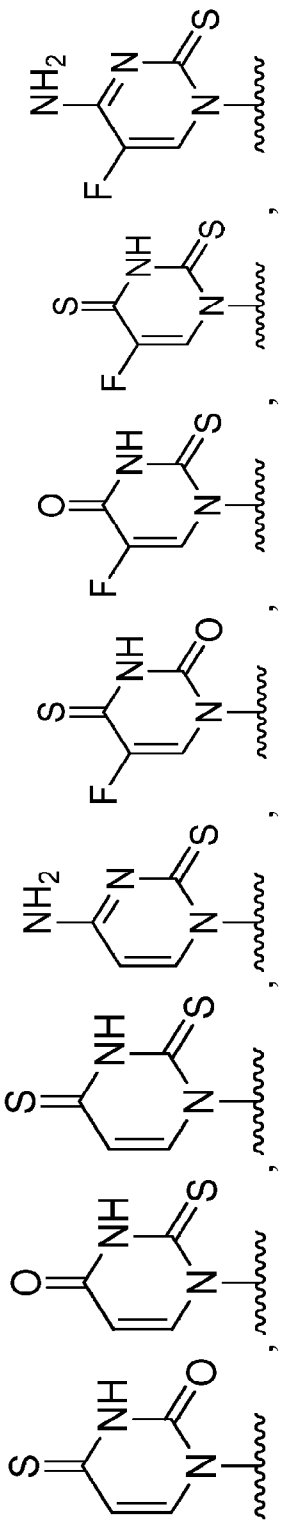


FIG. 2

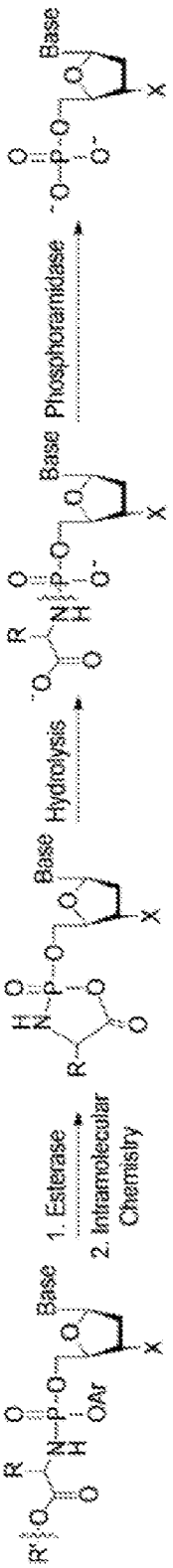

1. Esterase
2. Intramolecular Chemistry
Hydrolysis
Phosphoramidase
Base
X
R
OAr

FIG. 3

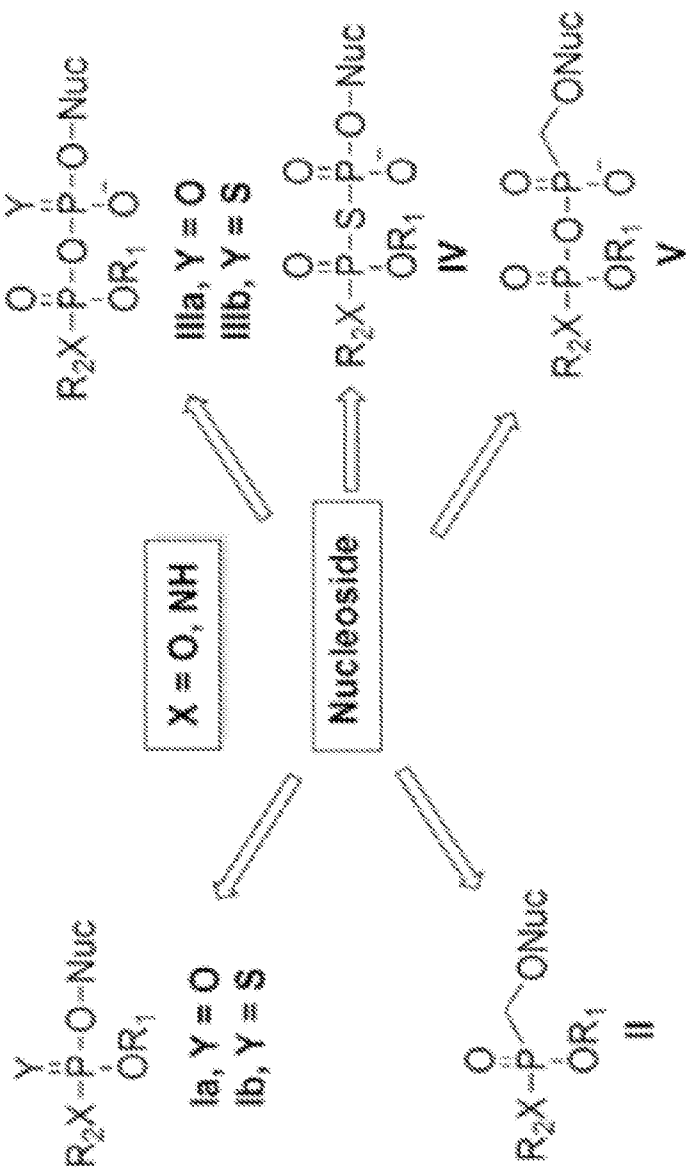


FIG. 4

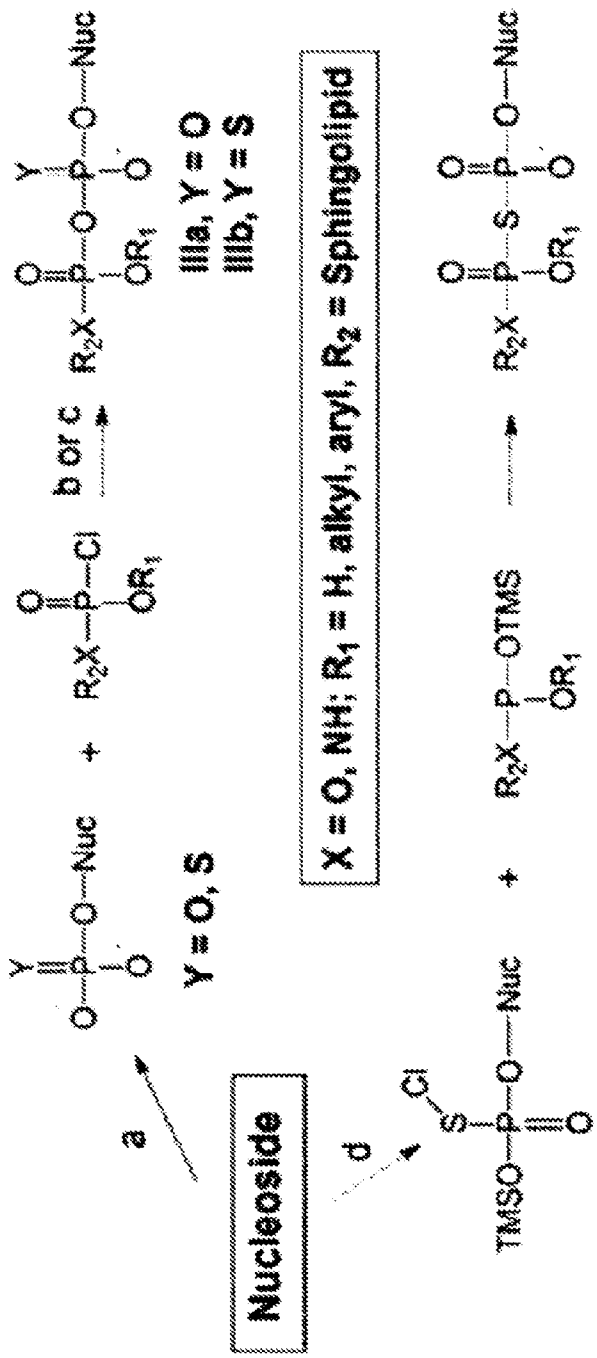


FIG. 5

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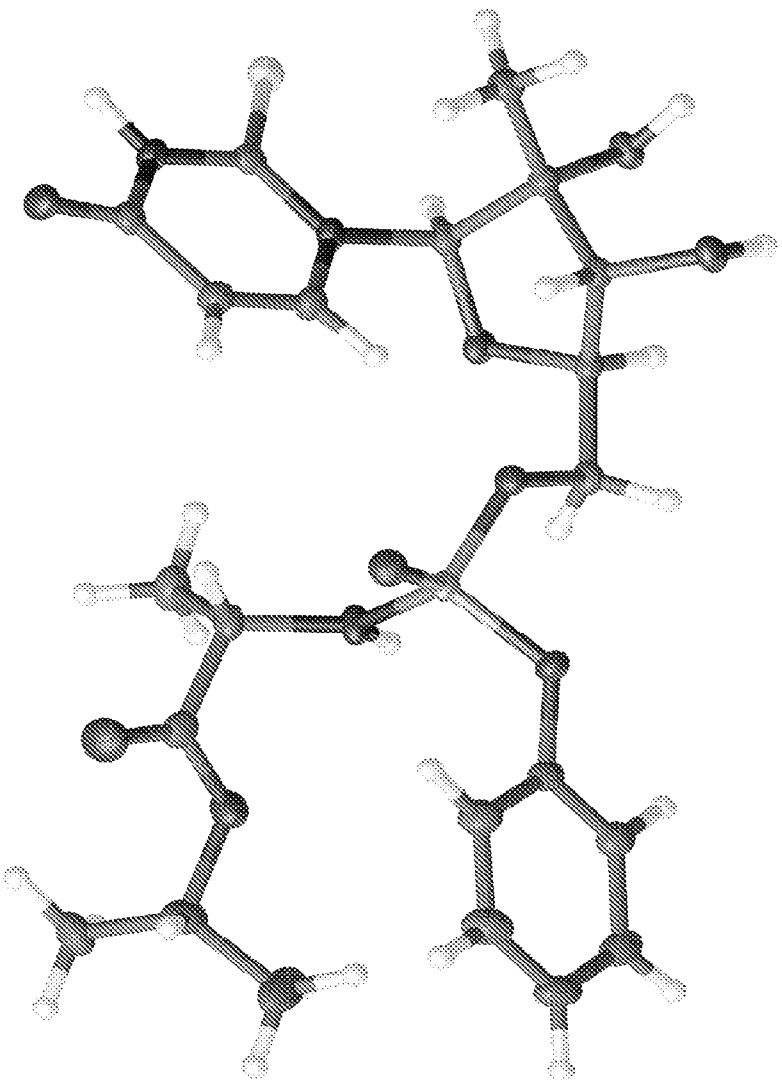


FIG. 6

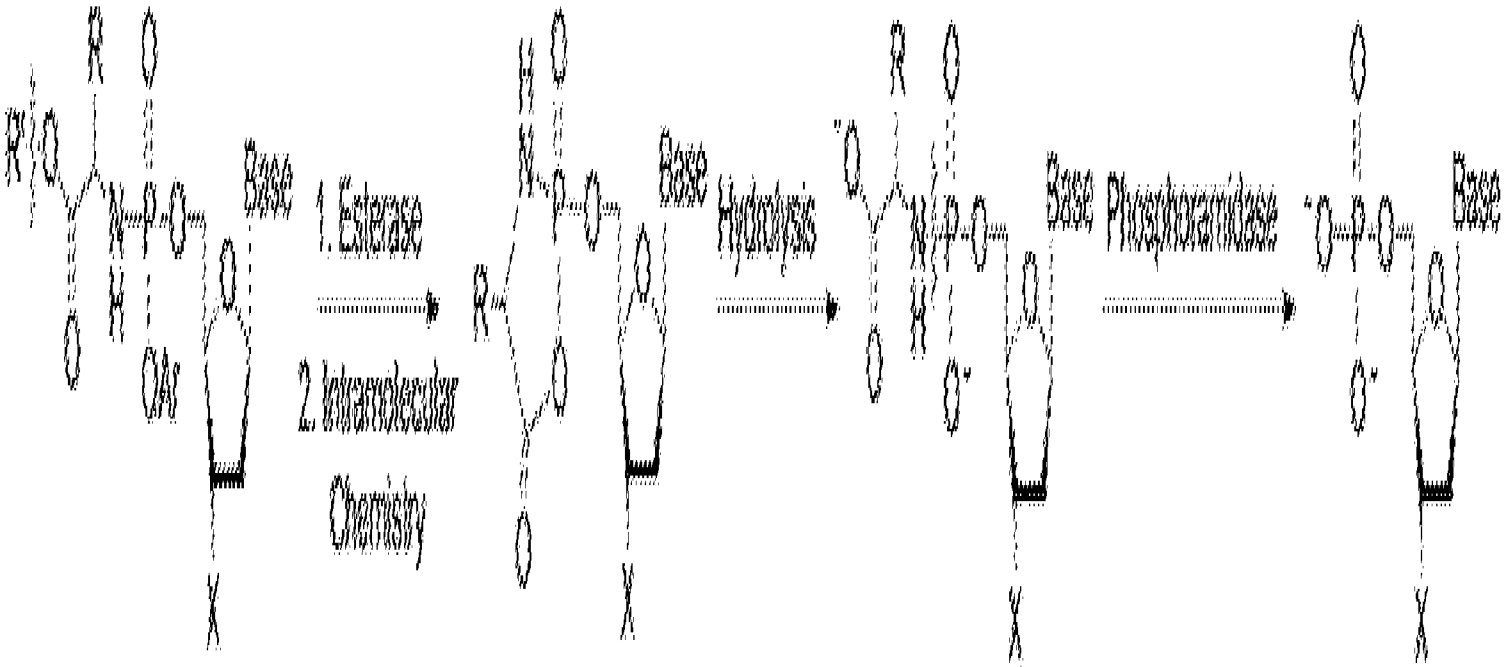

1. Esterase
2. Intramolecular
Chemistry
Base
Hydrolysis
Phosphoramidase

FIG. 3