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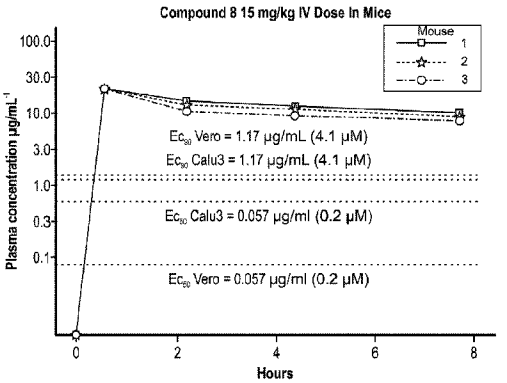
(54) **Titre : THIONUCLEOSIDES EN GUISE D'AGENTS ANTIVIRAUX**
(54) **Title: THIONUCLEOSIDES AS ANTIVIRAL AGENTS**



IV	15	mg/kg				
ID	1	2	3	mean	SD	%CV
C_{max}, (µg/ml)	18.6	20.5	20.9	20	1.23	6.14
Tmax, (hr)	0.5	0.5	0.5	0.5	0	0
AUCinf, (µg/mL.hr)	175.2	160.3	205.6	180.4	23.1	12.8
$t_{1/2}$, (hr)	9.77	7.03	8.80	8.53	1.39	16.29
MRT, (hr)	13.39	10.09	12.66	12.05	1.73	14.37
CL/F, (L/hr)/kg	0.086	0.094	0.073	0.084	0.010	12.35

Compound 8 concentrations were > *in vitro* EC_{90} for > 7hr after IV administration.

(57) **Abrégé/Abstract:**
Compounds, compositions and methods for preventing, treating or curing a coronavirus infection in human subjects or other animal hosts. In one embodiment, the compounds can be used to treat an infection with a severe acute respiratory syndrome virus, such as human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, and SARS-CoV-2. In another embodiment, the methods are used to treat a patient infected with a Flavivirus, Picornavus, Togavirus, or Bunyavirus.

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Abstract:

Compounds, compositions and methods for preventing, treating or curing a coronavirus infection in human subjects or other animal hosts. In one embodiment, the compounds can be used to treat an infection with a severe acute respiratory syndrome virus, such as human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, and SARS-CoV-2. In another embodiment, the methods are used to treat a patient infected with a Flavivirus, Picornavus, Togavirus, or Bunyavirus.

THIONUCLEOSIDES AS ANTIVIRAL AGENTS

Field

Compounds, methods and compositions for treating or preventing coronavirus infections are disclosed. More specifically, certain nucleoside and nucleotide analogs, pharmaceutically acceptable salts, or other derivatives thereof, and the use thereof in the treatment of coronaviruses, especially SARS-CoV-2, are disclosed.

Background

Coronaviruses are a species of virus belonging to the subfamily Coronavirinae in the family Coronaviridae, and are enveloped viruses with a positive-sense single-stranded RNA genome and with a nucleocapsid of helical symmetry.

Coronaviruses primarily infect the upper respiratory and gastrointestinal tract of mammals and birds, though several known strains infect humans as well. Coronaviruses are believed to cause a significant percentage of all common colds in human adults and children.

Coronaviruses cause colds in humans, primarily in the winter and early spring seasons. Coronaviruses can also cause pneumonia, either direct viral pneumonia or a secondary bacterial pneumonia, bronchitis, either direct viral bronchitis or a secondary bacterial bronchitis, and severe acute respiratory syndrome (SARS).

Coronaviruses also cause a range of diseases in farm animals and domesticated pets, some of which can be serious and are a threat to the farming industry. In chickens, the infectious bronchitis virus (IBV), a coronavirus, targets not only the respiratory tract but also the uro-genital tract. The virus can spread to different organs throughout the chicken.

Economically significant coronaviruses of farm animals include porcine coronavirus (transmissible gastroenteritis coronavirus, TGE) and bovine coronavirus, which both result in diarrhea in young animals. Feline Coronavirus: two forms, Feline enteric coronavirus is a pathogen of minor clinical significance, but spontaneous mutation of this virus can result in feline infectious peritonitis (FIP), a disease associated with high mortality. There are two types of canine coronavirus (CCoV), one that causes mild gastrointestinal disease and one that has been found to cause respiratory disease. Mouse hepatitis virus (MHV) is a coronavirus that

causes an epidemic murine illness with high mortality, especially among colonies of laboratory mice.

Some strains of MHV cause a progressive demyelinating encephalitis in mice which has been used as a murine model for multiple sclerosis.

More recently a coronavirus pandemic has caused a dual threat to the health and the economy of the U.S. and the world. COVID-19 was first identified in December 2019 in Wuhan, Hubei province, China, resulting in the ongoing 2019-2020 pandemic. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Common symptoms of the disease include fever (88%), dry cough (68%), shortness of breath (19%), and loss of smell (15 to 30%). Complications may include pneumonia, viral sepsis, acute respiratory distress syndrome, diarrhea, renal disease, cardiac issues and encephalitis. As of January 2022, the total number of infected worldwide stood at over 306 million and at least 5.5 million had died, and, according to the Johns Hopkins University Coronavirus Resource Center, almost 60 million people had tested positive for coronavirus in the U.S. and over eight hundred thousand people had died of the disease. Local transmission of the disease has been recorded in over 200 countries. Risk factors include travel and viral exposure, and prevention is assisted by social distancing and quarantine.

Current treatments for these infections are mainly supportive, minimizing the symptoms rather than treating the underlying viral infection. For example, patients may be treated with analgesics to relieve pain, and patients with enteroviral carditis can be treated for complications such as arrhythmias, pericardial effusion, and cardiac failure.

It would be advantageous to provide new antiviral agents, compositions including these agents, and methods of treatment using these agents to treat coronaviruses. The present disclosure provides such agents, compositions and methods.

Summary

The present disclosure relates to compounds, methods and compositions for treating or preventing coronaviruses and/or other viral infections in a host. The methods involve administering a therapeutically or prophylactically-effective amount of at least one compound described herein to treat or prevent an infection by, or an amount sufficient to reduce the biological activity of, coronaviruses or other viral infections including, but not limited to,

SARS-CoV-2, MERS, SARS, and OC-43. In other embodiments, the compounds described herein can be used for treating or preventing infections by Flaviviruses, Picornaviridae, Togavirodae and Bunyaviridae.

In one embodiment, the disclosure relates to methods of using potent, selective antiviral agents to target coronaviruses and other viral infections and thus help eliminate and/or treat infection in patients infected by these viruses.

In one aspect of this embodiment, the compounds used include one or more of the specific nucleoside inhibitors described herein.

In another embodiment, pharmaceutical compositions including one or more of the compounds described herein are disclosed, which in one embodiment comprises a combination of a cytidine and a uridine analog, in combination with a pharmaceutically acceptable carrier or excipient. These compositions can be used to treat a host infected with a coronavirus or other viral infections, to prevent one of these infections, and/or to reduce the biological activity of one of these viruses. The compositions can include a combination of one or more of the compounds described herein, optionally with other antiviral compounds or biological agents, including anti-SARS-CoV2 compounds and biological agents, fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, such as remdesivir, GS-441524, N^4-hydroxycytidine, and other compounds disclosed in U.S. Patent No. 9,809,616, and their prodrugs, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-2 specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

In yet another embodiment, the present disclosure relates to processes for preparing the specific nucleoside compounds described herein.

In some embodiments, the compounds described herein are deuterated at one or more positions. Where the compounds are nucleosides, deuteration can be present in one or more positions on the sugar moiety of the compounds, the base portion of the compounds, and/or the prodrug portion of the compounds, at any position.

In some embodiments, ester prodrugs were prepared to allow more drug, when given orally, to reach the plasma and not be trapped in the gut as a triphosphate.

In another embodiment, ester prodrugs were prepared to improve the oral bioavailability of drugs.

The present disclosure will be better understood with reference to the following Detailed Description.

Brief Description of the Figures

Figure 1 is a chart showing the plasma levels, over time, after IV dosing (15 mg/kg) of Compound 8.

Detailed Description

The compounds described herein show inhibitory activity against Coronaviridae in cell-based assays. Therefore, the compounds can be used to treat or prevent a Coronaviridae infection in a host, or reduce the biological activity of the virus. The host can be a mammal, and in particular, a human, infected with Coronaviridae virus. The compounds are also effective against Flaviviridae, Picornaviridae, Togavirodae and Bunyaviridae viruses. The methods involve administering an effective amount of one or more of the compounds described herein.

Pharmaceutical formulations including one or more compounds described herein, in combination with a pharmaceutically acceptable carrier or excipient, are also disclosed. In one embodiment, the formulations include at least one compound described herein and at least one further therapeutic agent.

The present disclosure will be better understood with reference to the following definitions:

I. Definitions

The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application. Thus, in a compound such as R"XYR", wherein R" is "independently carbon or nitrogen," both R" can be carbon, both R" can be nitrogen, or one R" can be carbon and the other R" nitrogen.

As used herein, the term "enantiomerically pure" refers to a compound composition that comprises at least approximately 95%, and, preferably, approximately 97%, 98%, 99% or 100% of a single enantiomer of that compound.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a compound composition that includes at least 85 to 90% by weight, preferably 95% to 98

% by weight, and, even more preferably, 99% to 100% by weight, of the designated enantiomer of that compound. In a preferred embodiment, the compounds described herein are substantially free of enantiomers.

Similarly, the term "isolated" refers to a compound composition that includes at least 85 to 90% by weight, preferably 95% to 98% by weight, and, even more preferably, 99% to 100% by weight, of the compound, the remainder comprising other chemical species or enantiomers.

The term "alkyl," as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbons, including both substituted and unsubstituted alkyl groups. The alkyl group can be optionally substituted with any moiety that does not otherwise interfere with the reaction or that provides an improvement in the process, including but not limited to but limited to halo, C_{1-6} haloalkyl, hydroxyl, carboxyl, C_{1-6} acyl, aryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di- C_{1-6}-alkylamino, arylamino, C_{1-6} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference. Specifically included are CF_3 and CH_2CF_3.

In the text, whenever the term C(alkyl range) is used, the term independently includes each member of that class as if specifically and separately set out. The term "alkyl" includes C_{1-22} alkyl moieties, and the term "lower alkyl" includes C_{1-6} alkyl moieties. It is understood to those of ordinary skill in the art that the relevant alkyl radical is named by replacing the suffix "-ane" with the suffix "-yl".

As used herein, a "bridged alkyl" refers to a bicyclo- or tricyclo alkane, for example, a 2:1:1 bicyclohexane.

As used herein, a "spiro alkyl" refers to two rings that are attached at a single (quaternary) carbon atom.

The term "alkenyl" refers to an unsaturated, hydrocarbon radical, linear or branched, in so much as it contains one or more double bonds. The alkenyl group disclosed herein can

be optionally substituted with any moiety that does not adversely affect the reaction process, including but not limited to but not limited to those described for substituents on alkyl moieties. Non-limiting examples of alkenyl groups include ethylene, methylethylene, isopropylidene, 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane- diyl, 1,2-propane-diyl, 1,3-butane-diyl, and 1,4-butane-diyl.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds. The alkynyl group can be optionally substituted with any moiety that does not adversely affect the reaction process, including but not limited to those described above for alkyl moeities. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, and hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals.

The term "alkylamino" or "arylamino" refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "fatty alcohol" as used herein refers to straight-chain primary alcohols with between 4 and 26 carbons in the chain, preferably between 8 and 26 carbons in the chain, and most preferably, between 10 and 22 carbons in the chain. The precise chain length varies with the source. Representative fatty alcohols include lauryl, stearyl, and oleyl alcohols. They are colourless oily liquids (for smaller carbon numbers) or waxy solids, although impure samples may appear yellow. Fatty alcohols usually have an even number of carbon atoms and a single alcohol group (-OH) attached to the terminal carbon. Some are unsaturated and some are branched. They are widely used in industry. As with fatty acids, they are often referred to generically by the number of carbon atoms in the molecule, such as "a C_{12} alcohol", that is an alcohol having 12 carbons, for example dodecanol.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis, and are described, for example, in Greene et al., Protective Groups in Organic Synthesis, supra.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings can be attached together in a

pendent manner or can be fused. Non-limiting examples of aryl include phenyl, biphenyl, or naphthyl, or other aromatic groups that remain after the removal of a hydrogen from an aromatic ring. The term aryl includes both substituted and unsubstituted moieties. The aryl group can be optionally substituted with any moiety that does not adversely affect the process, including but not limited to but not limited to those described above for alkyl moieties. Non-limiting examples of substituted aryl include heteroarylamino, N-aryl-N- alkylamino, N-heteroarylamino-N-alkylamino, heteroaralkoxy, arylamino, aralkylamino, arylthio, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, hydroxyaralkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl, carboaralkoxy.

The terms "alkaryl" or "alkylaryl" refer to an alkyl group with an aryl substituent. The terms "aralkyl" or "arylalkyl" refer to an aryl group with an alkyl substituent.

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

The term "acyl" refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from the group consisting of straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl, including, but not limited to methoxymethyl, aralkyl, including, but not limited to, benzyl, aryloxyalkyl, such as phenoxymethyl, aryl, including, but not limited to, phenyl, optionally substituted with halogen (F, Cl, Br, or I), alkyl (including but not limited to C_1, C_2, C_3, and C_4) or alkoxy (including but not limited to C_1, C_2, C_3, and C_4), sulfonate esters such as alkyl or aralkyl sulphonyl including but not limited to methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, and trialkylsilyl (e.g., dimethyl-t-butylsilyl or diphenylmethylsilyl). Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals having alkyl moieties, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals can be further substituted

with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy.

The term "alkylamino" denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respectively, attached to an amino radical. The term "aralkylamino", embraces aralkyl radicals attached to an amino radical. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "heteroatom," as used herein, refers to oxygen, sulfur, nitrogen and phosphorus.

The terms "heteroaryl" or "heteroaromatic," as used herein, refer to an aromatic that includes at least one sulfur, oxygen, nitrogen or phosphorus in the aromatic ring.

The term "heterocyclic," "heterocyclyl," and cycloheteroalkyl refer to a nonaromatic cyclic group wherein there is at least one heteroatom, such as oxygen, sulfur, nitrogen, or phosphorus in the ring.

Nonlimiting examples of heteroaryl and heterocyclic groups include furyl, furanyl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, pyrrolyl, quinazolinyl, cinnolinyl, phthalazinyl, xanthinyl, hypoxanthinyl, thiophene, furan, pyrrole, isopyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, pyrimidine or pyridazine, and pteridinyl, aziridines, thiazole, isothiazole, 1,2,3-oxadiazole, thiazine, pyridine, pyrazine, piperazine, pyrrolidine, oxaziranes, phenazine, phenothiazine, morpholinyl, pyrazolyl, pyridazinyl, pyrazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, adenine, N^6-alkylpurines, N^6-benzylpurine, N^6-halopurine, N^6- vinypurine, N^6-acetylenic

purine, N^6-acyl purine,N^6-hydroxyalkyl purine, N^6-thioalkyl purine, thymine, cytosine, 6-azapyrimidine, 2-mercaptopyrmidine, uracil, N^5- alkylpyrimidines, N^5-benzylpyrimidines, N^5-halopyrimidines, N^5-vinylpyrimidine, N^5- acetylenic pyrimidine, N^5-acyl pyrimidine, N^5-hydroxyalkyl purine, and N^6-thioalkyl purine, and isoxazolyl. The heteroaromatic group can be optionally substituted as described above for aryl. The heterocyclic or heteroaromatic group can be optionally substituted with one or more substituents selected from the group consisting of halogen, haloalkyl, alkyl, alkoxy, hydroxy, carboxyl derivatives, amido, amino, alkylamino, and dialkylamino. The heteroaromatic can be partially or totally hydrogenated as desired. As a nonlimiting example, dihydropyridine can be used in place of pyridine. Functional oxygen and nitrogen groups on the heterocyclic or heteroaryl group can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenelsulfonyl. The heterocyclic or heteroaromatic group can be substituted with any moiety that does not adversely affect the reaction, including but not limited to but not limited to those described above for aryl.

The term "host," as used herein, refers to a unicellular or multicellular organism in which the virus can replicate, including but not limited to cell lines and animals, and, preferably, humans. Alternatively, the host can be carrying a part of the viral genome, whose replication or function can be altered by the compounds described herein. The term host specifically refers to infected cells, cells transfected with all or part of the viral genome and animals, in particular, primates (including but not limited to chimpanzees) and humans. In most animal applications of the present disclosure, the host is a human being. Veterinary applications, in certain indications, however, are clearly contemplated by the present disclosure (such as for use in treating chimpanzees).

The term nucleoside also includes ribonucleosides, and representative ribonucleosides are disclosed, for example, in the Journal of Medicinal Chemistry, 43(23), 4516-4525 (2000), Antimicrobial Agents and Chemotherapy, 45(5), 1539-1546 (2001), and PCT WO 2000069876.

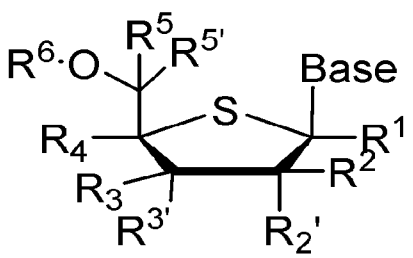
The term "peptide" refers to a natural or synthetic compound containing two to one hundred amino acids linked by the carboxyl group of one amino acid to the amino group of another.

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester) compound which, upon administration to a patient, provides the compound. Pharmaceutically-acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art.

Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound described herein. Typical examples of prodrugs include compounds that have biologically labile protecting groups on functional moieties of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. The prodrug forms of the compounds described herein can possess antiviral activity, can be metabolized to form a compound that exhibits such activity, or both.

II. Active Compounds

In one embodiment, the compounds are compounds of Formula (**A**):



Formula A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is H, deuterium, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl or N_3,

R^2 and $R^{2'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7,

each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,
wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

with the proviso that R^2 and $R^{2'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7.

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

R^3 and $R^{3'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7, wherein

each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

with the proviso that R^3 and $R^{3'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7,

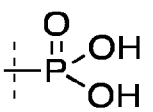
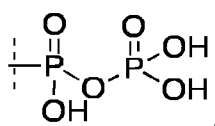
R^4 is selected from the group consisting of H, deuterium, CN, halo, N_3, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, substituted or unsubstituted (C_{1-8}) haloalkyl and N_3,

R^5 is and $R^{5'}$ are, independently, H, CH_3, CH_2F, CHF_2, or CF_3, wherein, when R^5 is CH_3, the carbon to which it is attached may be wholly or partially *R* or *S* or any mixture thereof, or R^5 and $R^{5'}$ can combine to form a C_{3-7} cycloalkyl ring;

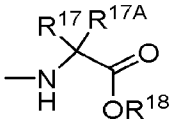
R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally

substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')$N(R')_2$, an optionally substituted O-C(O)$N(R')_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

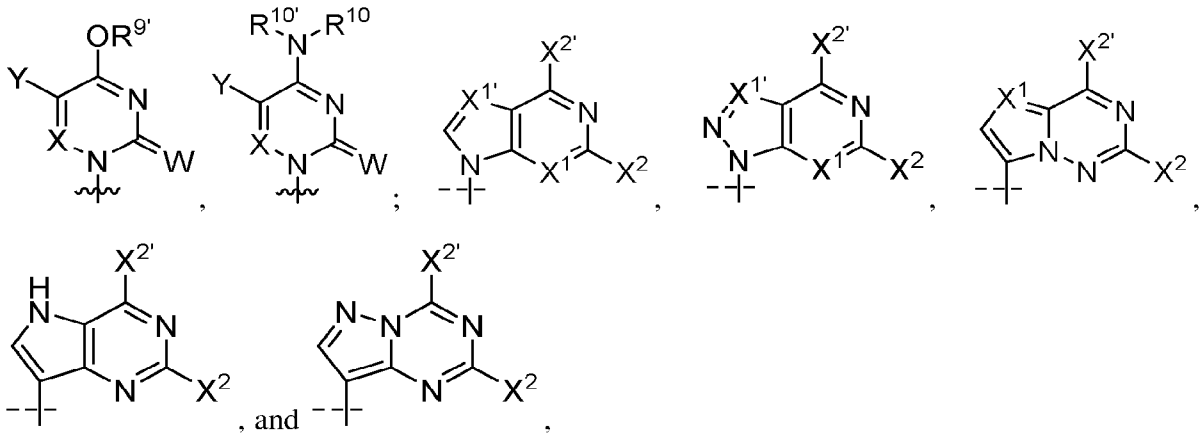
R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')$N(R')_2$, optionally substituted –O-C(O)$N(R')_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl;

Base is selected from the group consisting of:



Y is H or halo,

X is N or CH,

W is O or S,

X^1 and $X^{1'}$ are, independently, CH, C-(C_{1-6})alkyl, C-(C_{2-6})alkenyl, C-(C_{2-6})alkynyl, C-(C_{3-7})cycloalkyl, C-(C_{1-6}) haloalkyl, C-(C_{1-6})hydroxyalkyl, C-OR^{22}, C-$N(R^{22})_2$, C-halo, C-CN or N,

X^2 and $X^{2'}$ are independently H, halo, $OR^{9'}$ or $NR^{10}R^{10'}$,

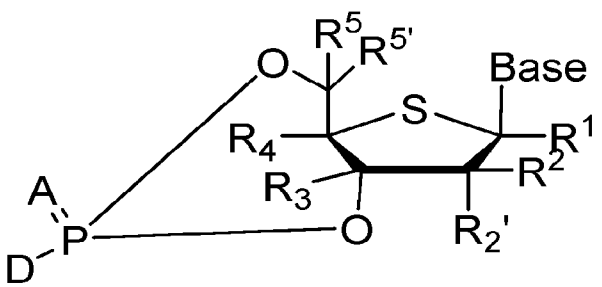
$R^{9'}$ is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, an (acyloxybenzyl)ester, an (acyloxybenzyl)ether, an optionally substituted bis-acyloxybenzyl)ester, an optionally substituted (acyloxybenzyl)ester,

an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12}-alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, (acyloxybenzyl)amide, (acyloxybenzyl)amine, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, PEG amide, PEG carbamate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid amide, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, or a lipid carbamate, wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), with the proviso that R^{10} and $R^{10'}$ cannot both be OH.

In another embodiment, the compounds are compounds of Formula B:



Formula B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

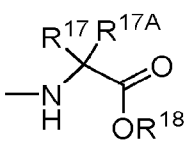
Base, R^1, R^2, $R^{2'}$, R^3, R^4, R^5 $R^{5'}$, R^7 and R^8 are as defined in Formula A,

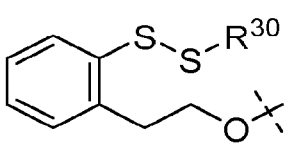
A is O or S, and

D is selected from the group consisting of:

(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

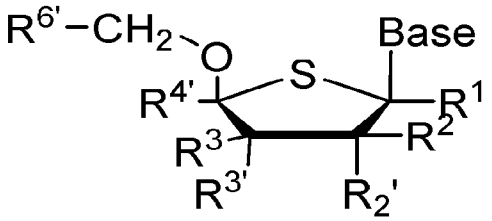
where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or

unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

In another embodiment, the compounds are compounds of Formula C:



Formula C

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base, R^1, R^2, $R^{2'}$, R^3 and $R^{3'}$ are as defined in Formula A,

$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

$R^{6'}$ is selected from the group consisting of -OR^6, -$P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

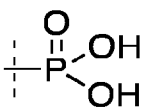
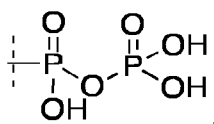
R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-$P(O)R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^7 is an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

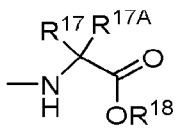
R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl, and

R^8 and $R^{8'}$ are independently selected from the group consisting of:

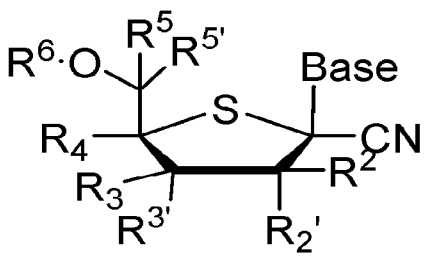
(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene,

C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

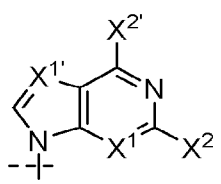
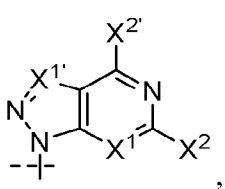
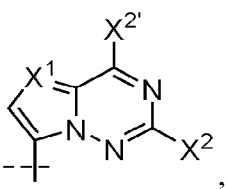
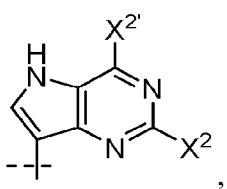
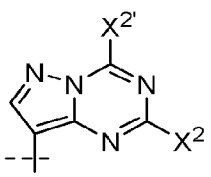
In still another embodiment, the compounds are compounds of Formula D:



Formula D

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

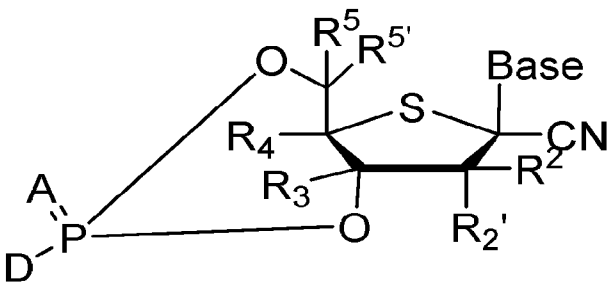
Base is selected from the group consisting of:

 ,  ,  ,  , and 

, and

X^1, $X^{1'}$, $X^{2'}$, X^2, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, R^5, $R^{5'}$ and R^6 are as defined in Formula A.

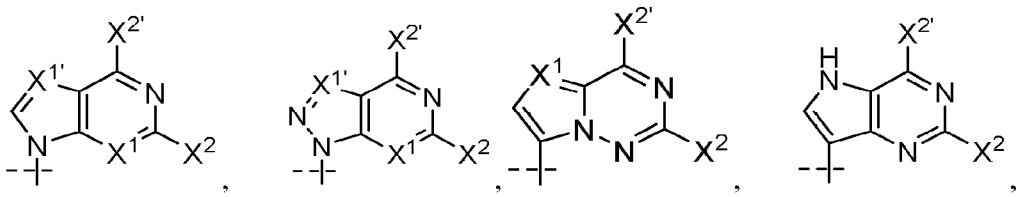
In a further embodiment, the compounds are compounds of Formula E:



Formula E

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is selected from the group consisting of:



, X¹, X¹', X²', X² R², R²', R³, R⁴, R⁵ and R⁵'are as defined in Formula A,

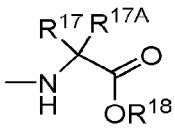
A is O or S, and

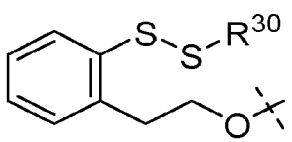
D is selected from the group consisting of:

(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

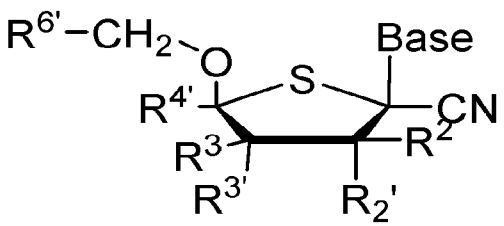
where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl,

substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

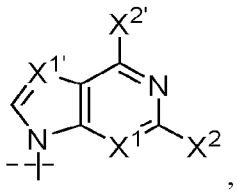
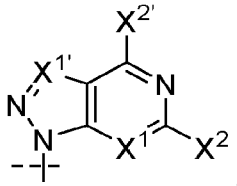
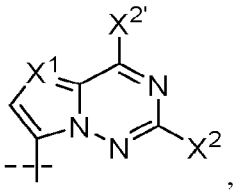
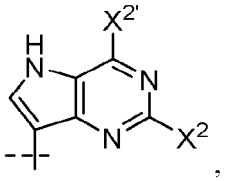
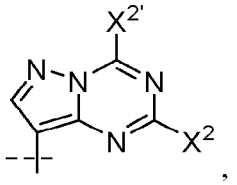
In still another embodiment, the compounds are compounds of Formula F:



Formula F

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is selected from the group consisting of:

 ,  ,  ,  , and  ,

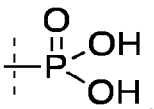
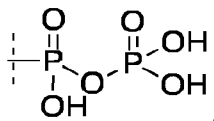
X^1, $X^{1'}$, $X^{2'}$, X^2 R^2, $R^{2'}$, R^3 and $R^{3'}$are as defined in Formula A,

$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

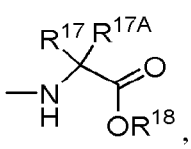
$R^{6'}$ is selected from the group consisting of $-OR^6$, $-P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted $-CH_2$-O-C(O)-R', an optionally substituted $-CH_2$-O-C(O)O-R', an optionally substituted $-CH_2-CH_2$-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')$N(R')_2$, an optionally substituted –O-C(O)$N(R')_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

In one embodiment of the compounds of Formula A, R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

In one embodiment of the compounds of Formula B, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

In one embodiment of the compounds of Formula C, R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H.

In one embodiment of the compounds of Formula D, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

In one embodiment of the compounds of Formula E, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

In one embodiment of the compounds of Formula F, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H

In one embodiment of the compounds of Formula A, $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

In one embodiment of the compounds of Formula B, $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

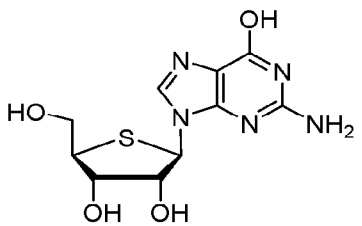
In one embodiment of the compounds of Formula C, $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

In one embodiment of the compounds of Formula D, $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

In one embodiment of the compounds of Formula E, $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

In one embodiment of the compounds of Formula F, $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

Representative compounds of Formula A include the following: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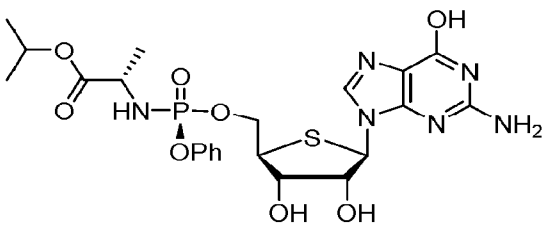
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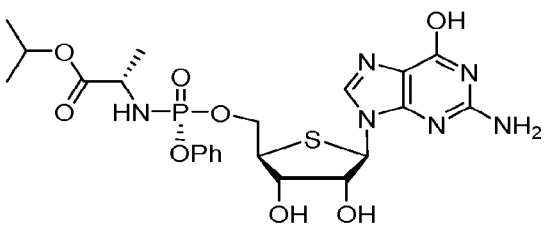
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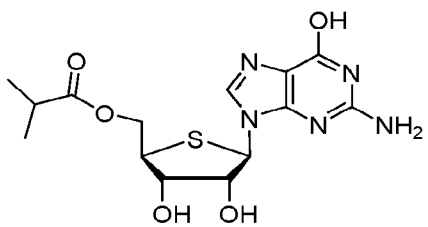
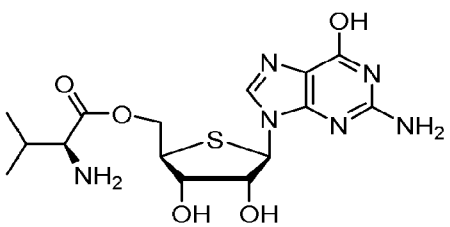
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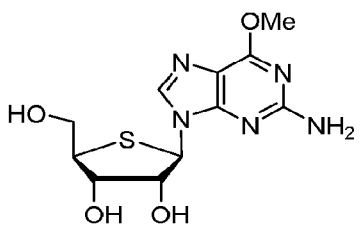
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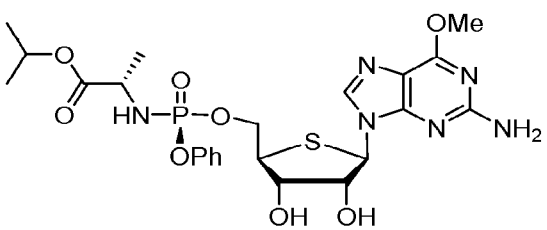
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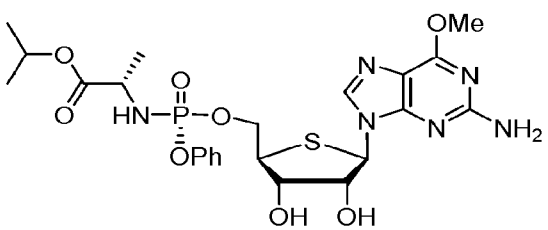
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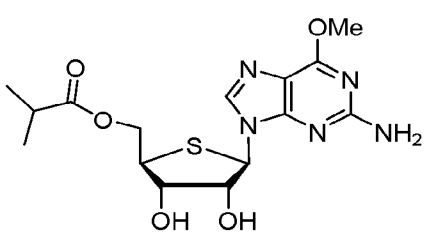
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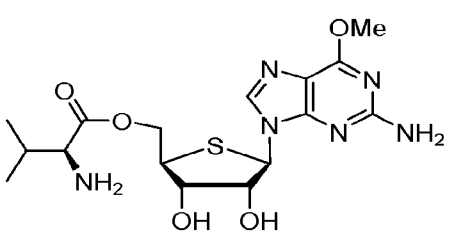
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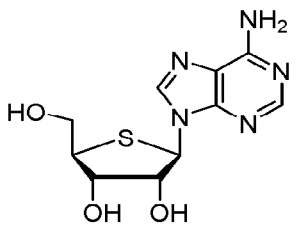
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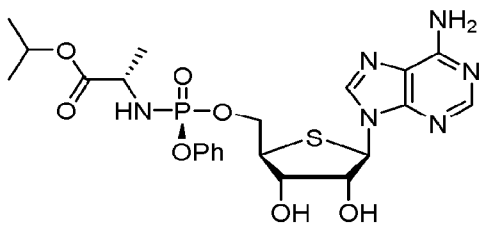
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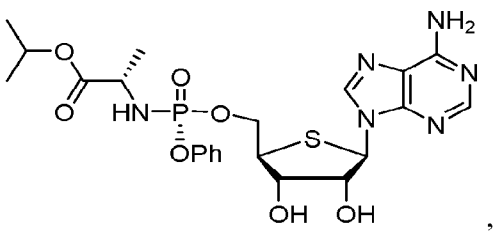
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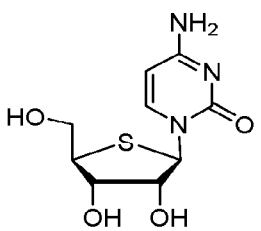
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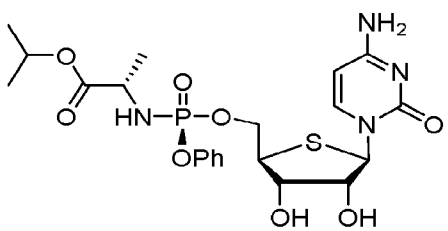
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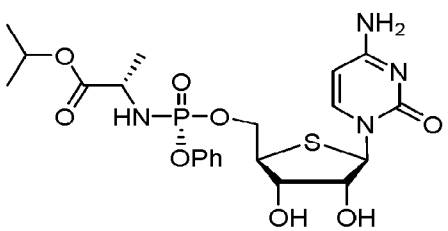
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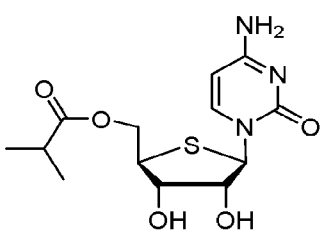
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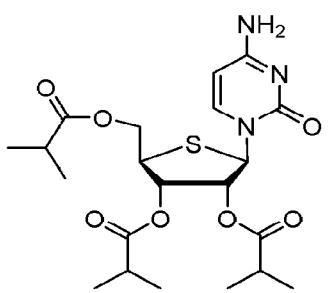
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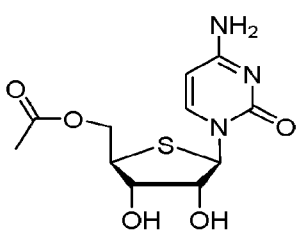
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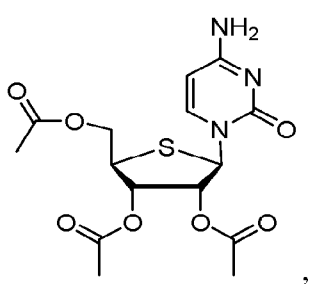
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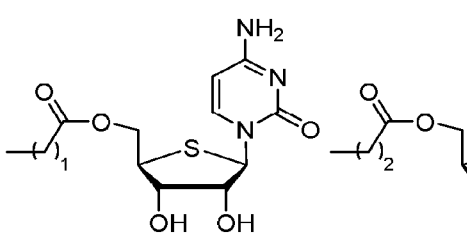
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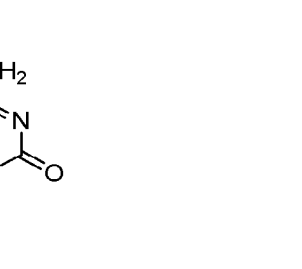
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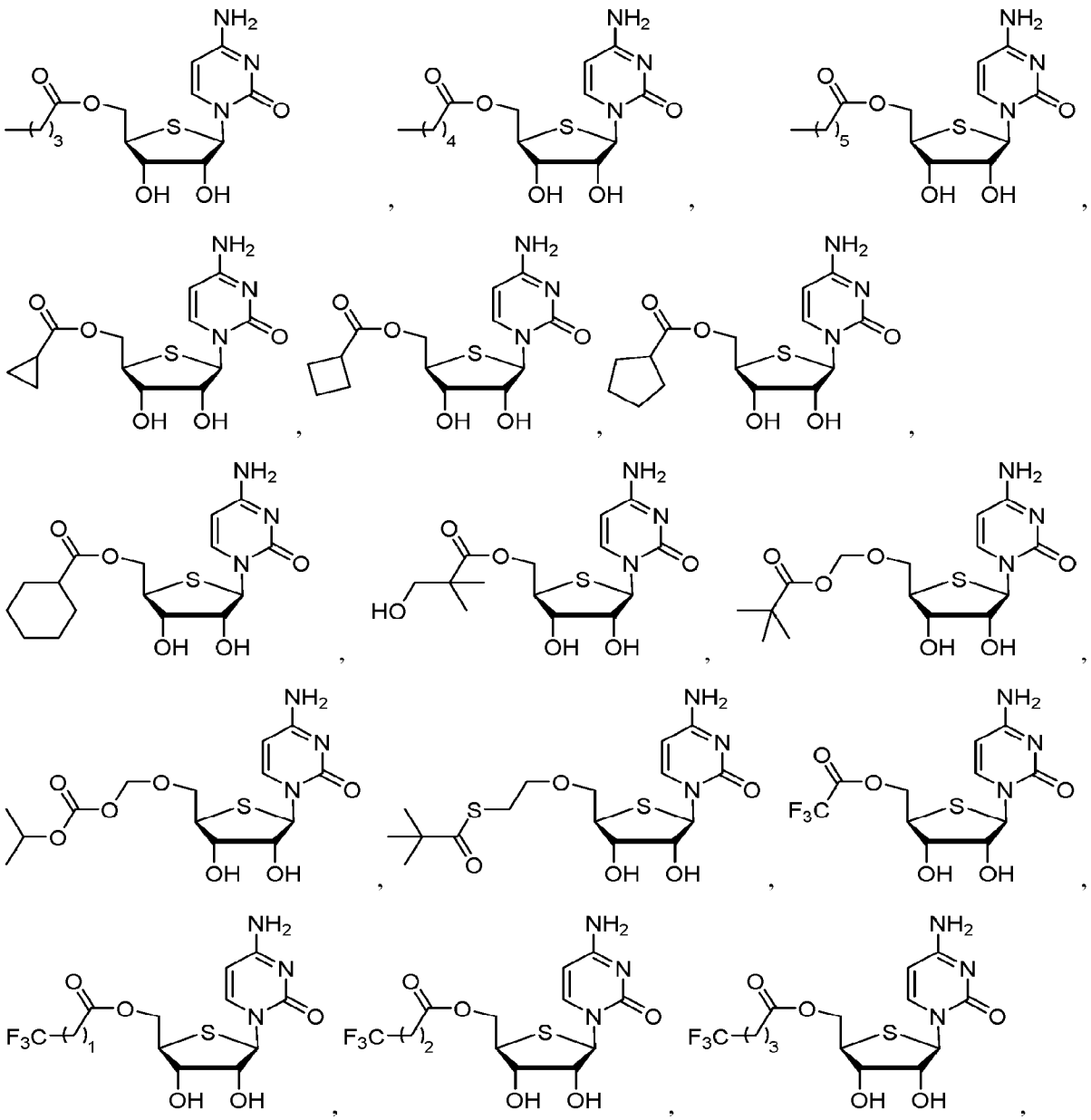

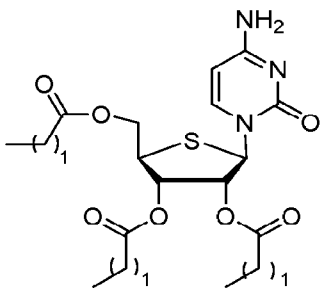
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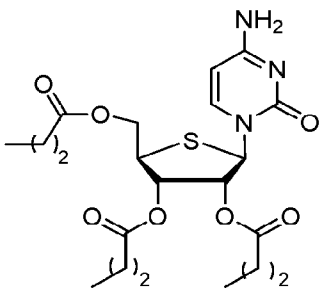
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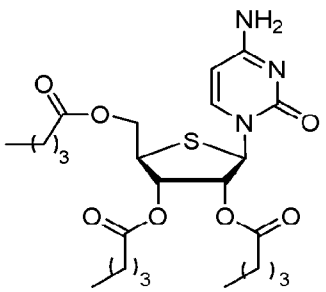
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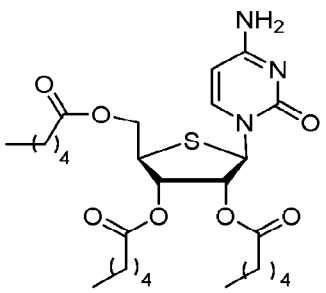
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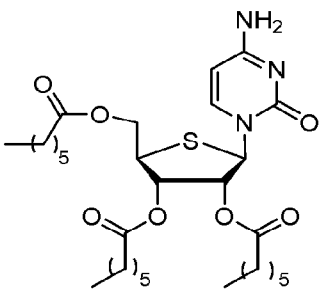
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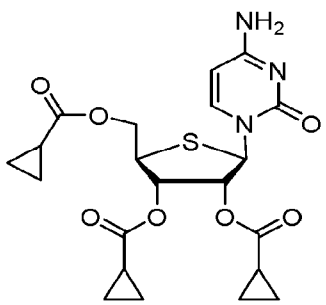
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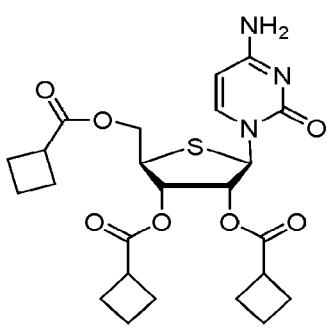
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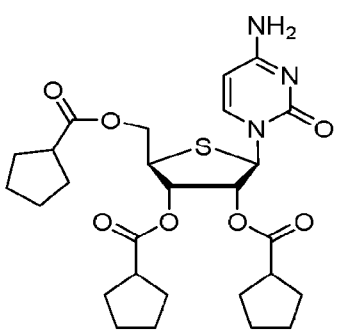
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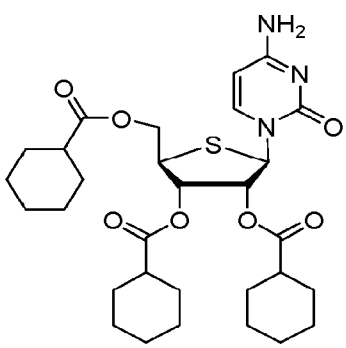
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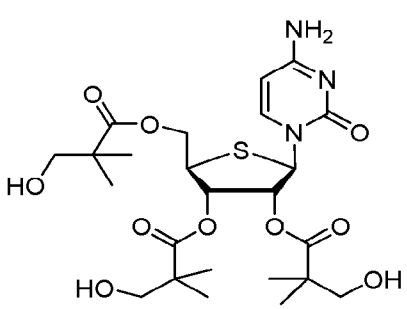
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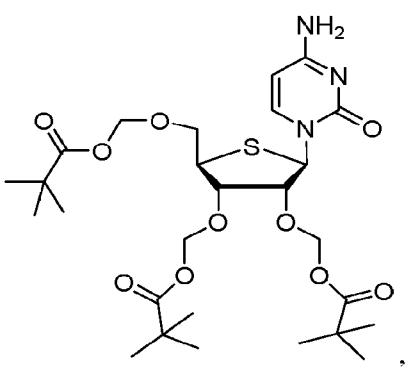
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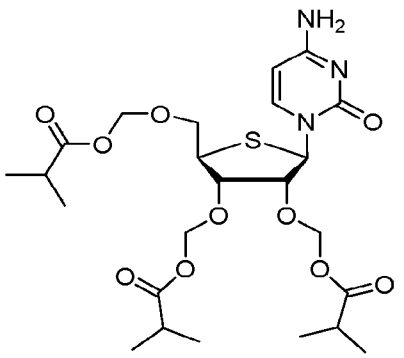
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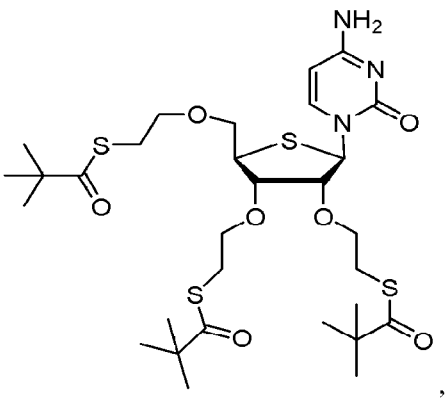
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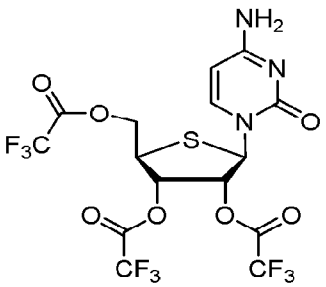
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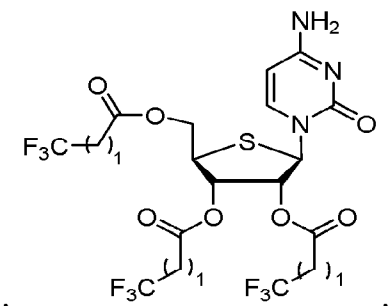
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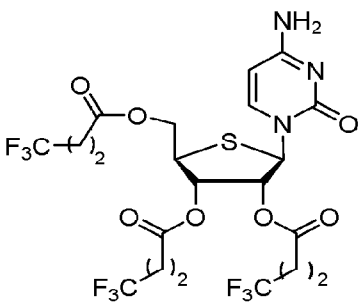
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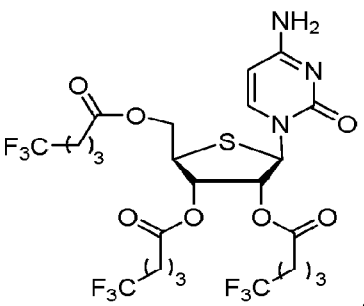
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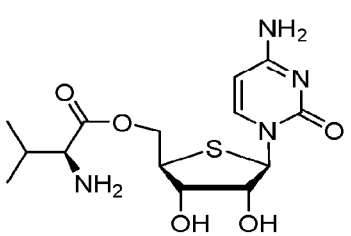
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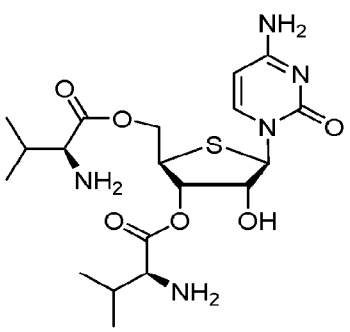
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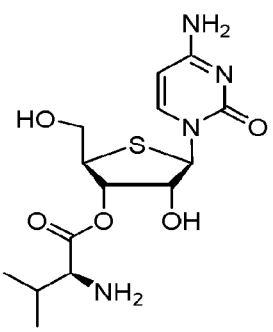
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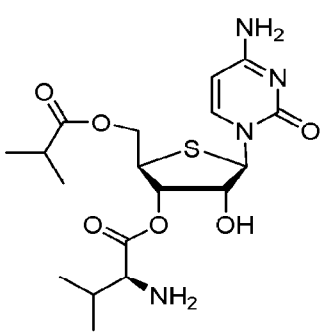
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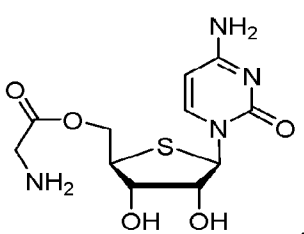
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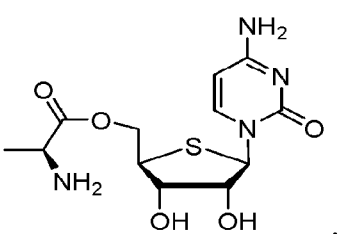
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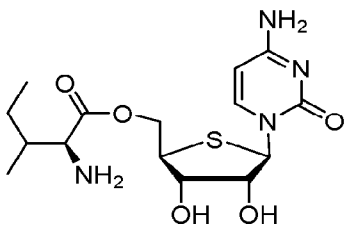
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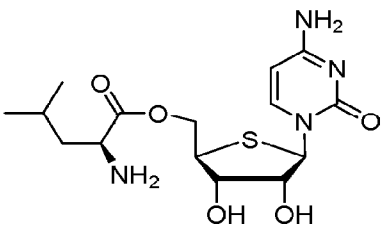
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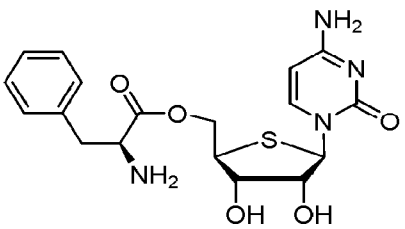
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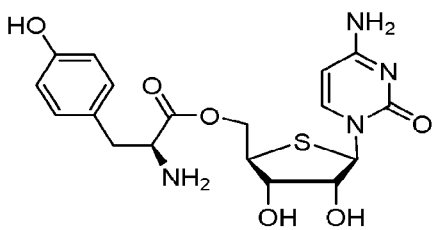
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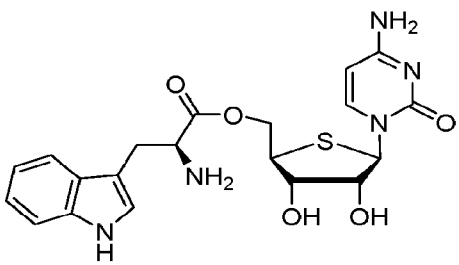
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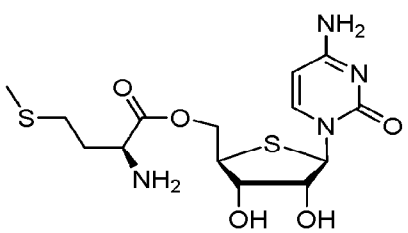
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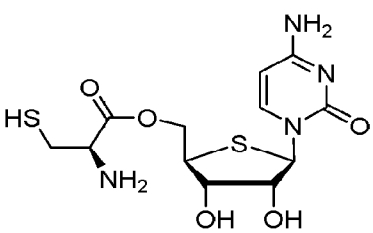
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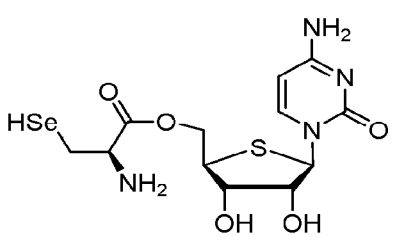
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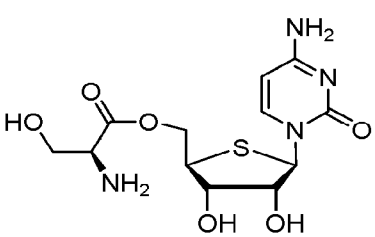
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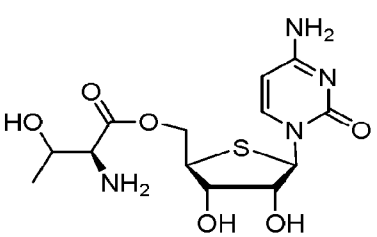
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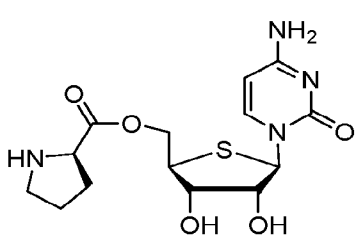
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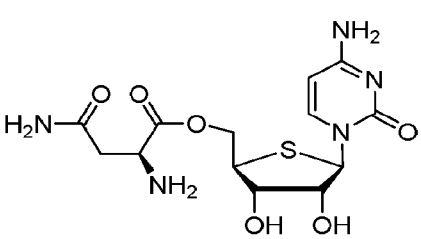
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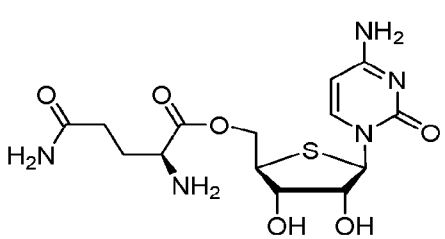
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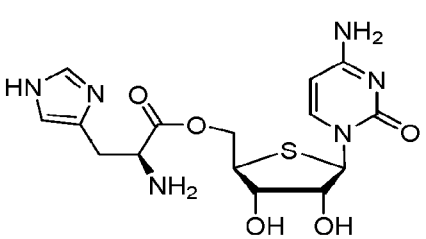
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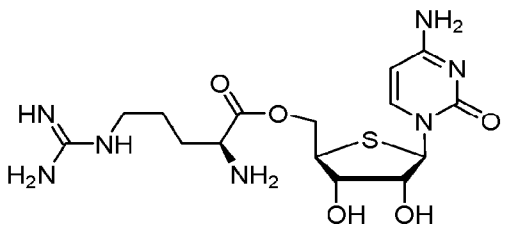
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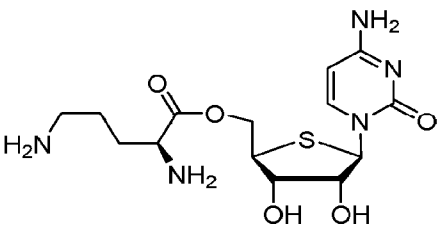
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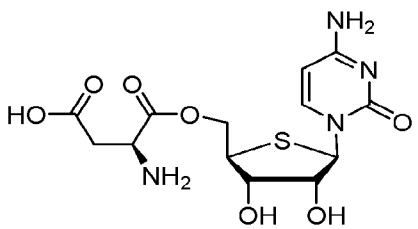
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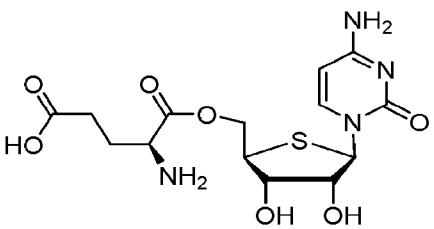
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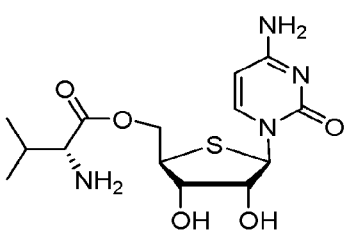
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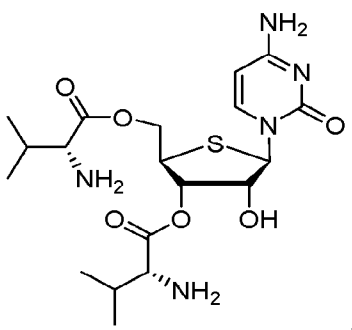
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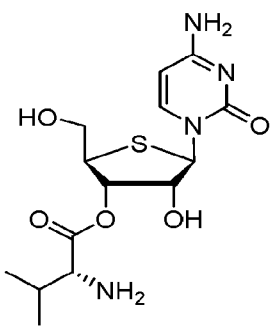
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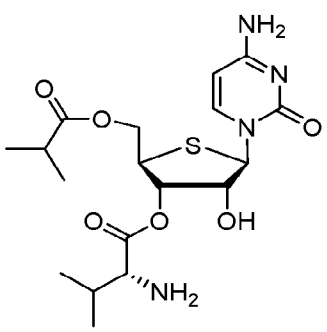
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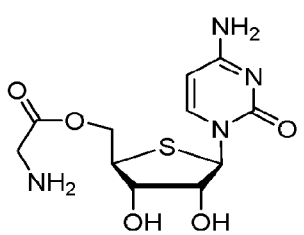
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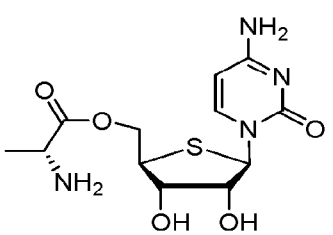
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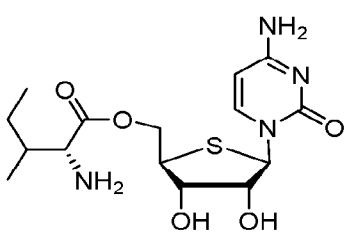
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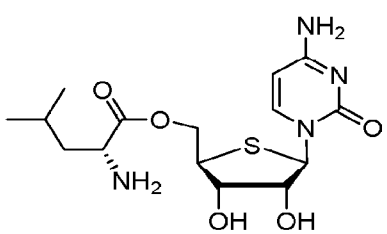
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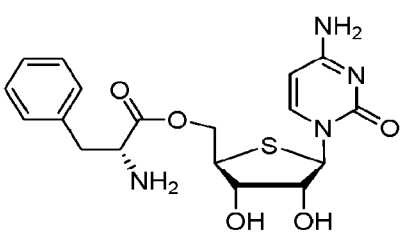
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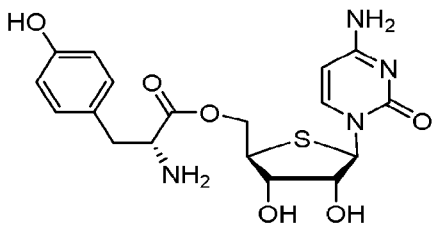
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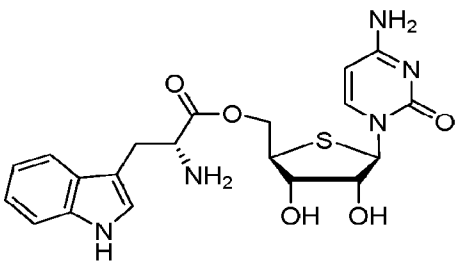
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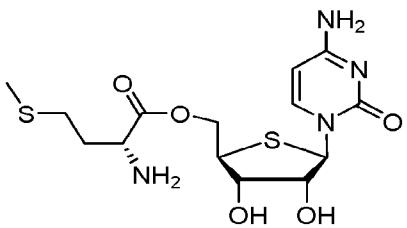
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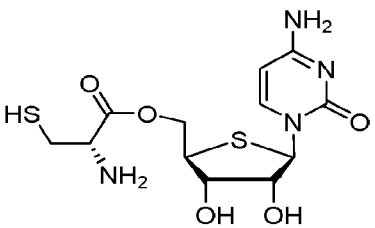
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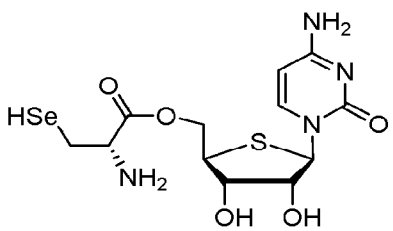
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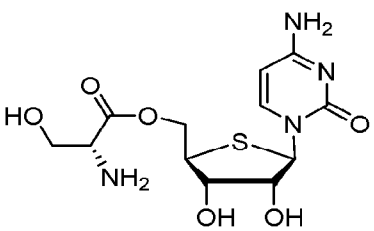
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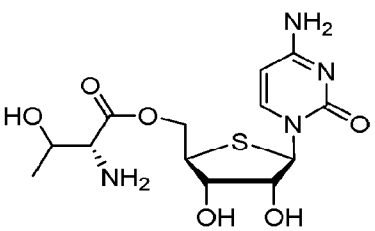
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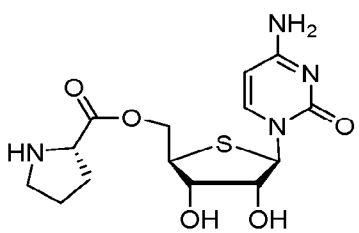
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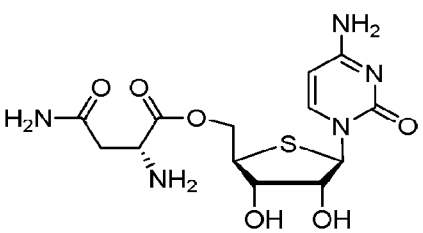
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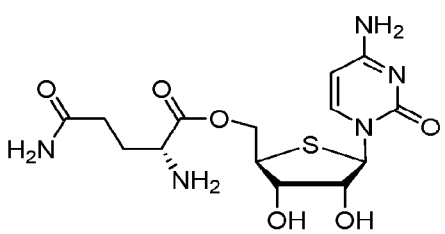
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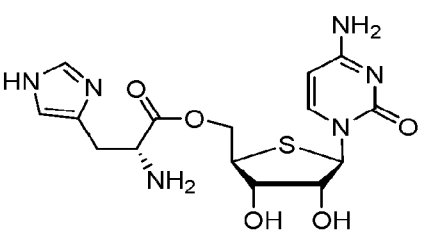
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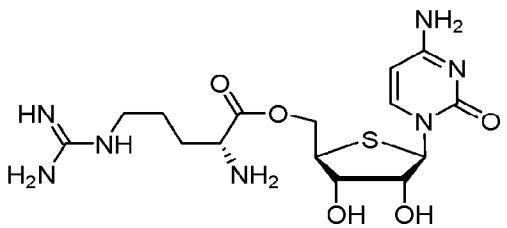
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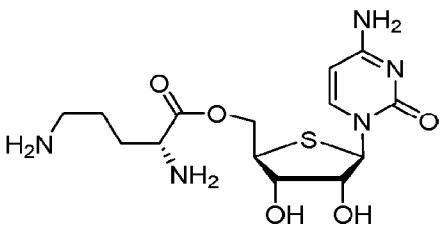
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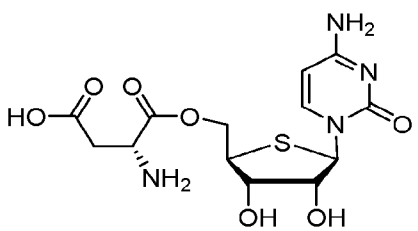
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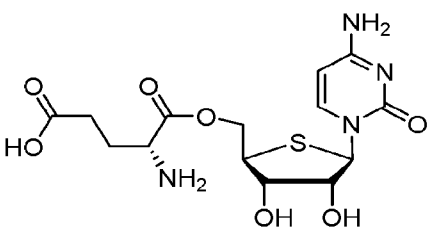
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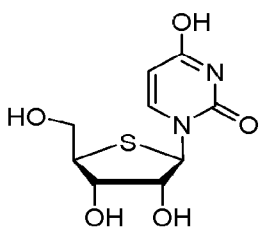
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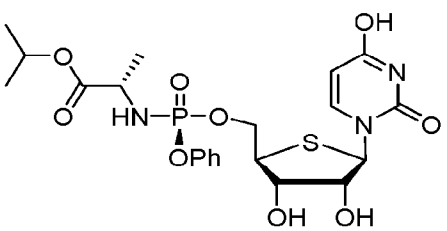
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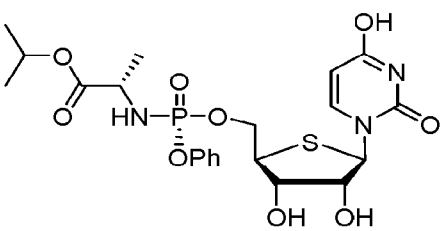
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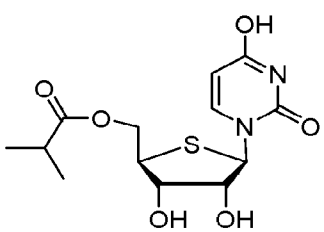
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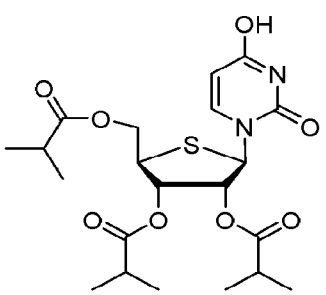
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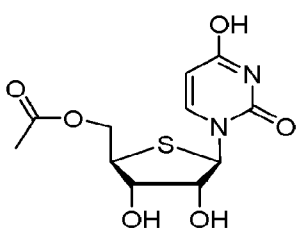
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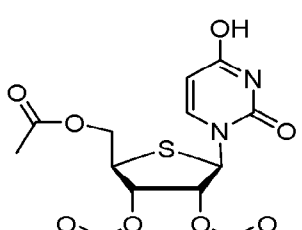
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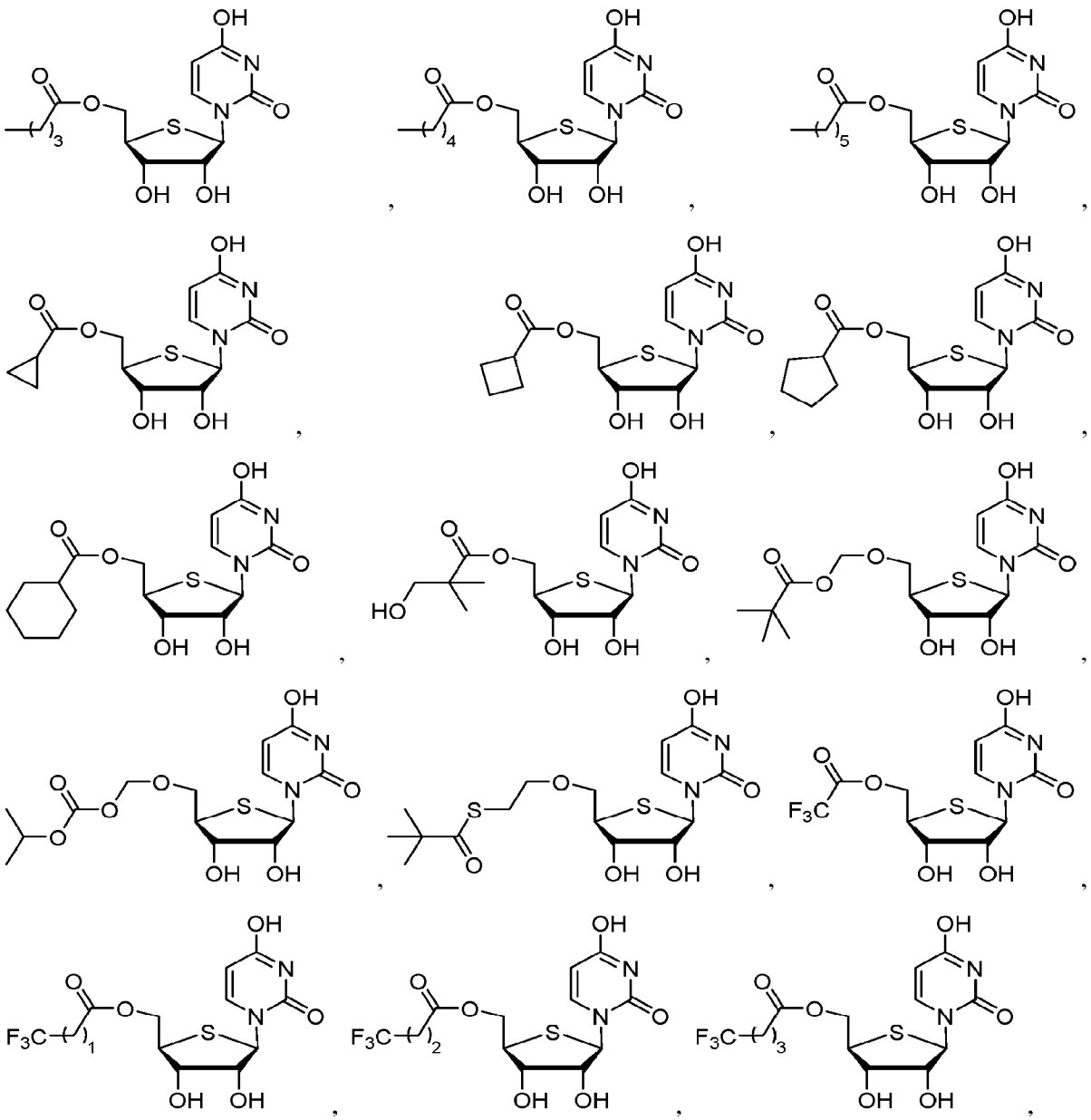

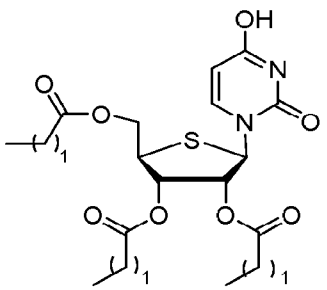
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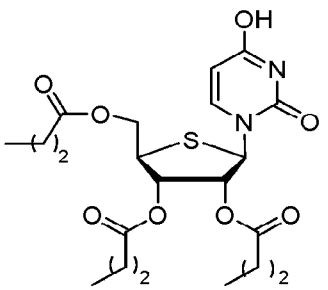
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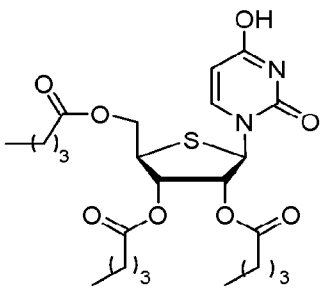
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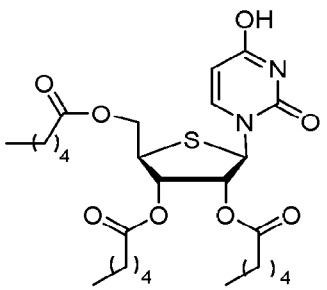
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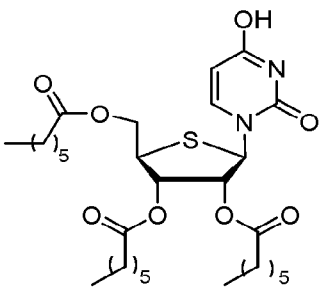
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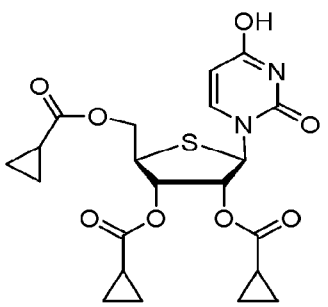
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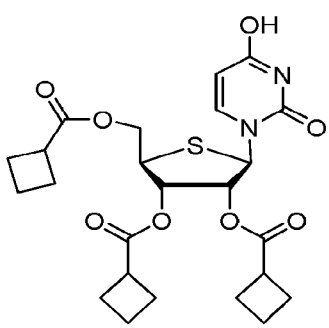
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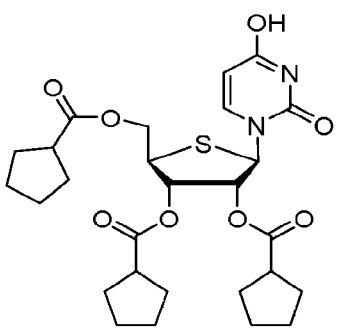
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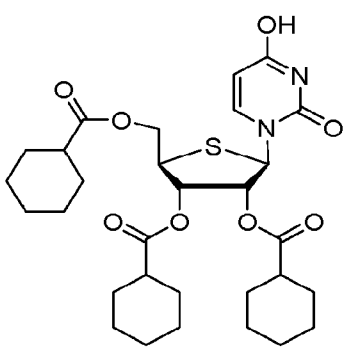
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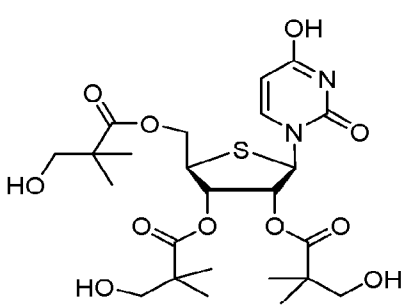
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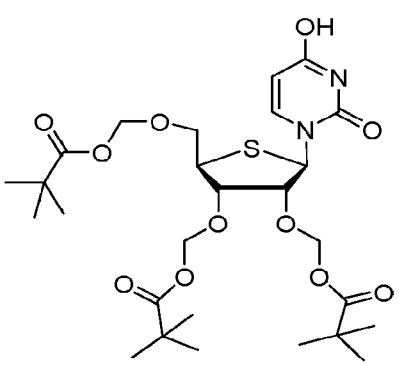
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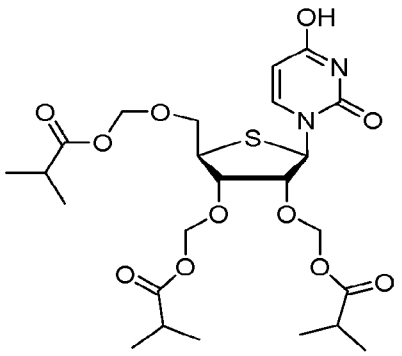
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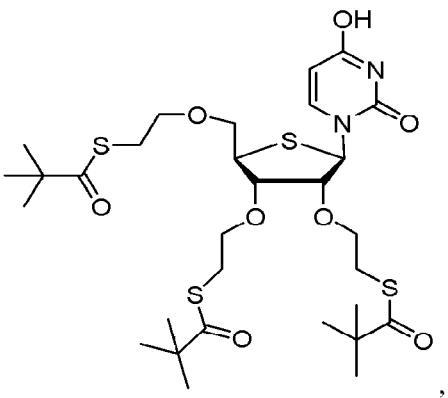
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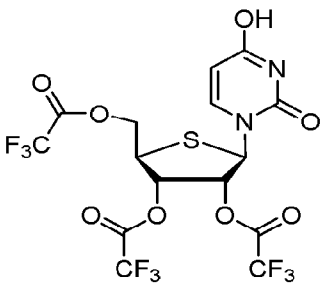
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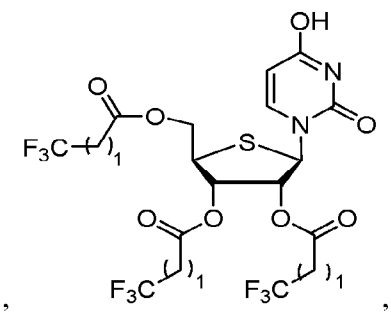
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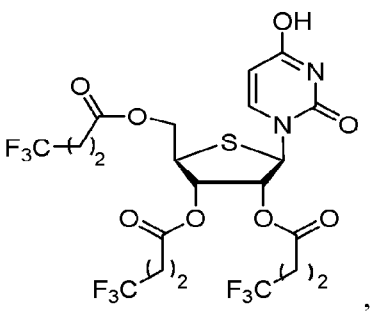
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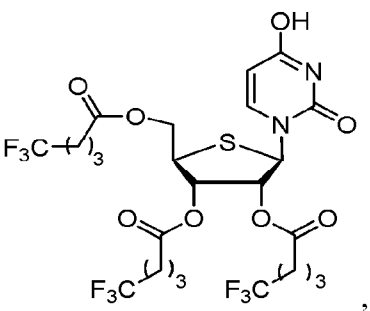
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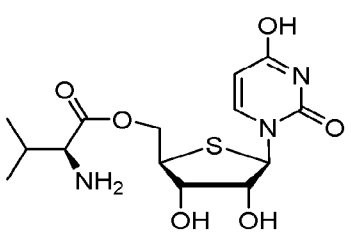
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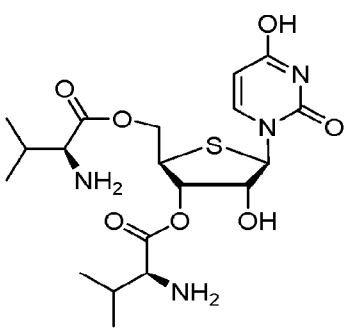
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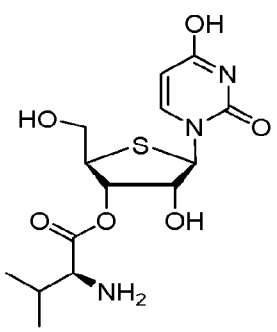
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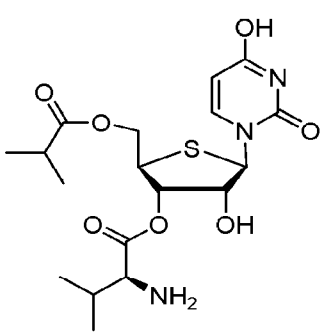
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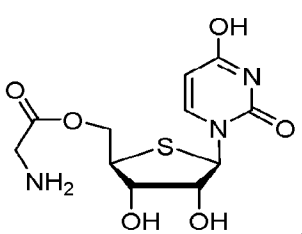
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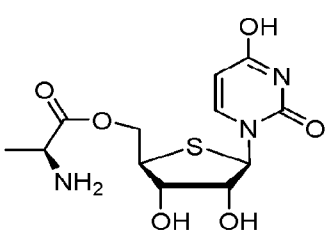
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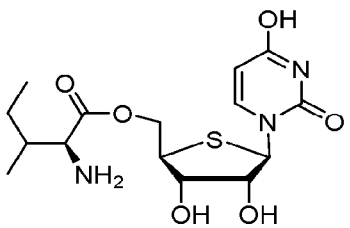
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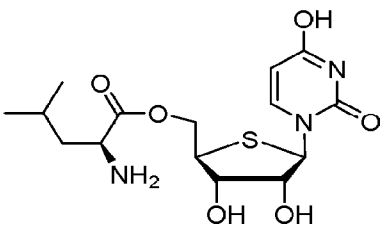
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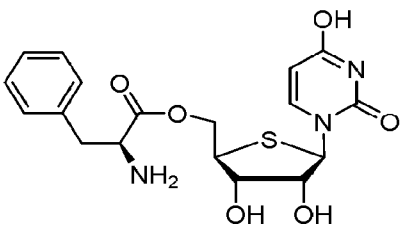
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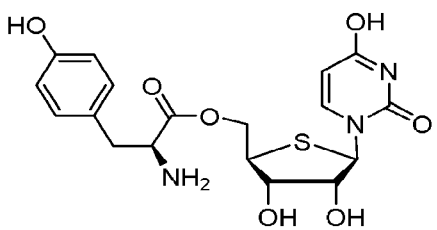
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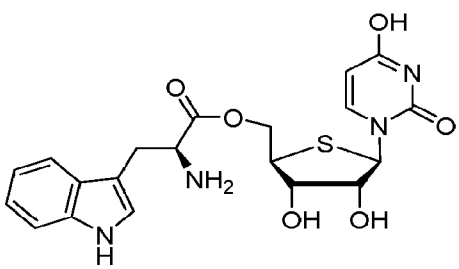
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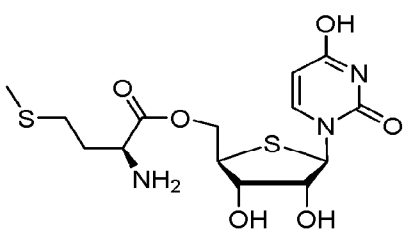
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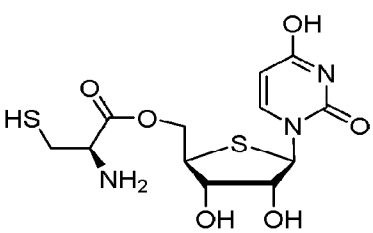
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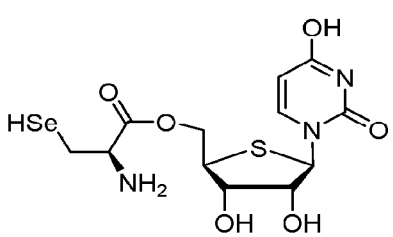
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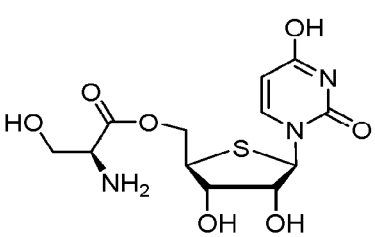
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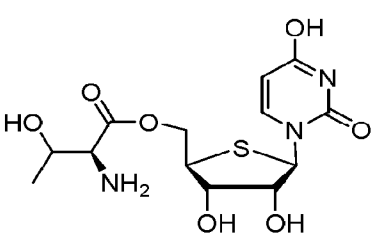
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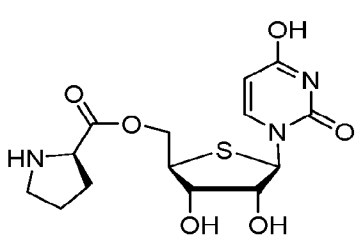
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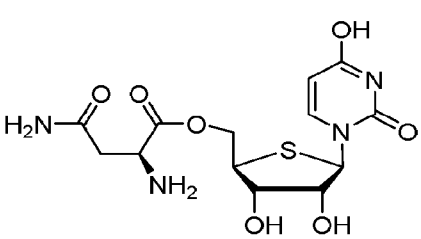
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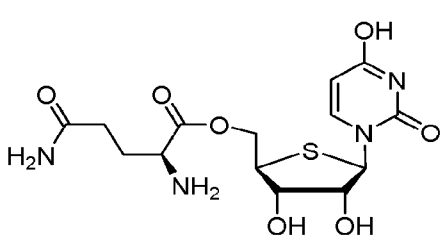
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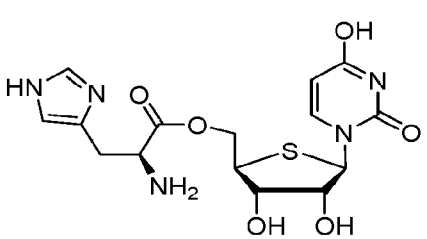
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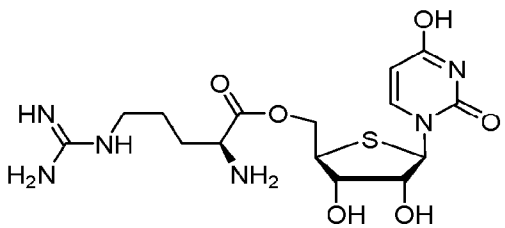
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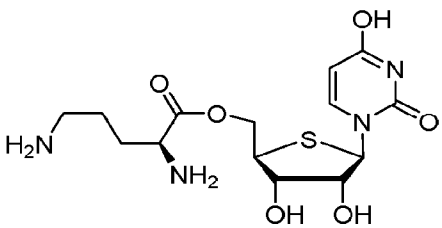
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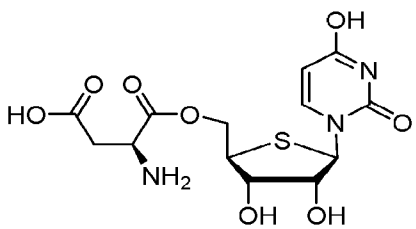
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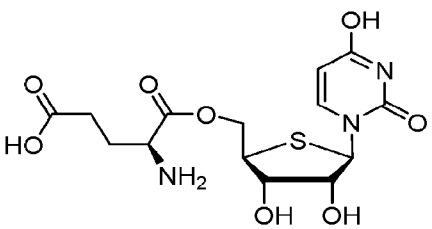
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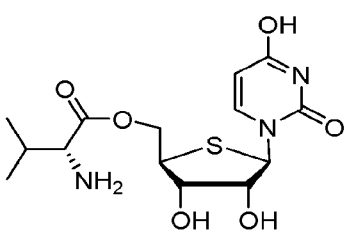
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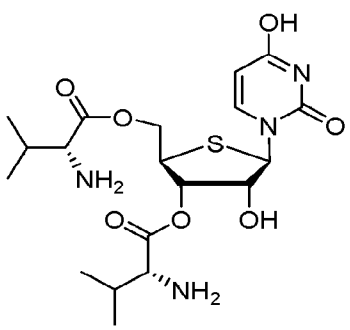
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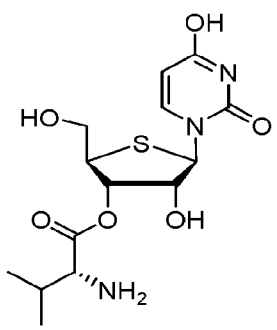
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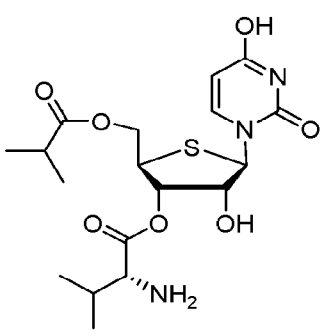
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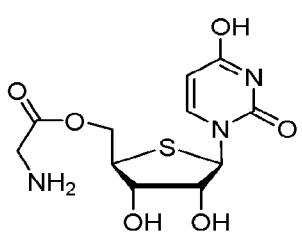
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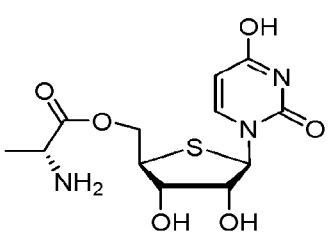
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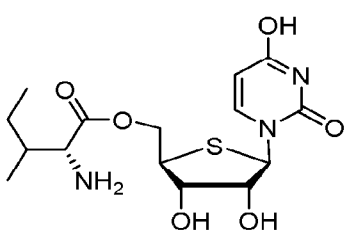
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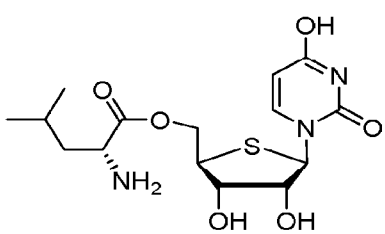
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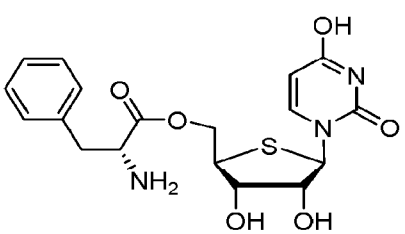
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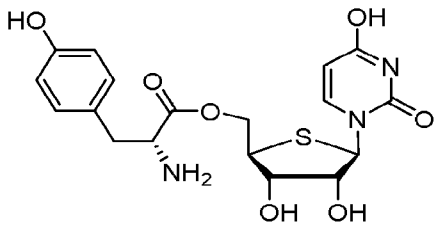
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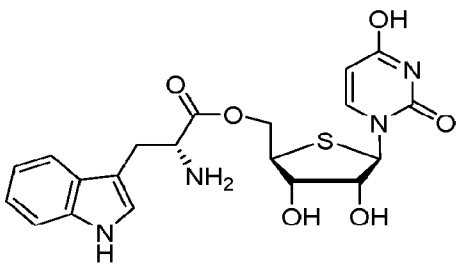
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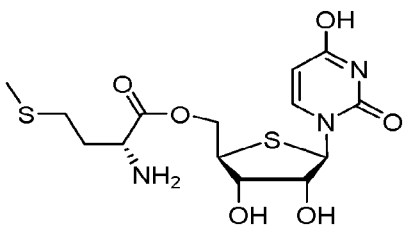
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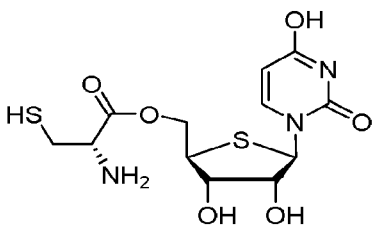
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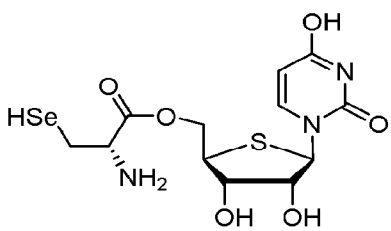
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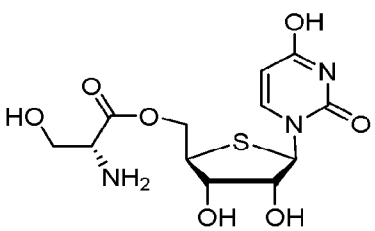
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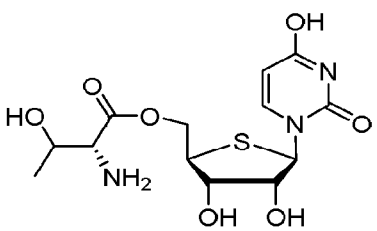
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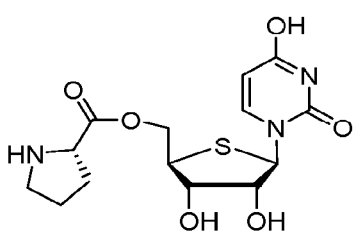
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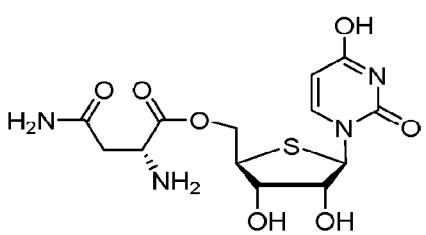
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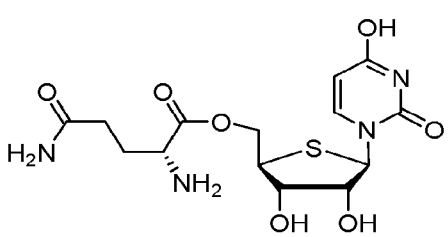
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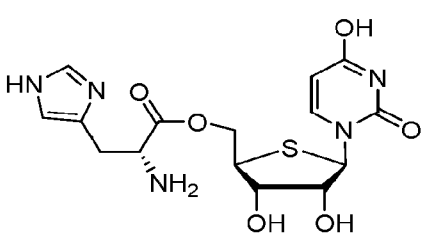
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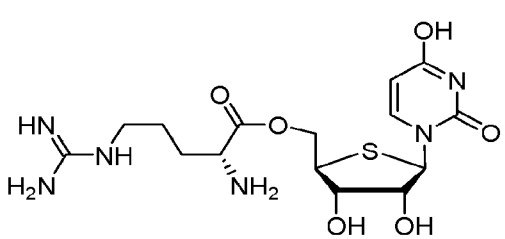
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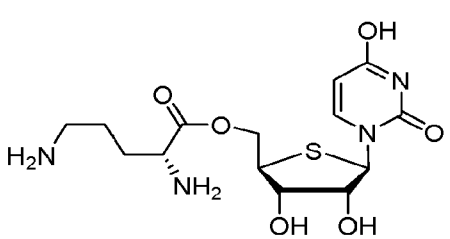
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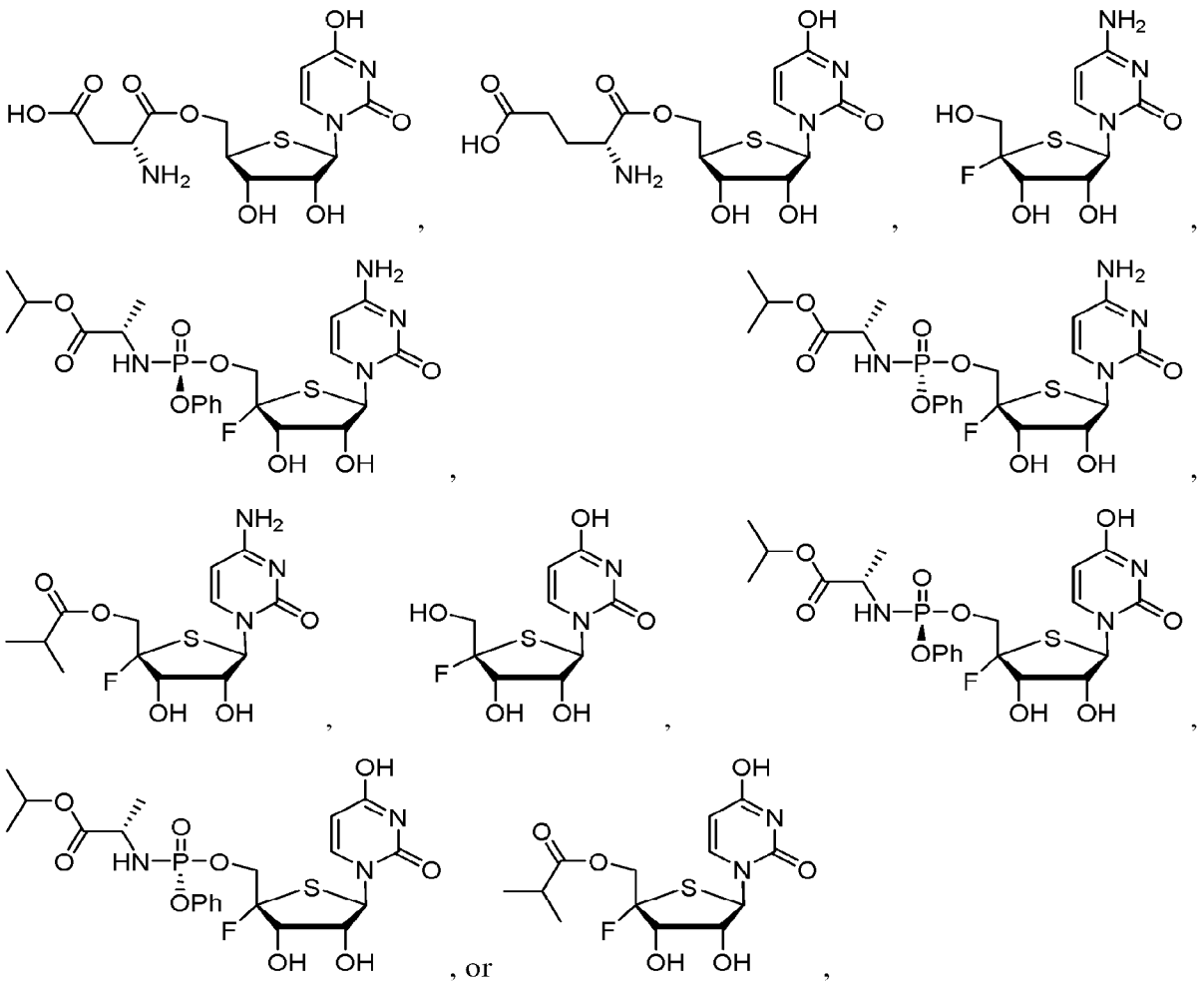
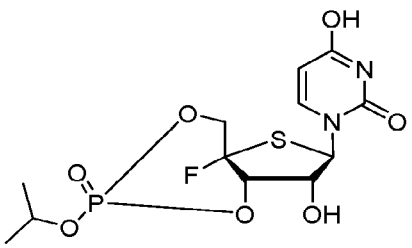


or a pharmaceutically acceptable salt or prodrug thereof.

Representative compounds of Formula B include the following:



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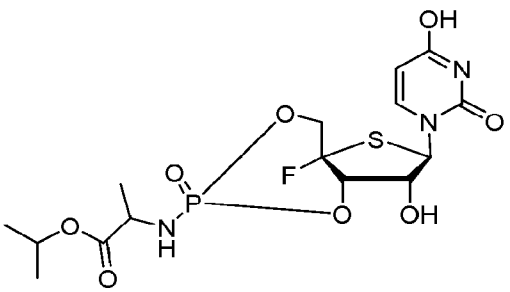

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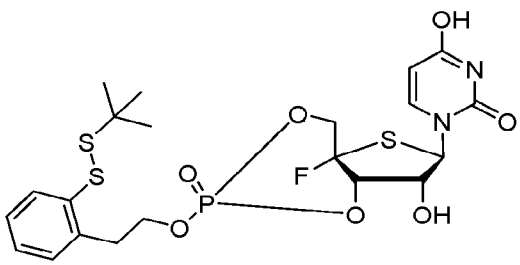

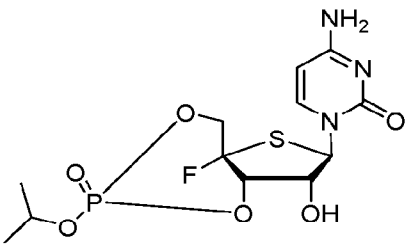

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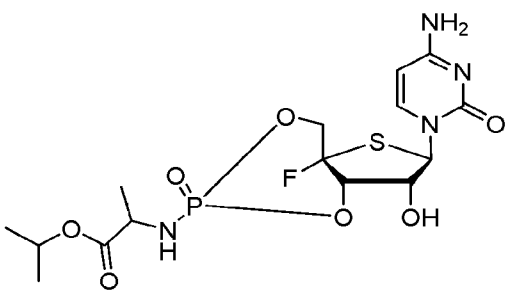

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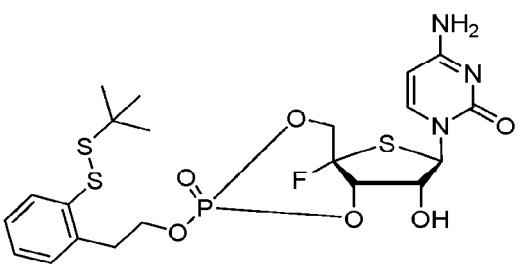

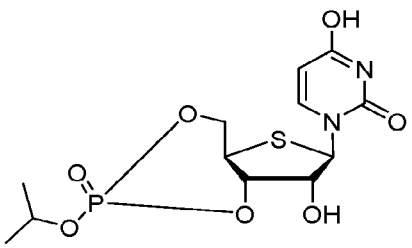
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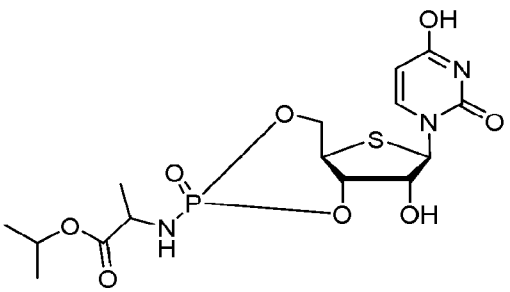
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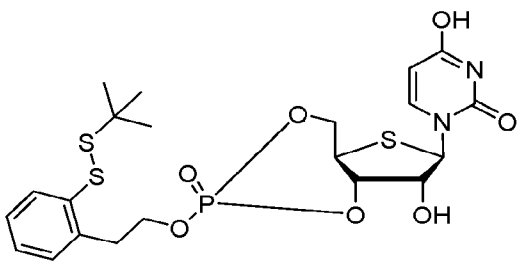
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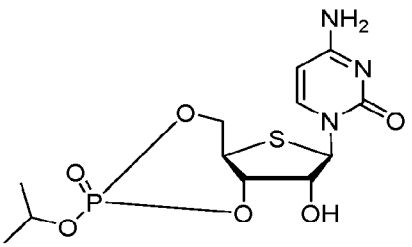
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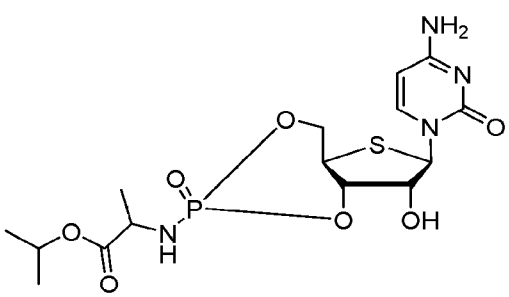
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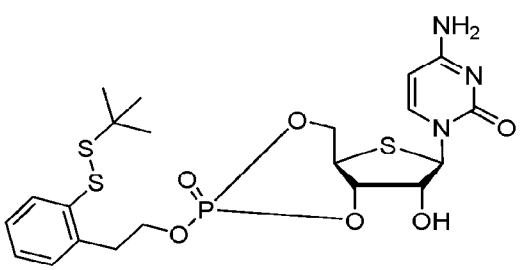
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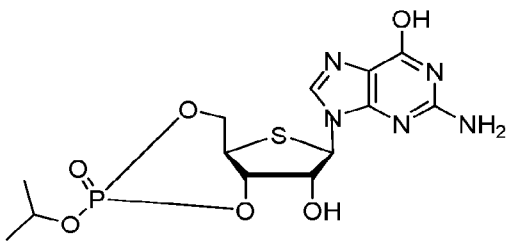
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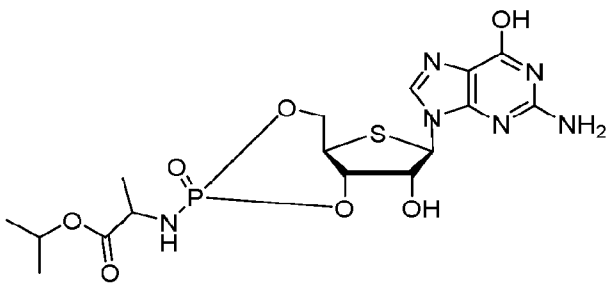
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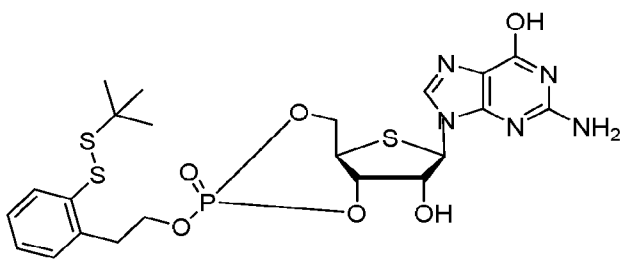
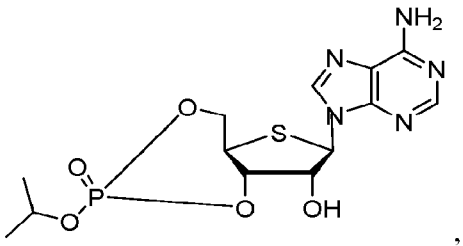
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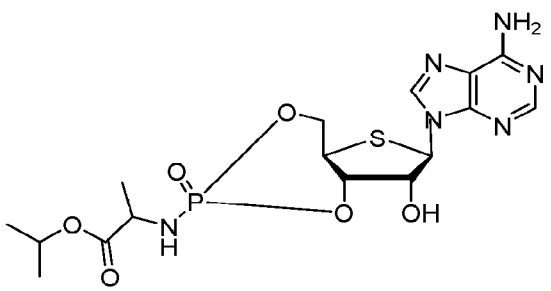
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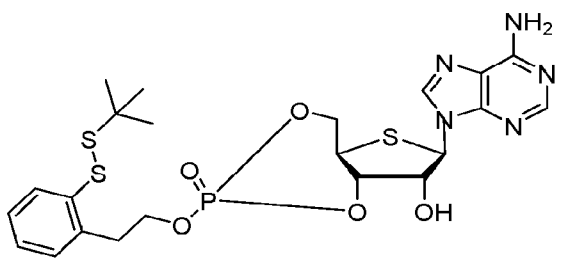
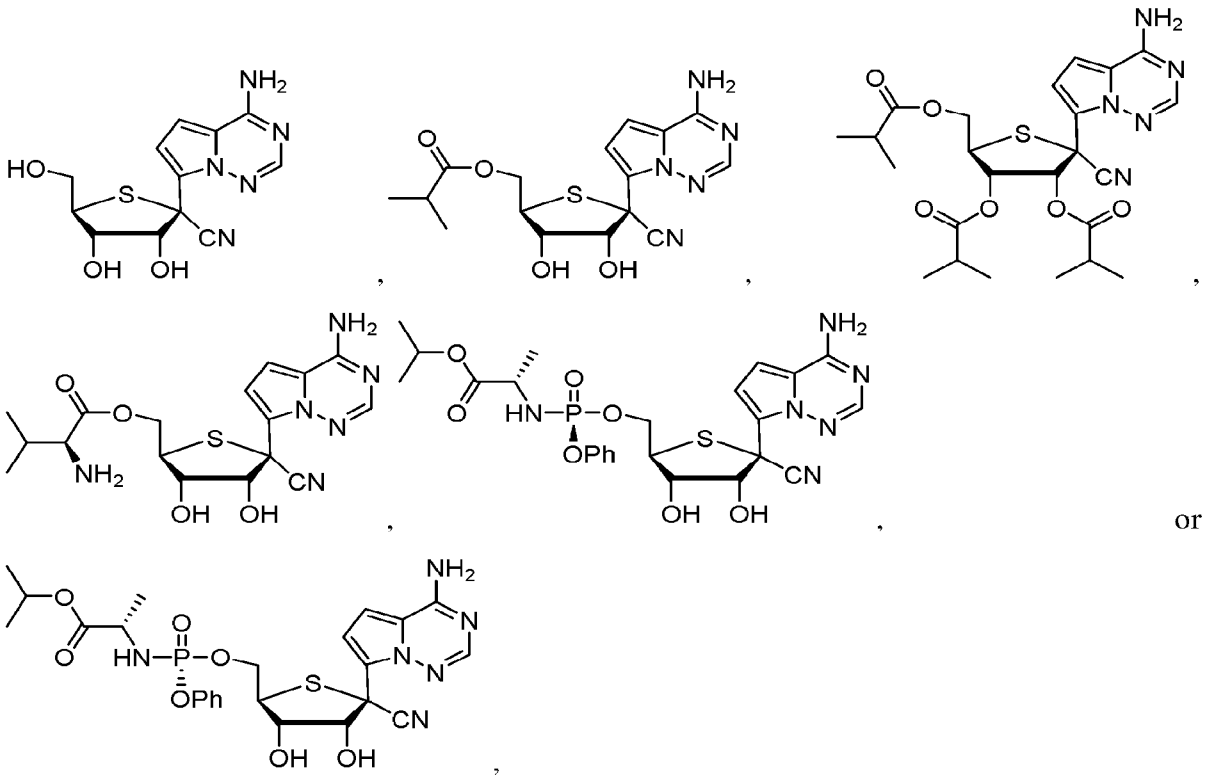


or a pharmaceutically acceptable salt or prodrug thereof.

Representative compounds of Formula D include the following:



or a pharmaceutically acceptable salt or prodrug thereof.

In any of these embodiments, the compounds can be present in the β-D or β-L configuration.

III Stereoisomerism and Polymorphism

The compounds described herein can have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers or enantiomers, with all isomeric forms being included in the present disclosure. Compounds described herein having a chiral center can exist in and be isolated in optically active and racemic forms. Some compounds can exhibit polymorphism. The present disclosure encompasses racemic, optically-active, polymorphic, or stereoisomeric forms, or mixtures thereof, of a compound described herein, which possess the useful properties described herein. The optically active forms can be prepared by, for example, 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 or by enzymatic resolution. One can either purify the respective compound, then derivatize the compound to form the compounds described herein, or purify the compound themselves.

Optically active forms of the compounds can be prepared using any method known in the art, including but not limited to 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.

Examples of methods to obtain optically active materials 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 can 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 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 (including but not limited to via chiral HPLC). 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 but not limited to simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

IV. Salt or Prodrug Formulations

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate and α-glycerophosphate. Suitable inorganic salts can also be formed, including but not limited to, sulfate, nitrate, bicarbonate and carbonate salts. For certain transdermal applications, it can be preferred to use fatty acid salts of the compounds described herein. The fatty acid salts can help penetrate the stratum corneum. Examples of suitable salts include salts of the compounds with stearic acid, oleic acid, lineoleic acid, palmitic acid, caprylic acid, and capric acid.

Pharmaceutically acceptable salts can be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid, affording a physiologically acceptable anion. In those cases where a compound includes multiple amine groups, the salts can be formed with any number of the amine groups. Alkali metal (e.g., sodium, potassium or lithium) or alkaline earth metal (e.g., calcium) salts of carboxylic acids can also be made.

A prodrug is a pharmacological substance that is administered in an inactive (or significantly less active) form and subsequently metabolized in vivo to an active metabolite. Getting more drug to the desired target at a lower dose is often the rationale behind the use of a prodrug and is generally attributed to better absorption, distribution, metabolism, and/or excretion (ADME) properties. Prodrugs are usually designed to improve oral bioavailability, with poor absorption from the gastrointestinal tract usually being the limiting factor. Additionally, the use of a prodrug strategy can increase the selectivity of the drug for its intended target thus reducing the potential for off target effects.

V. Methods of Treatment

In one embodiment, the compounds described herein can be used to prevent, treat or cure coronavirus infections, specifically including SARS-CoV2 infections, such as SARS-CoV-2, MERS, SARS, and OC-43. In other embodiments, the compounds described herein can be used to prevent, treat or cure infections by Flaviviruses, Picornaviridae, Togavirodae and Bunyaviridae.

The methods involve administering a therapeutically or prophylactically-effective amount of at least one compound as described herein to treat, cure or prevent an infection by, or an amount sufficient to reduce the biological activity of, a coronavirus infection, or a Flavivirus, Picornavus, Togavirus, or Bunyavirus infection.

In another embodiment, the compounds described herein can be used to inhibit a coronoviral, flaviviral, picornaviral, togaviral, or bunyaviral protease in a cell. The method includes contacting the cell with an effective amount of a compound described herein,

Hosts, including but not limited to humans infected with a coronavirus, flavivirus, picornavirus, togavirus, or bunyavirus, or a gene fragment thereof, can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, transdermally, subcutaneously, or topically, in liquid or solid form.

There are several species within the Coronavirus genus including, but not limited to, Middle East respiratory syndrome coronavirus (MERS-CoV), SARS coronavirus (SARS-CoV) and SARS-Cov2. In some embodiments, a compound described herein can ameliorate and/or treat a MERS-CoV infection, SARS-CoV infection, or SARS-Cov2 infection. An effective amount of a compound described herein can be administered to a subject infected with these viruses, and/or by contacting a cell infected with these viruses with an effective amount of a compound described herein. In some embodiments, a compound described herein can inhibit replication of these viruses. In some embodiments, a compound described herein can ameliorate one or more symptoms of these infections. Symptoms include, but are not limited to, extreme fatigue, malaise, headache, high fever (e.g., >100.4° F.), lethargy, confusion, rash, loss of appetite, myalgia, chills, diarrhea, dry cough, runny nose, sore throat, shortness of breath, breathing problems, gradual fall in blood-oxygen levels (such as, hypoxia) and pneumonia.

Some embodiments disclosed herein relate to a method of treating and/or ameliorating an infection caused by a Togaviridae virus that can include administering to a subject an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes a compound described herein. Some embodiments described herein relate to using one or more compounds described herein in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Togaviridae virus that can include administering to a subject an effective amount of one or more compounds described herein.

Some embodiments disclosed herein relate to methods of ameliorating and/or treating an infection caused by a Togaviridae virus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein. Other embodiments described herein relate to using one or more compounds described herein in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Togaviridae virus that can include contacting a cell infected with the virus with an effective amount of said compound(s).

In some embodiments, the Togaviridae virus can be an Alphavirus. One species of an Alphavirus is a Venezuelan equine encephalitis virus (VEEV). In some embodiments, a compound described herein can ameliorate and/or treat a VEEV infection. In other embodiments, one or more compounds described herein, can be manufactured into a medicament for ameliorating and/or treating an infection caused by a VEEV that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein, can be used for ameliorating and/or treating an infection caused by a VEEV that can include contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiment, the VEEV can be an epizootic subtype. In some embodiment, the VEEV can be an enzootic subtype. As described herein, the Venezuelan equine encephalitis complex of viruses includes multiple subtypes that are further divided by antigenic variants. In some embodiments, a compound described herein can be effective against more than one subtype of a VEEV, such as 2, 3, 4, 5 or 6 subtypes. In some embodiments, a compound can be used to treat, ameliorate and/or prevent VEEV subtype I. In some embodiments, a compound described herein can be effective against more than one antigenic variants of a VEEV. In some embodiments, a compound can

ameliorate one or more symptoms of a VEEV infection. Examples of symptoms manifested by a subject infected with VEEV include flu-like symptoms, such as high fever, headache, myalgia, fatigue, vomiting, nausea, diarrhea, and pharyngitis. Subjects with encephalitis show one or more of the following symptoms: somnolence, convulsions, confusion, photophobia, coma and bleeding of the brain, lung(s) and/or gastrointestinal tract. In some embodiments, the subject can be human. In other embodiments, the subject can be a horse.

Chikungunya (CHIKV) is another Alphavirus species. In some embodiments, a compound described herein can ameliorate and/or treat a CHIKV infection. In other embodiments, one or more compounds described herein can be manufactured into a medicament for ameliorating and/or treating an infection caused by a CHIKV that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein, can be used for ameliorating and/or treating an infection caused by a CHIKV that can include contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, one or more symptoms of a CHIKV infection can be ameliorated by administering an effective amount of a compound to a subject infected with CHIKV and/or by contacting an CHIKV infected cell with an effective amount of a compound described herein. Clinical symptoms of a CHIKV infection include fever, rash (such as petechial and/or maculopapular rash), muscle pain, joint pain, fatigue, headache, nausea, vomiting, conjunctivitis, loss of taste, photophobia, insomnia, incapacitating joint pain and arthritis.

Other species of Alphaviruses include Barmah Forest virus, Mayaro virus (MAYV), O'nyong'nyong virus, Ross River virus (RRV), Semliki Forest virus, Sindbis virus (SINV), Una virus, Eastern equine encephalitis virus (EEE) and Western equine encephalomyelitis (WEE). In some embodiments, one or more compounds described herein, can be used for ameliorating and/or treating an infection caused by an Alphavirus that can include contacting a cell infected with the virus with an effective amount of one or more of said compound(s) and/or administering to a subject (such as, a subject infected with the virus) an effective amount of one or more of said compound(s), wherein the Alphavirus can be selected from Barmah Forest virus, Mayaro virus (MAYV), O'nyong'nyong virus, Ross River virus (RRV), Semliki Forest virus, Sindbis virus (SINV), Una virus, Eastern equine encephalitis virus (EEE) and Western equine encephalomyelitis (WEE).

Another genus of a Coronaviridae virus is a Rubivirus. Some embodiments disclosed herein relate to methods of ameliorating and/or treating an infection caused by a Rubivirus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein. Other embodiments described herein relate to using one or more compounds described herein, in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Rubivirus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, that can be used for ameliorating and/or treating an infection caused by a Rubivirus by contacting a cell infected with the virus with an effective amount of said compound(s).

Some embodiments disclosed herein relate to a method of treating and/or ameliorating an infection caused by a Bunyaviridae virus that can include administering to a subject an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes a compound described herein. Other embodiments disclosed herein relate to a method of treating and/or ameliorating an infection caused by a Bunyaviridae virus that can include administering to a subject identified as suffering from the viral infection an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes a compound described herein.

Some embodiments disclosed herein relate to methods of ameliorating and/or treating an infection caused by a Bunyaviridae virus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein. Other embodiments described herein relate to using one or more compounds described herein, in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Bunyaviridae virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, that can be used for ameliorating and/or treating an infection caused by a Bunyaviridae virus by contacting a cell infected with the virus with an effective amount of said compound(s).

Some embodiments disclosed herein relate to methods of inhibiting replication of a Bunyaviridae virus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein. Other embodiments described herein relate to using one or more compounds described herein, in the manufacture of a medicament for inhibiting replication of a Bunyaviridae virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to a compound described herein, that can be used for inhibiting replication of a Bunyaviridae virus by contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, a compound described herein can inhibit a RNA dependent RNA polymerase of a Bunyaviridae virus, and thereby, inhibit the replication of RNA. In some embodiments, a polymerase of a Bunyaviridae virus can be inhibited by contacting a cell infected with the Bunyaviridae virus with a compound described herein.

In some embodiments, the Bunyaviridae virus can be a Bunyavirus. In other embodiments, the Bunyaviridae virus can be a Hantavirus. In still other embodiments, the Bunyaviridae virus can be a Nairovirus. In yet still other embodiments, the Bunyaviridae virus can be a Phlebovirus. In some embodiments, the Bunyaviridae virus can be an Orthobunyavirus. In other embodiments, the Bunyaviridae virus can be a Tospovirus.

A species of the Phlebovirus genus is Rift Valley Fever virus. In some embodiments, a compound described herein can ameliorate and/or treat a Rift Valley Fever virus infection. In other embodiments, one or more compounds described herein, can be manufactured into a medicament for ameliorating and/or treating an infection caused by a Rift Valley Fever virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein can be used for ameliorating and/or treating an infection caused by a Rift Valley Fever virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, a compound described herein can inhibit replication of Rift Valley Fever virus, wherein said compound is administering to a subject infected with Rift Valley Fever virus and/or wherein said compound contacts a cell infected with Rift Valley Fever.

In some embodiments, a compound described herein can ameliorate, treat, and/or inhibit replication of one or more of the ocular form, the meningoencephalitis form, or the hemorrhagic

fever form of Rift Valley Fever virus. In some embodiments, one or more symptoms of a Rift Valley Fever virus infection can be ameliorated. Examples of symptoms of a Rift Valley Fever viral infection include headache, muscle pain, joint pain, neck stiffness, sensitivity to light, loss of appetite, vomiting, myalgia, fever, fatigue, back pain, dizziness, weight loss, ocular form symptoms (for example, retinal lesions, blurred vision, decreased vision and/or permanent loss of vision), meningoencephalitis form symptoms (such as, intense headache, loss of memory, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma) and hemorrhagic fever form symptoms (for example, jaundice, vomiting blood, passing blood in the feces, a purpuric rash, ecchymoses, bleeding from the nose and/or gums, menorrhagia and bleeding from a venepuncture site).

Another species of the Phlebovirus genus is thrombocytopenia syndrome virus. In some embodiments, a compound described herein can ameliorate, treat, and/or inhibit replication thrombocytopenia syndrome virus. In some embodiments, a compound can ameliorate and/or treat severe fever with thrombocytopenia syndrome (SFTS). In some embodiments, a compound described herein can ameliorate one or more symptoms of SFTS. Clinical symptoms of include the following: fever, vomiting, diarrhea, multiple organ failure, thrombocytopenia, leucopenia, and elevated liver enzyme levels.

Crimean-Congo hemorrhagic fever virus (CCHF) is a species within the Nairovirus genus. In some embodiments, a compound described herein can ameliorate, treat, and/or inhibit replication of Crimean-Congo hemorrhagic fever virus. Subjects infected with CCHF have one or more of the following symptoms: flu-like symptoms (such as high fever, headache, myalgia, fatigue, vomiting, nausea, diarrhea, and/or pharyngitis), hemorrhage, mood instability, agitation, mental confusion, throat petechiae, nosebleeds, bloody urine, vomiting, black stools, swollen and/or painful liver, disseminated intravascular coagulation, acute kidney failure, shock and acute respiratory distress syndrome. In some embodiments, a compound described herein can ameliorate one or more symptoms of CCHF.

California encephalitis virus is another virus of the Bunyaviridae family, and is a member of the Orthobunavirus genus. Symptoms of a California encephalitis virus infection include, but are not limited to fever, chills, nausea, vomiting, headache, abdominal pain, lethargy, focal neurologic findings, focal motor abnormalities, paralysis, drowsiness, lack of mental alertness and orientation and seizures. In some embodiments, a compound described

herein can ameliorate, treat, and/or inhibit replication of California encephalitis virus. In some embodiments, a compound described herein can ameliorate one or more symptoms of a California encephalitis viral infection.

Viruses within the Hantavirus genus can cause hantavirus hemorrhagic fever with renal syndrome (HFRS) (caused by viruses such as Hantaan River virus, Dobrava-Belgrade virus, Saaremaa virus, Seoul virus, and Puumala virus) and hantavirus pulmonary syndrome (HPS). Viruses that can cause HPS include, but are not limited to, Black Creek Canal virus (BCCV), New York virus (NYV), Sin Nombre virus (SNV). In some embodiments, a compound described herein can ameliorate and/or treat HFRS or HPS. Clinical symptoms of HFRS include redness of cheeks and/or nose, fever, chills, sweaty palms, diarrhea, malaise, headaches, nausea, abdominal and back pain, respiratory problems, gastro-intestinal problems, tachycardia, hypoxemia, renal failure, proteinuria and diuresis. Clinical symptoms of HPS include flu-like symptoms (for example, cough, myalgia, headache, lethargy and shortness-of-breath that can deteriorate into acute respiratory failure). In some embodiments, a compound described herein can ameliorate one or more symptoms of HFRS or HPS.

Various indicators for determining the effectiveness of a method for treating and/or ameliorating a Coronaviridae, a Togaviridae, a Hepeviridae and/or a Bunyaviridae viral infection are known to those skilled in the art. Example of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), a reduction of morbidity or mortality in clinical outcomes, and/or other indicator(s) of disease response. Further indicators include one or more overall quality of life health indicators, such as reduced illness duration, reduced illness severity, reduced time to return to normal health and normal activity, and reduced time to alleviation of one or more symptoms. In some embodiments, a compound described herein can result in the reduction, alleviation or positive indication of one or more of the aforementioned indicators compared to a subject who is untreated subject.

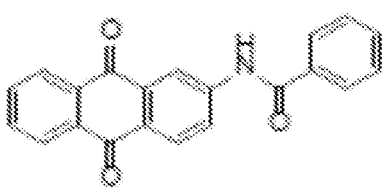
VI. Combination or Alternation Therapy

In one embodiment, the compounds described herein can be employed together with at least one other active agent, which can be an antiviral agent. In one aspect of this embodiment, the at least one other active agent is selected from the group consisting of fusion

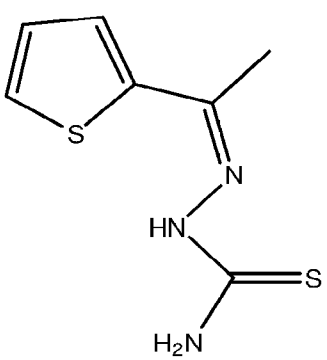
inhibitors, entry inhibitors, protease inhibitors such as PF-07304814 (Pfizer) or PF-07321332 (Pfizer), optionally co-administered with a relatively low dose of ritonavir, polymerase inhibitors, antiviral nucleosides, such as remdesivir, GS-441524, AT-527 (ATEA), N4-hydroxycytidine, Molnupiravir (an N4-hydroxycytidine prodrug), and other compounds disclosed in U.S. Patent No. 9,809,616, and their prodrugs, 4'-fluorourine and prodrugs thereof, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

Umifenovir (also known as Arbidol) is a representative fusion inhibitor.

Representative entry inhibitors include Camostat, luteolin, MDL28170, SSAA09E2, SSAA09E1 (which acts as a cathepsin L inhibitor), SSAA09E3, and tetra-O-galloyl-β-D-glucose (TGG). The chemical formulae of certain of these compounds are provided below:



SSAA09E3



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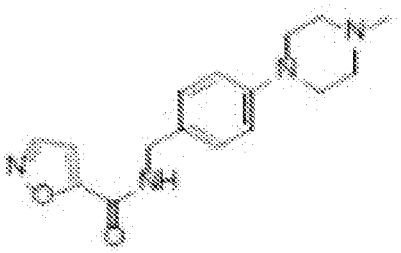
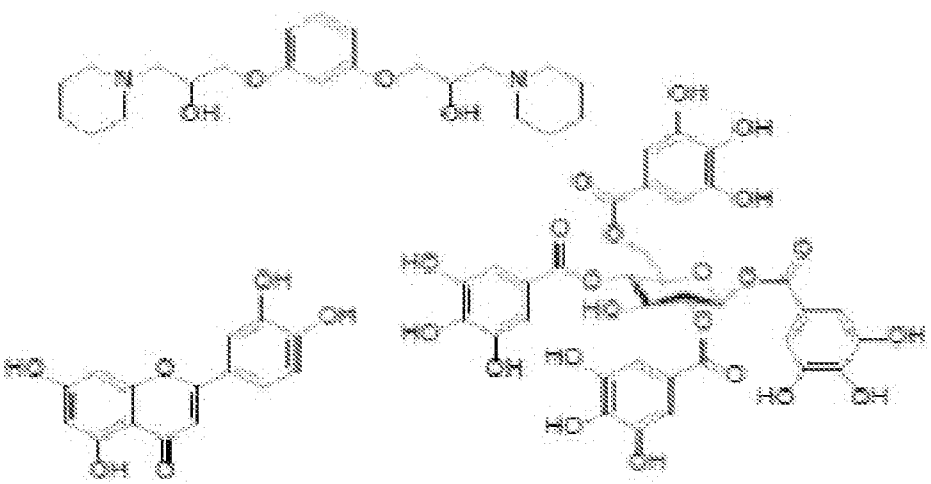
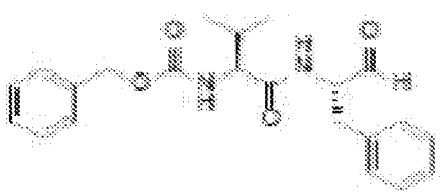


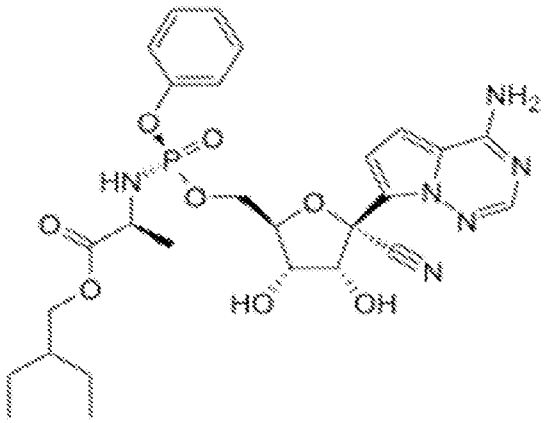
SSAA09E2

Other entry inhibitors include the following:

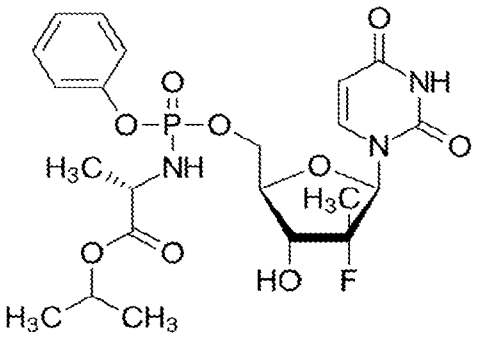




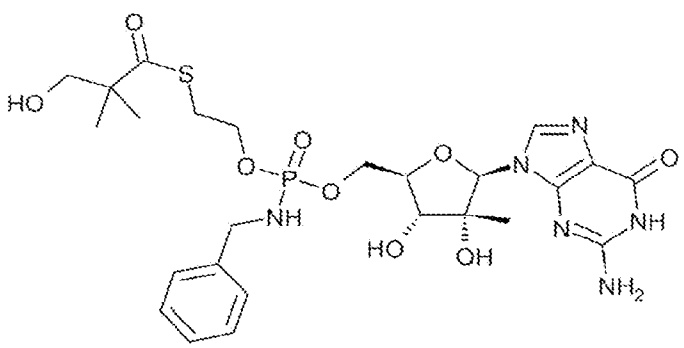
Remdesivir, Sofosbuvir, ribavirin, IDX-184 and GS-441524 have the following formulas:



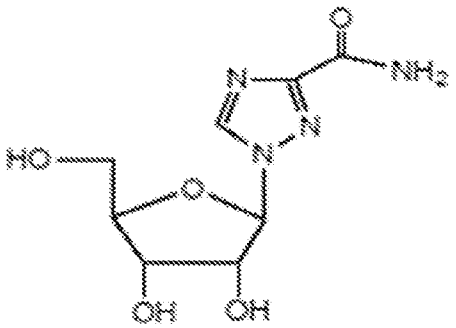
Remdesivir



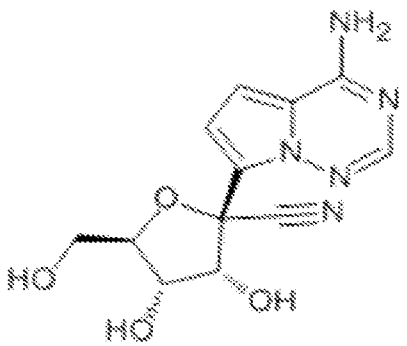
Sofosbuvir



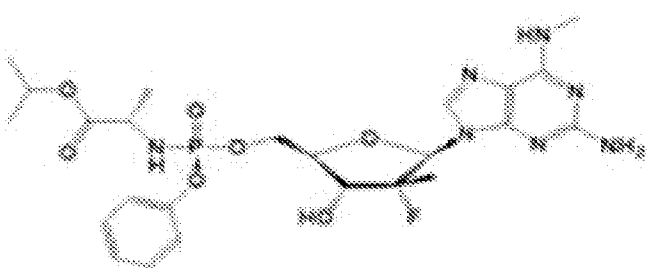
IDX-184



Ribavirin



GS-441524



AT-527

Additionally, one can administer compounds which inhibit the cytokine storm, anti-coagulants and/or platelet aggregation inhibitors that address blood clots, compounds which chelate iron ions released from hemoglobin by viruses such as COVID-19, cytochrome P-450 (CYP450) inhibitors and/or NOX inhibitors.

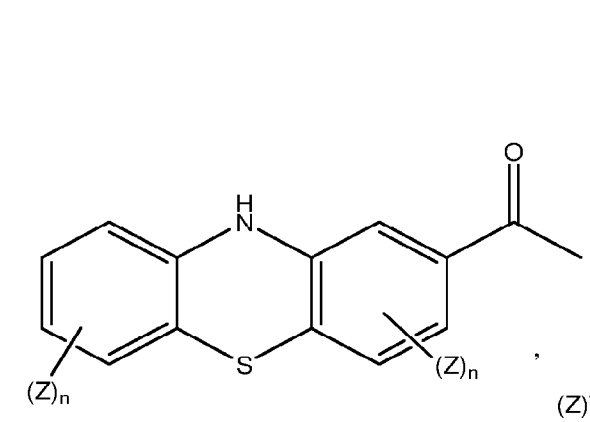
Representative NOX inhibitors are disclosed in PCT/US2018/067674, and include AEBSF, Apocyanin, DPI, GK-136901, ML171, Plumbagin, S17834, VAS2870, VAS3947, GKT-831, GKT771, GTL003 or amido thiadiazole derivatives thereof, as described in AU2015365465, EP20140198597; and WO2015/59659, Schisandrin B, as described in

CN104147001 and CN20131179455), bi-aromatic and tri-aromatic compounds described in U.S. Publication No. 2015045387, GB 20110016017, and WO201200725, methoxyflavone derivatives described in JP 2015227329, JP 20140097875, and JP 20150093939, peptides, such as NOX2ds-tat and PR-39, as described in U.S. Publication No. 2015368301, TN 2015000295, U.S. Publication No. 201514689803, U.S. Publication No. 201462013916, PCT WO 201450063, and EP 20130150187, piperazine derivatives described in U.S. Publication No. 2014194422, U.S. Patent No. 9428478, U.S. Publication No. 201214123877, U.S. Publication No. 201161496161, and PCT WO 2012US41988, pyrazole derivatives disclosed in KR101280198, KR20110025151, and KR20090082518, pyrazoline dione derivatives disclosed in HK1171748, PCT WO201054329, and EP 20090171466, pyrazolo piperidine derivatives disclosed in KR20130010109, KR20130002317, EP20100153927, PCT WO201150667, EP20100153929, and PCT WO2011IB50668, pyrazolo pyridine derivatives described in KR20170026643, HK1158948, HK1141734, HK1159096, HK1159092, EP20080164857, PCT WO200954156, PCT WO200954150, EP20080164853, PCT WO200853390, U.S. Publication No. 20070896284, EP20070109555, PCT WO 200954148, EP20080164847, PCT WO200954155, and EP20080164849, quinazoline and quinoline derivatives disclosed in EP2886120, U.S. Publication No. 2014018384, U.S. Publication No. 20100407925, EP20110836947, GB20110004600, and PCT WO 201250586, tetrahydroindole derivatives disclosed in U.S. Publication No. 2010120749, U.S. Patent No. 8,288,432, U.S. Publication No. 20080532567, EP20070109561, U.S. Publication No. 20070908414, and PCT WO 200853704, tetrahydroisoquinoline derivatives disclosed in U.S. Publication No. 2016083351, U.S. Publication No. 201414888390, U.S. Publication No. 201361818726, and PCT WO 201436402, Scopoletin, described in TW201325588 and TW20110147671, and 2,5-disubstituted benzoxazole and benzothiazole derivatives disclosed in TW201713650 and PCT WO 201554662. Representative NOX inhibitors also include those disclosed in PCT WO2011062864.

Exemplary Nox inhibitors also include 2-phenylbenzo[d]isothiazol-3(2H)-one, 2-(4-methoxyphenyl)benzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-fluorophenyl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)-5-fluorobenzo[d]isothiazol-3(2H)-one, 5-fluoro-2-(4-fluorophenyl)benzo[d]isothiazol-3(2H)-

one, 2-(2-chloro-6-methylphenyl)-5-fluorobenzo[d]isothiazol-3(2H)-one, 5-fluoro-2-phenylbenzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-5-fluorobenzo[d]isothiazol-3(2H)-one, methyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 4-(5-fluoro-3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, ethyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, tert-butyl 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 2-methoxy-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, methyl 3-chloro-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, 4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzonitrile, methyl 2-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzoate, 2-(4-acetylphenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-nitrophenyl)benzo[d]isothiazol-3(2H)-one, 2-(4-hydroxyphenyl)benzo[d]isothiazol-3(2H)-one, methyl 6-(3-oxobenzo[d]isothiazol-2(3H)-yl)nicotinate, 6-(3-oxobenzo[d]isothiazol-2(3H)-yl)nicotinonitrile, 2-(4-(hydroxymethyl)phenyl)benzo[d]isothiazol-3(2H)-one, 2-benzylbenzo[d]isothiazol-3(2H)-one, N-methyl-4-(3-oxobenzo[d]isothiazol-2(3H)-yl)benzamide, 2-(4-hydroxyphenyl)benzo[d]isothiazol-3(2H)-one, 2-(2,4-dimethylphenyl)-1-methyl-1H-indazol-3(2H)-one, 2-(4-fluorophenyl)- 1 -methyl- 1 H-indazol-3 (2H)-one, 2-(2,4-dimethylphenyl)-1H-indazol-3(2H)-one, 1 -methyl-2-phenyl- 1 H-indazol-3 (2H)-one, 2-(1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-phenyl-1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(ethylthio)-1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(methylthio)-1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 5-fluoro-2-(1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(tert-butyl)-1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)benzo[d]isothiazol-3(2H)-one 2-(4-methylthiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(4,5-dimethylthiazol-2-yl)benzo[d]isothiazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-4,5-difluorobenzo[d][1,2]selenazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-5-fluorobenzo[d][1,2]selenazol-3(2H)-one, 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-fluorobenzo[d][1,2]selenazol-3(2H)-2-(4-(1,3-dioxolan-2-yl)phenyl)benzo[d][1,2]selenazol-3(2H)-one, 2-(benzo[d][1,3]dioxol-5-yl)-6, 7-dimethoxybenzo[d][1,2]selenazol-3(2H)-one, methyl 4-(3-oxobenzo[d][1,2]selenazol-2(3H)-yl)benzoate, methyl 4-(3-oxoisothiazolo[5,4-b]pyridin-2(3H)-yl)benzoate, and ethyl 4-(3-oxoisothiazol-2(3H)-yl)benzoate, and pharmaceutically acceptable salts and prodrugs thereof.

Additional representative NOX inhibitors include:



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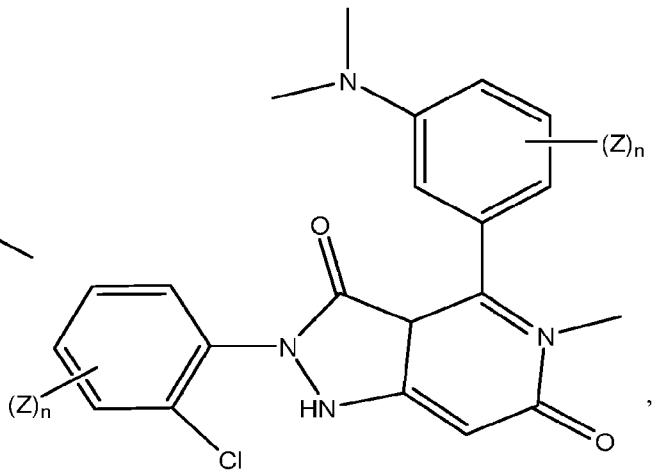

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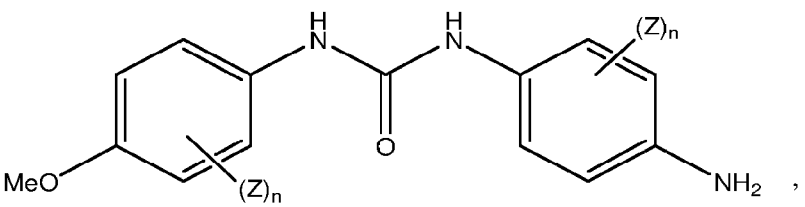

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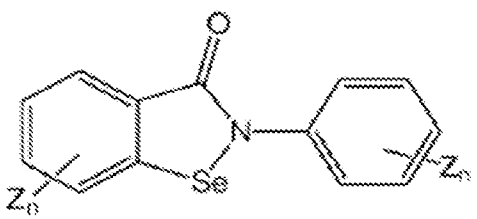
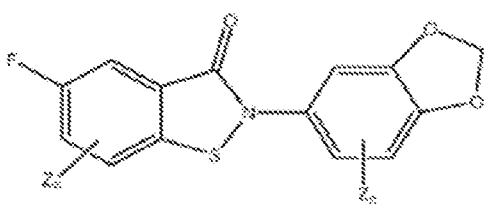
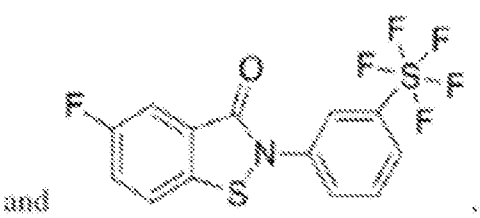
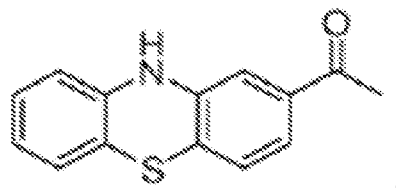






and .

Specific examples of these compounds include



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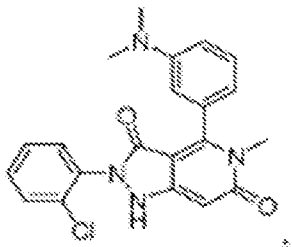

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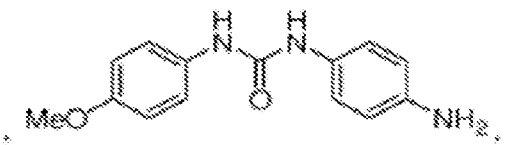

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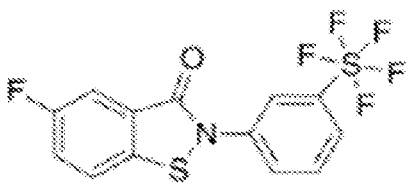

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deuterated analogs thereof, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the NOX inhibitor is Ebselen, Neopterin, APBA, Diapocynin, or a deuterated analog thereof, or a pharmaceutically-acceptable salt or prodrug thereof.

In another embodiment, the NOX compounds are those disclosed in PCT WO 2010/035221.

In still another embodiment, the compounds are NOX inhibitors disclosed in PCT WO 2013/068972, which are selected from the group consisting of:

4-(2-fluoro-4-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(4-chlorophenyl)-2-(2-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-[(l-methyl-lH-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-[(2-methoxypyridin-4-yl)methyl] -4-methyl-1H-pyrazo lo [4,3 -c] pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-methyl-5 -(pyridin-3-ylmethyl)-1H-pyrazo lo [4,3 -c]pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c] pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3 -ylmethyl)- 1 H-pyrazo lo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-[(6-methoxypyridin-3-yl)methyl]-4-methyl-1H-pyrazolo[4,3-c] pyridine-3,6 (2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3-ylmethyl)-1H-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(5-chloro-2-fluorophenyl)-2-(2-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-methyl-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6 (2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6 (2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazo lo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(3-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl)methyl]-1H-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-4-methoxyphenyl)-2-(2-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl)methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-[(1-methyl-1H-pyrazo-1-3-yl)methyl]-1H-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(3-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(4-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-[(2-methoxypyridin-4-yl)methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluoro-4-methoxyphenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,6-difluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-methyl-5-[(1-methyl-lH-pyrazol-3-yl)methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

4-(3-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-5-methyl-4-[3-(methylamino)phenyl]-1H-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2-fluorophenyl)-5-(pyridin-2-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,5-difluorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(4-chlorophenyl)-5-(l,3-thiazol-2-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-[(1-methyl-1H-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(3,5-dichlorophenyl)-5-(pyridin-4-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(3-chloro-2-fluorophenyl)-2-(2-chlorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-(pyridin-3-ylmethyl)-lH-pyrazolo [4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,6-difluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione;

4-(2-fluoro-5-methoxyphenyl)-2-(2-methoxyphenyl)-5-(pyrazin-2-ylmethyl)-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione;

2-(2-chlorophenyl)-4-(2,5-difluorophenyl)-5-(pyridin-3-ylmethyl)-lH-pyrazolo[4,3-c] pyridine-3,6(2H,5H)-dione; and

2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-[(1-methyl-1H-pyrazol-3-yl) methyl]-lH-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione.

Representative CYP450 inhibitors include, but are not limited to, amiodarone, amlodipine, apigenin, aprepitant, bergamottin (grapefruit), buprenorphine, bupropion, caffeine, cafestol, cannabidiol, celecoxib, chloramphenicol, chlorphenamine, chlorpromazine, cimetidine, cinacalcet, ciprofloxacin, citalopram, clarithromycin, clemastine, clofibrate, clomipramine, clotrimazole, cobicistat, cocaine,curcumin (turmeric), cyclizine, delavirdine, desipramine, disulfiram, diltiazem, diphenhydramine, dithiocarbamate, domperidone, doxepin, doxorubicin, duloxetine, echinacea, entacapone, erythromycin, escitalopram, felbamate, fenofibrate, flavonoids (grapefruit), fluoroquinolones (e.g., ciprofloxacin), fluoxetine, fluvoxamine, fluconazole, fluvastatin, gabapentin, gemfibrozil, gestodene, halofantrine, haloperidol, hydroxyzine, imatinib, indomethacin, indinavir, interferon, isoniazid, itraconazole, JWH-018, ketoconazole, letrozole, lovastatin, levomepromazine, memantine, methylphenidate,

metoclopramide, methadone, methimazole, methoxsalen, metyrapone, mibefradil, miconazole, midodrine, mifepristone, milk thistle, moclobemide, modafinil, montelukast, moclobemide, naringenin (grapefruit), nefazodone, nelfinavir, niacin, niacinamide, nicotine, nicotinamide,nilutamide, norfloxacin, orphenadrine, paroxetine, perphenazine, pilocarpine, piperine, phenylbutazone, probenecid, promethazine, proton pump inhibitors (e.g., lansoprazole, omeprazole, pantoprazole, rabeprazole), quercetin, quinidine, ranitidine, risperidone, ritonavir, saquinavir, selegiline, sertraline, star fruit, St. John's wort, sulconazole, sulfamethoxazole, sulfaphenazole, telithromycin, teniposide, terbinafine, thiazolidinediones, thioridazine, ticlopidine, tioconazole, thiotepa, trimethoprim, topiramate, tranylcypromine, tripelennamine, valerian, valproic acid, verapamil, voriconazole, zafirlukast, and zuclopenthixol.

Representative ACE-2 inhibitors include sulfhydryl-containing agents, such as alacepril, captopril (capoten), and zefnopril, dicarboxylate-containing agents, such as enalapril (vasotec), ramipril (altace), quinapril (accupril), perindopril (coversyl), lisinopril (listril), benazepril (lotensin), imidapril (tanatril), trandolapril (mavik), and cilazapril (inhibace), and phosphonate-containing agents, such as fosinopril (fositen/monopril).

For example, when used to treat or prevent infection, the active compound or its prodrug or pharmaceutically acceptable salt can be administered in combination or alternation with another antiviral agent including, but not limited to, those of the formulae above. In general, in combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially. The dosage will depend on absorption, inactivation and excretion rates of the drug, as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

A number of agents for combination with the compounds described herein are disclosed in Ghosh et al., "Drug Development and Medicinal Chemistry Efforts Toward SARS-Coronavirus and Covid-19 Therapeutics," ChemMedChem 10.1002/cmdc.202000223.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include those listed below.

Compounds for Inhibiting the Cytokine Storm

Throughout its activation, the inflammatory response must be regulated to prevent a damaging systemic inflammation, also known as a "cytokine storm." A number of cytokines with anti-inflammatory properties are responsible for this, such as IL-10 and transforming growth factor β (TGF-β). Each cytokine acts on a different part of the inflammatory response. For example, products of the Th2 immune response suppress the Th1 immune response and vice versa.

By resolving inflammation, one can minimize collateral damage to surrounding cells, with little or no long-term damage to the patient. Accordingly, in addition to using the compounds described herein to inhibit the viral infection, one or more compounds which inhibit the cytokine storm can be co-administered.

Compounds which inhibit the cytokine storm include compounds that target fundamental immune pathways, such as the chemokine network and the cholinergic anti-inflammatory pathway.

JAK inhibitors, such as JAK 1 and JAK 2 inhibitors, can inhibit the cytokine storm, and in some cases, are also antiviral. Representative JAK inhibitors include those disclosed in U.S. Patent No. 10,022,378, such as Jakafi, Tofacitinib, and Baricitinib, as well as LY3009104/INCB28050, Pacritinib/SB1518, VX-509, GLPG0634, INC424, R-348, CYT387, TG 10138, AEG 3482, and pharmaceutically acceptable salts and prodrugs thereof.

Still further examples include CEP-701 (Lestaurtinib), AZD1480, INC424, R-348, CYT387, TG 10138, AEG 3482, 7-iodo-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(4-aminophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl) acrylamide, 7-(3-aminophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl) acrylamide, N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, methyl 2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxylate, N-(4-morpholinophenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine, 7-(4-amino-3-methoxyphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 4-(2-(4-

morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzene- sulfonamide, N,N-dimethyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 1-ethyl-3-(2-methoxy-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)urea, N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)metha- nesulfonamide, 2-methoxy-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)pheno- l, 2-cyano-N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, N-(cyanomethyl)-2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidine-7-carboxamide, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, 1-ethyl-3-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)-2-(trifluoromethoxy)phenyl)urea, N-(3-nitrophenyl)-7-phenylthieno[3,2-d]pyrimidin-2-amine, 7-iodo-N-(3-nitrophenyl)thieno[3,2-d]pyrimidin-2-amine, N1-(7-(2-ethylphenyl)thieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine, N-tert-butyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N1-(7-iodothieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine, 7-(4-amino-3-(trifluoromethoxy)phenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(2-ethylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)aceta- mide, N-(cyanomethyl)-N-(3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, N-(cyanomethyl)-N-(4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, N-(3-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)phenyl)methanesulfonamide, 4-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)b-enzenesulfonamide, N-(4-(5-methyl-2-(4-morpholinophenylamino)-5H-pyrrolo[3,2-d]pyrimidin-7-y-l)phenyl)methanesulfonamide, 7-iodo-N-(4-morpholinophenyl)-5H-pyrrolo[3,2-d]pyrimidin-2-amine, 7-(2-isopropylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-bromo-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N7-(2-isopropylphenyl)-N2-(4-morpholinophenyl)thieno[3,2-d]pyrimidine-2,7-diamine, N7-(4-isopropylphenyl)-N2-(4-morpholinophenyl)thieno[3,2-d]pyrimidine-2,7-diamine, 7-(5-amino-2-methylphenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, 7-iodo-N-(3-

morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(4-amino-3-nitrophenyl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, 7-(2-methoxypyridin-3-yl)-N-(4-morpholinophenyl)thieno[3,2-d]pyrimidin-2-amine, (3-(7-iodothieno[3,2-d]pyrimidin-2-ylamino)phenyl)methanol, N-tert-butyl-3-(2-(3-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-tert-butyl-3-(2-(3-(hydroxymethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-(4-morpholinophenyl)-7-(4-nitrophenylthio)-5H-pyrrolo[3,2-d]pyrimidin-2- -amine, N-tert-butyl-3-(2-(3,4,5-trimethoxyphenylamino)thieno[3,2-d]pyrimi- din-7-yl)benzenesulfonamide, 7-(4-amino-3-nitrophenyl)-N-(3,4-dimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2-methoxypyridin-3-yl)thieno[3,2-d]pyrimidin-2-amine, N-tert-butyl-3-(2-(3,4-dimethoxyphenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 7-(2-aminopyrimidin-5-yl)-N-(3,4-dimethoxyphenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2,6-dimethoxypyridin-3-yl)thieno[3,2-d]-pyrimidin-2-amine, N-(3,4-dimethoxyphenyl)-7-(2,4-dimethoxypyrimidin-5-yl)thieno[3,2-d]pyrim- idin-2-amine, 7-iodo-N-(4-(morpholinomethyl)phenyl)thieno[3,2-d]pyrimidin-2-amine, N-tert-butyl-3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, 2-cyano-N-(4-methyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, ethyl 3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzoate, 7-bromo-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)thieno[3,2-d]pyrimidin-2-amine, N-(3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)phenyl)acetamide, N-(cyanomethyl)-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, N-tert-butyl-3-(2-(4-morpholinophenylamino)thieno[3,2-d]pyrimidin-7-yl)benzamide, N-tert-butyl-3-(2-(4-(1-ethylpiperidin-4-yloxy)phenylamino)thieno- [3,2-d]pyrimidin-7-yl)benzenesulfonamide, tert-butyl-4-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimidin-7- -yl)-1H-pyrazole-1-carboxylate, 7-bromo-N-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)thieno[3,2-d]pyrimidin- -2-amine, N-tert-butyl-3-(2-(4-((4-ethylpiperazin-1-yl)methyl)phenylamino)- thieno[3,2-d]pyrimidin-7-yl)benzenesulfonamide, N-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-7-(1H-pyrazol-4-yl)thieno[3,2-d]pyrimidin-2-amine, N-(cyanomethyl)-3-(2-(4-(morpholinomethyl)phenylamino)thieno[3,2-d]pyrimi- din-7-yl)benzamide, N-tert-butyl-3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]-pyrimidin-7-yl)benzenesulfonamide, tert-butyl pyrrolidin-1-yl)ethoxy)phenylamino)thieno[3,2-d]pyrimidin-7-yl)benzylcarb- amate,

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phenylthieno[3,2-d]pyrimidin-2-amine, and pharmaceutically acceptable salts and prodrugs thereof.

HMGB1 antibodies and COX-2 inhibitors can be used, which downregulate the cytokine storm. Examples of such compounds include Actemra (Roche). Celebrex (celecoxib), a COX-2 inhibitor, can be used. IL-8 (CXCL8) inhibitors can also be used.

Chemokine receptor CCR2 antagonists, such as PF-04178903 can reduce pulmonary immune pathology.

Selective α7Ach receptor agonists, such as GTS-21 (DMXB-A) and CNI-1495, can be used. These compounds reduce TNF-α. The late mediator of sepsis, HMGB1, downregulates IFN-γ pathways, and prevents the LPS-induced suppression of IL-10 and STAT 3 mechanisms.

Compounds for Treating or Preventing Blood Clots

Viruses that cause respiratory infections, including Coronaviruses such as Covid-19, can be associated with pulmonary blood clots, and blood clots that can also do damage to the heart.

The compounds described herein can be co-administered with compounds that inhibit blood clot formation, such as blood thinners, or compounds that break up existing blood clots, such as tissue plasminogen activator (TPA), Integrilin (eptifibatide), abciximab (ReoPro) or tirofiban (Aggrastat).

Blood thinners prevent blood clots from forming, and keep existing blood clots from getting larger. There are two main types of blood thinners. Anticoagulants, such as heparin or warfarin (also called Coumadin), slow down biological processes for producing clots, and antiplatelet aggregation drugs, such as Plavix, aspirin, prevent blood cells called platelets from clumping together to form a clot.

By way of example, Integrilin® is typically administered at a dosage of 180 mcg/kg intravenous bolus administered as soon as possible following diagnosis, with 2 mcg/kg/min continuous infusion (following the initial bolus) for up to 96 hours of therapy.

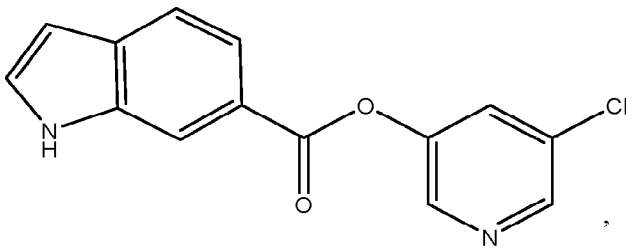
Representative platelet aggregation inhibitors include glycoprotein IIB/IIIA inhibitors, phosphodiesterase inhibitors, adenosine reuptake inhibitors, and adenosine diphosphate (ADP) receptor inhibitors. These can optionally be administered in combination with an anticoagulant.

Representative anti-coagulants include coumarins (vitamin K antagonists), heparin and derivatives thereof, including unfractionated heparin (UFH), low molecular weight heparin (LMWH), and ultra-low-molecular weight heparin (ULMWH), synthetic pentasaccharide inhibitors of factor Xa, including Fondaparinux, Idraparinux, and Idrabiotaparinux, directly acting oral anticoagulants (DAOCs), such as dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban, and antithrombin protein therapeutics/thrombin inhibitors, such as bivalent drugs hirudin, lepirudin, and bivalirudin and monovalent argatroban.

Representative platelet aggregation inhibitors include pravastatin, Plavix (clopidogrel bisulfate), Pletal (cilostazol), Effient (prasugrel), Aggrenox (aspirin and dipyridamole), Brilinta (ticagrelor), caplacizumab, Kengreal (cangrelor), Persantine (dipyridamole), Ticlid (ticlopidine), Yosprala (aspirin and omeprazole).

Small Molecule Covalent CoV 3CLpro Inhibitors

Representative small molecule covalent CoV 3CLpro inhibitors include the following compounds:



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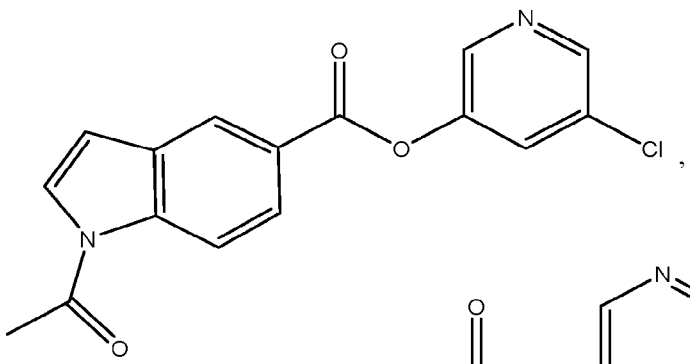

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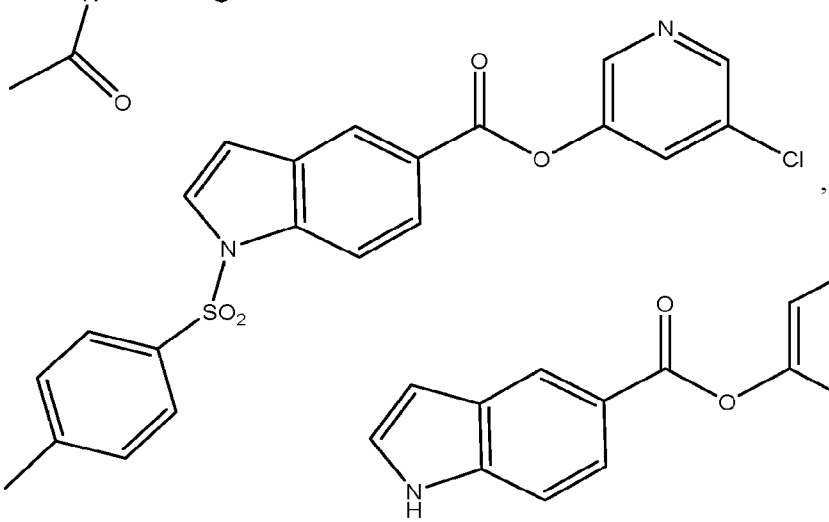

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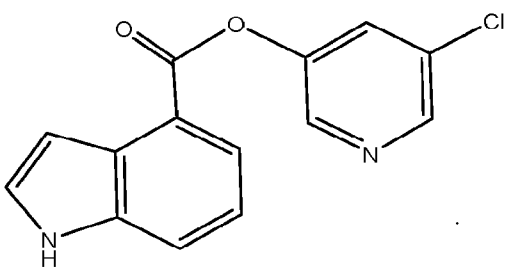

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Non-Covalent CoV 3CLpro Inhibitors

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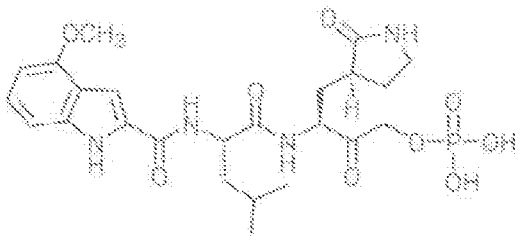

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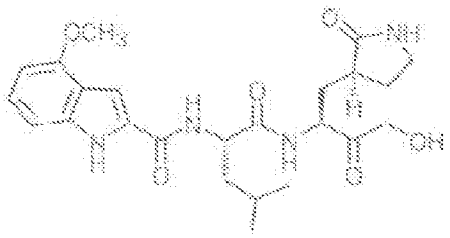

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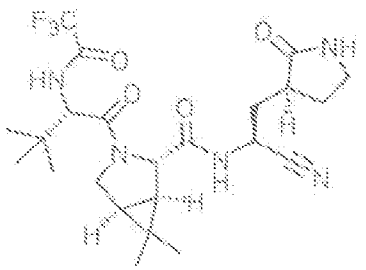

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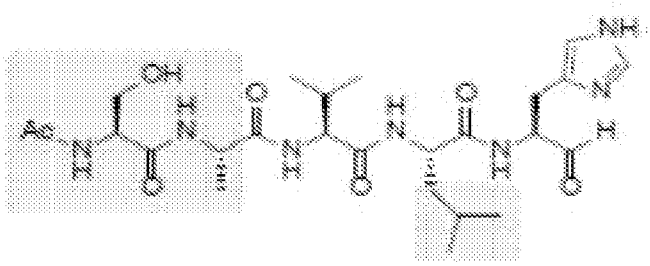

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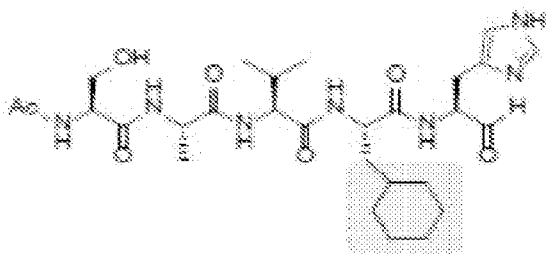

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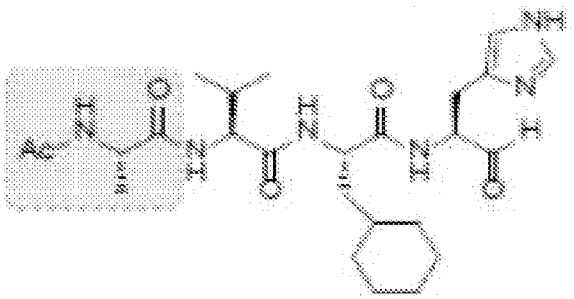
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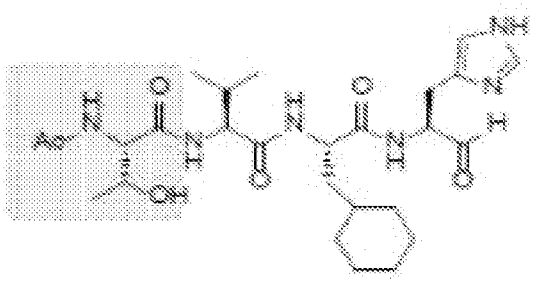
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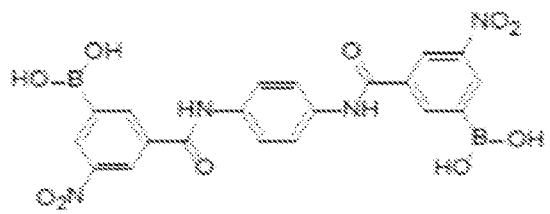
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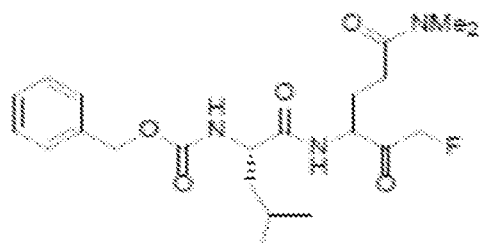
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SARS-CoV PLpro Inhibitors

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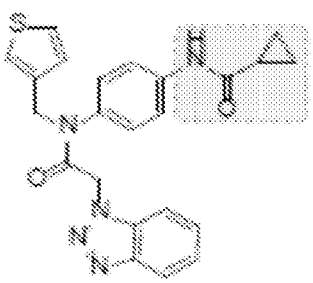
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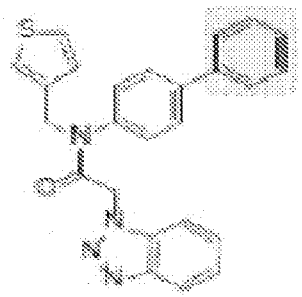
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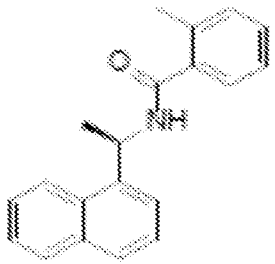
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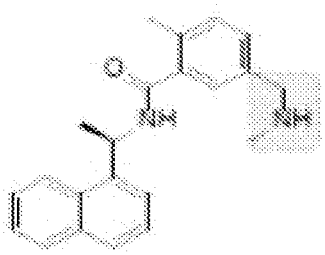
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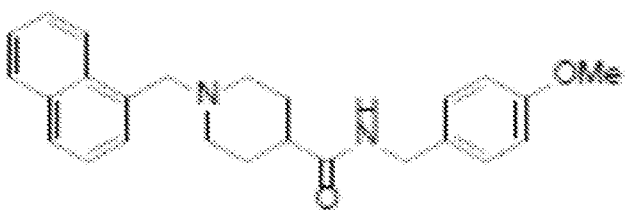
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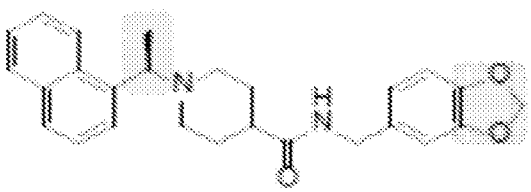
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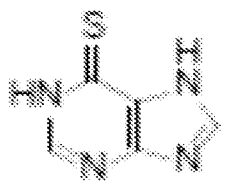
Additional compounds include the following: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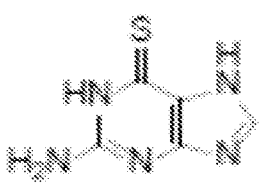
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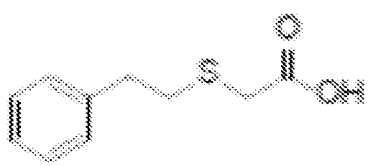
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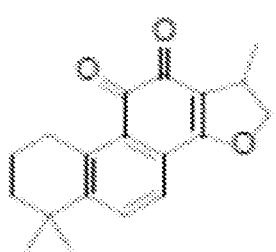
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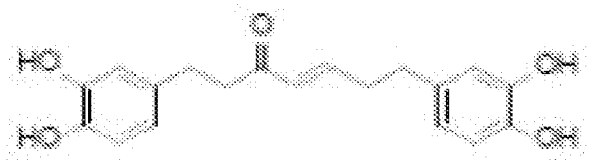


Additional Compounds that can be Used

Additional compounds and compound classes that can be used in combination therapy include the following: Antibodies, including monoclonal antibodies (mAb), Arbidol (umifenovir), Actemra (tocilizumab), APN01 (Aperion Biologics), ARMS-1 (which includes Cetylpyridinium chloride (CPC)), ASC09 (Ascletis Pharma), AT-001 (Applied Therapeutics Inc.) and other aldose reductase inhibitors (ARI), ATYR1923 (aTyr Pharma, Inc.), Aviptadil (Relief Therapeutics), Azvudine, Bemcentinib, BLD-2660 (Blade Therapeutics), Bevacizumab, Brensocatib, Calquence (acalabrutinib), Camostat mesylate (a TMPRSS2 inhibitor), Camrelizumab, CAP-1002 (Capricor Therapeutics), CD24Fcm, Clevudine, (OncoImmune), CM4620-IE (CalciMedica Inc., CRAC channel inhibitor), Colchicine, convalescent plasma, CYNK-001 (Sorrento Therapeutics), DAS181 (Ansun Pharma), Desferal, Dipyridamole (Persantine), Dociparstat sodium (DSTAT), Duvelisib, Eculizumab, EIDD-2801 (Ridgeback Biotherapeutics), Emapalumab, Fadraciclib (CYC065) and seliciclib (roscovitine) (Cyclin-dependent kinase (CDK) inhibitors), Farxiga (dapagliflozin), Favilavir/Favipiravir/T-705/Avigan, Galidesivir, Ganovo (danoprevir), Gilenya (fingolimod) (sphingosine 1-phosphate receptor modulator), Gimsilumab, IFX-1, Ilaris (canakinumab), intravenous immunoglobulin, Ivermectin (importin α/β inhibitor), Kaletra/Aluvia (lopinavir/ritonavir), NS5A inhibitors, such as Daclastavir, Kevzara (sarilumab), Kineret (anakinra), LAU-7b (fenretinide), Lenzilumab, Leronlimab (PRO 140), LY3127804 (an anti-Ang2 antibody), Leukine (sargramostim, a granulocyte macrophage colony stimulating factor), Losartan, Valsartan, and Telmisartan (Angiotensin II receptor antagonists), Meplazumab, Metablok (LSALT peptide, a DPEP1 inhibitor), Methylprednisolone and other corticosteroids, MN-166 (ibudilast, Macrophage migration inhibitory factor (MIF) inhibitor), MRx-4DP0004 (a strain of bifidobacterium breve, 4D Pharma), Nafamostat (a serine protease inhibitor), Neuraminidase inhibitors like Tamiflu (oseltamivir), Nitazoxanide (nucleocapsid (N) protein inhibitor), Nivolumab, OT-101 (Mateon), Novaferon (man-made Interferon), Opaganib (yeliva) (Sphingosine kinase-2

inhibitor), Otilimab, PD-1 blocking antibody, peginterferons, such as peginterferon lambda, Pepcid (famotidine), Piclidenoson (A3 adenosine receptor agonist), Prezcobix (darunavir), PUL-042 (Pulmotect, Inc., toll-like receptor (TLR) binder), Rebif (interferon beta-1a), RHB-107 (upamostat) (serine protease inhibitor, RedHill Biopharma Ltd.), Selinexor (selective inhibitor of nuclear export (SINE)), SNG001 (Synairgen, inhaled interferon beta-1a), Solnatide, stem cells, including mesenchymal stem cells, MultiStem (Athersys), and PLX (Pluristem Therapeutics), Sylvant (siltuximab), Thymosin, TJM2 (TJ003234), Tradipitant (neurokinin-1 receptor antagonist), Truvada (emtricitabine and tenofovir), Ultomiris (ravulizumab-cwvz), Vazegepant (CGRP receptor antagonist or blocker), and Xofluza (baloxavir marboxil).

Repurposed Antiviral Agents

A number of pharmaceutical agents, including agents active against other viruses, have been evaluated against Covid-19, and found to have activity. Any of these compounds can be combined with the compounds described herein. Representative compounds include lopinavir, ritonavir, niclosamide, promazine, PNU, UC2, cinanserin (SQ 10,643), Calmidazolium (C3930), tannic acid, 3-isotheaflavin-3-gallate, theaflavin-3,3'-digallate, glycyrrhizin, S-nitroso-N-acetylpenicillamine, nelfinavir, niclosamide, chloroquine, hydroxychloroquine, 5-benzyloxygramine, ribavirin, Interferons, such as Interferon (IFN)-α, IFN-β, and pegylated versions thereof, as well as combinations of these compounds with ribavirin, chlorpromazine hydrochloride, triflupromazine hydrochloride, gemcitabine, imatinib mesylate, dasatinib, and imatinib.

VIII. Pharmaceutical Compositions

Hosts, including but not limited to humans, infected with a Coronviridae virus, or the other viruses described, herein can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for will be in the range of between about 0.01 and about 10 mg/kg, more generally, between about 0.1 and 5 mg/kg, and, preferably, between about 0.5 and about 2 mg/kg, of body weight of the recipient per day, until the patient has recovered. In some cases, a compound may be administered at a dosage of up to 10 μM, which might be considered a relatively high dose if administered for an extended period of time, but which can be acceptable when administered for the duration of an infection with one or more of the viruses described herein, which is typically on the order of several days to several weeks.

The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent compound to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to but not limited to one containing 7 to 600 mg, preferably 70 to 600 mg of active ingredient per unit dosage form. An oral dosage of 5-400 mg is usually convenient.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient can be administered at once, or can be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, unit dosage forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup can contain, in addition to the active compound(s), sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti- inflammatories or other antiviral compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid; buffers, such as acetates, citrates or phosphates, and agents for the adjustment of tonicity, such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

Transdermal Formulations

In some embodiments, the compositions are present in the form of transdermal formulations, such as that used in the FDA-approved agonist rotigitine transdermal (Neupro patch). Another suitable formulation is that described in U.S. Publication No. 20080050424,

entitled "Transdermal Therapeutic System for Treating Parkinsonism." This formulation includes a silicone or acrylate-based adhesive, and can include an additive having increased solubility for the active substance, in an amount effective to increase dissolving capacity of the matrix for the active substance.

The transdermal formulations can be single-phase matrices that include a backing layer, an active substance-containing self-adhesive matrix, and a protective film to be removed prior to use. More complicated embodiments contain multiple-layer matrices that may also contain non-adhesive layers and control membranes. If a polyacrylate adhesive is used, it can be crosslinked with multivalent metal ions such as zinc, calcium, aluminum, or titanium ions, such as aluminum acetylacetonate and titanium acetylacetonate.

When silicone adhesives are used, they are typically polydimethylsiloxanes. However, other organic residues such as, for example, ethyl groups or phenyl groups may in principle be present instead of the methyl groups. Because the active compounds are amines, it may be advantageous to use amine-resistant adhesives. Representative amine- resistant adhesives are described, for example, in EP 0 180 377.

Representative acrylate-based polymer adhesives include acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate, vinylpyrrolidone, and combinations thereof.

The adhesive must have a suitable dissolving capacity for the active substance, and the active substance most be able to move within the matrix, and be able to cross through the contact surface to the skin. Those of skill in the art can readily formulate a transdermal formulation with appropriate transdermal transport of the active substance.

Certain pharmaceutically acceptable salts tend to be more preferred for use in transdermal formulations, because they can help the active substance pass the barrier of the stratum corneum. Examples include fatty acid salts, such as stearic acid and oleic acid salts. Oleate and stearate salts are relatively lipophilic, and can even act as a permeation enhancer in the skin.

Permeation enhancers can also be used. Representative permeation enhancers include fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its fatty acid esters,

N-methylpyrrolidone, terpenes such as limonene, alpha-pinene, alpha- terpineol, carvone, carveol, limonene oxide, pinene oxide, and 1,8-eucalyptol.

The patches can generally be prepared by dissolving or suspending the active agent in ethanol or in another suitable organic solvent, then adding the adhesive solution with stirring. Additional auxiliary substances can be added either to the adhesive solution, the active substance solution or to the active substance-containing adhesive solution. The solution can then be coated onto a suitable sheet, the solvents removed, a backing layer laminated onto the matrix layer, and patches punched out of the total laminate.

Nanoparticulate Compositions

The compounds described herein can also be administered in the form of nanoparticulate compositions. In one embodiment, controlled release nanoparticulate formulations comprise a nanoparticulate active agent to be administered and a rate-controlling polymer which prolongs the release of the agent following administration. In this embodiment, the compositions can release the active agent, following administration, for a time period ranging from about 2 to about 24 hours or up to 30 days or longer. Representative controlled release formulations including a nanoparticulate form of the active agent are described, for example, in U.S. Patent No. 8,293,277.

Nanoparticulate compositions can comprise particles of the active agents described herein, having a non-crosslinked surface stabilizer adsorbed onto, or associated with, their surface.

The average particle size of the nanoparticulates is typically less than about 800 nm, more typically less than about 600 nm, still more typically less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, or less than about 50 nm. In one aspect of this embodiment, at least 50% of the particles of active agent have an average particle size of less than about 800, 600, 400, 300, 250, 100, or 50 nm, respectively, when measured by light scattering techniques.

A variety of surface stabilizers are typically used with nanoparticulate compositions to prevent the particles from clumping or aggregating. Representative surface stabilizers are selected from the group consisting of gelatin, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl

ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, poloxamine 908, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), SA9OHCO, decanoyl-N-methylglucamide, n-decyl -D-glucopyranoside, n-decyl-D-maltopyranoside, n-dodecyl-D-glucopyranoside, n-dodecyl-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-D-glucopyranoside, n-heptyl-D-thioglucoside, n-hexyl-D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-D-glucopyranoside, and octyl-D-thioglucopyranoside. Lysozymes can also be used as surface stabilizers for nanoparticulate compositions. Certain nanoparticles such as poly(lactic-co-glycolic acid) (PLGA)-nanoparticles are known to target the liver when given by intravenous (IV) or subcutaneously (SQ).

Representative rate controlling polymers into which the nanoparticles can be formulated include chitosan, polyethylene oxide (PEO), polyvinyl acetate phthalate, gum arabic, agar, guar gum, cereal gums, dextran, casein, gelatin, pectin, carrageenan, waxes, shellac, hydrogenated vegetable oils, polyvinylpyrrolidone, hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcelluose (HPMC), sodium carboxymethylcellulose (CMC), poly(ethylene) oxide, alkyl cellulose, ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydrophilic cellulose derivatives, polyethylene glycol, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl acetaldiethylamino acetate, poly(alkylmethacrylate), poly(vinyl acetate), polymers derived from acrylic or methacrylic acid and their respective esters, and copolymers derived from acrylic or methacrylic acid and their respective esters.

Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;"

U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No.

5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of

Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for targeting drug delivery to the upper and/or lower gastrointestinal tract," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water- Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

Certain nanoformulations can enhance the absorption of drugs by releasing drug into the lumen in a controlled manner, thus reducing solubility issues. The intestinal wall is designed to absorb nutrients and to act as a barrier to pathogens and macromolecules. Small amphipathic and lipophilic molecules can be absorbed by partitioning into the lipid bilayers and crossing the intestinal epithelial cells by passive diffusion, while nanoformulation absorption may be more

complicated because of the intrinsic nature of the intestinal wall. The first physical obstacle to nanoparticle oral absorption is the mucus barrier which covers the luminal surface of the intestine and colon. The mucus barrier contains distinct layers and is composed mainly of heavily glycosylated proteins called mucins, which have the potential to block the absorption of certain nanoformulations. Modifications can be made to produce nanoformulations with increased mucus-penetrating properties (Ensign et al., "Mucus penetrating nanoparticles: biophysical tool and method of drug and gene delivery," Adv Mater 24: 3887–3894 (2012)).

Once the mucus coating has been traversed, the transport of nanoformulations across intestinal epithelial cells can be regulated by several steps, including cell surface binding, endocytosis, intracellular trafficking and exocytosis, resulting in transcytosis (transport across the interior of a cell) with the potential involvement of multiple subcellular structures. Moreover, nanoformulations can also travel between cells through opened tight junctions, defined as paracytosis. Non-phagocytic pathways, which involve clathrin-mediated and caveolae-mediated endocytosis and macropinocytosis, are the most common mechanisms of nanoformulation absorption by the oral route.

Non-oral administration can provide various benefits, such as direct targeting to the desired site of action and an extended period of drug action. Transdermal administration has been optimized for nanoformulations, such as solid lipid nanoparticles (SLNs) and NEs, which are characterized by good biocompatibility, lower cytotoxicity and desirable drug release modulation (Cappel and Kreuter, "Effect of nanoparticles on transdermal drug delivery. J Microencapsul 8: 369–374 (1991)). Nasal administration of nanoformulations allows them to penetrate the nasal mucosal membrane, via a transmucosal route by endocytosis or via a carrier- or receptor-mediated transport process (Illum, "Nanoparticulate systems for nasal delivery of drugs: a real improvement over simple systems?" J. Pharm. Sci 96: 473–483 (2007)), an example of which is the nasal administration of chitosan nanoparticles of tizanidine to increase brain penetration and drug efficacy in mice (Patel et al., "Improved transnasal transport and brain uptake of tizanidine HCl-loaded thiolated chitosan nanoparticles for alleviation of pain," J. Pharm. Sci 101: 690–706 (2012)). Pulmonary administration provides a large surface area and relative ease of access. The mucus barrier, metabolic enzymes in the tracheobronchial region and macrophages in the alveoli are typically the main barriers for drug penetration. Particle size is a major factor determining the diffusion of nanoformulation in the bronchial

tree, with particles in the nano-sized region more likely to reach the alveolar region and particles with diameters between 1 and 5 μm expected to deposit in the bronchioles (Musante et al., "Factors affecting the deposition of inhaled porous drug particles," J Pharm Sci 91: 1590–1600 (2002)). A limit to absorption has been shown for larger particles, presumably because of an inability to cross the air-blood barrier. Particles can gradually release the drug, which can consequently penetrate into the blood stream or, alternatively, particles can be phagocytosed by alveolar macrophages (Bailey and Berkland, "Nanoparticle formulations in pulmonary drug delivery," Med. Res. Rev., 29: 196–212 (2009)).

Certain nanoformulations have a minimal penetration through biological membranes in sites of absorption and for these, i.v. administration can be the preferred route to obtain an efficient distribution in the body (Wacker, "Nanocarriers for intravenous injection–The long hard road to the market," Int. J. Pharm., 457: 50–62., 2013).

The distribution of nanoformulations can vary widely depending on the delivery system used, the characteristics of the nanoformulation, the variability between individuals, and the rate of drug loss from the nanoformulations. Certain nanoparticles, such as solid drug nanoparticles (SDNs), improve drug absorption, which does not require them to arrive intact in the systemic circulation. Other nanoparticles survive the absorption process, thus altering the distribution and clearance of the contained drug.

Nanoformulations of a certain size and composition can diffuse in tissues through well-characterized processes, such as the enhanced permeability and retention effect, whereas others accumulate in specific cell populations, which allows one to target specific organs. Complex biological barriers can protect organs from exogenous compounds, and the blood–brain barrier (BBB) represents an obstacle for many therapeutic agents. Many different types of cells including endothelial cells, microglia, pericytes and astrocytes are present in the BBB, which exhibits extremely restrictive tight junctions, along with highly active efflux mechanisms, limiting the permeation of most drugs. Transport through the BBB is typically restricted to small lipophilic molecules and nutrients that are carried by specific transporters. One of the most important mechanisms regulating diffusion of nanoformulations into the brain is endocytosis by brain capillary endothelial cells.

Recent studies have correlated particle properties with nanoformulation entry pathways and processing in the human BBB endothelial barrier, indicating that uncoated nanoparticles

have limited penetration through the BBB and that surface modification can influence the efficiency and mechanisms of endocytosis (Lee et al., "Targeting rat anti-mouse transferrin receptor monoclonal antibodies through blood-brain barrier in mouse," J. Pharmacol. Exp. Ther. 292: 1048–1052 (2000)). Accordingly, surface-modified nanoparticles which cross the BBB, and deliver one or more of the compounds described herein, are within the scope of the invention.

Macrophages in the liver are a major pool of the total number of macrophages in the body. Kupffer cells in the liver possess numerous receptors for selective phagocytosis of opsonized particles (receptors for complement proteins and for the fragment crystallizable part of IgG). Phagocytosis can provide a mechanism for targeting the macrophages, and providing local delivery (i.e., delivery inside the macrophages) of the compounds described herein (TRUE?).

Nanoparticles linked to polyethylene glycol (PEG) have minimal interactions with receptors, which inhibits phagocytosis by the mononuclear phagocytic system (Bazile et al., "Stealth Me.PEG-PLA nanoparticles avoid uptake by the mononuclear phagocytes system," J. Pharm. Sci. 84: 493–498 (1995)).

Representative nanoformulations include inorganic nanoparticles, SDNs, SLNs, NEs, liposomes, polymeric nanoparticles and dendrimers. The compounds described herein can be contained inside a nanoformulation, or, as is sometimes the case with inorganic nanoparticles and dendrimers, attached to the surface. Hybrid nanoformulations, which contain elements of more than one nanoformulation class, can also be used.

SDNs are lipid-free nanoparticles, which can improve the oral bioavailability and exposure of poorly water-soluble drugs (Chan, "Nanodrug particles and nanoformulations for drug delivery," Adv. Drug. Deliv. Rev. 63: 405 (2011)). SDNs include a drug and a stabilizer, and are produced using 'top-down' (high pressure homogenization and wet milling) or bottom-up (solvent evaporation and precipitation) approaches.

SLNs consist of a lipid (or lipids) which is solid at room temperature, an emulsifier and water. Lipids utilized include, but are not limited to, triglycerides, partial glycerides, fatty acids, steroids and waxes. SLNs are most suited for delivering highly lipophilic drugs.

Liquid droplets of less than a 1000 nm dispersed in an immiscible liquid are classified as NEs. NEs are used as carriers for both hydrophobic and hydrophilic agents, and can be

administered orally, transdermally, intravenously, intranasally, and ocularly. Oral administration can be preferred for chronic therapy, and NEs can effectively enhance oral bioavailability of small molecules, peptides and proteins.

Polymeric nanoparticles are solid particles typically around 200–800 nm in size, which can include synthetic and/or natural polymers, and can optionally be pegylated to minimize phagocytosis. Polymeric nanoparticles can increase the bioavailability of drugs and other substances, compared with traditional formulations. Their clearance depends on several factors, including the choice of polymers (including polymer size, polymer charge and targeting ligands), with positively charged nanoparticles larger than 100 nm being eliminated predominantly via the liver (Alexis et al., Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm 5: 505–515 (2008)).

Dendrimers are tree-like, nanostructured polymers which are commonly 10–20 nm in diameter.

Liposomes are spherical vesicles which include a phospholipid bilayer. A variety of lipids can be utilized, allowing for a degree of control in degradation level. In addition to oral dosing, liposomes can be administered in many ways, including intravenously (McCaskill et al., 2013), transdermally (Pierre and Dos Santos Miranda Costa, 2011), intravitreally (Honda et al., 2013) and through the lung (Chattopadhyay, 2013). Liposomes can be combined with synthetic polymers to form lipid-polymer hybrid nanoparticles, extending their ability to target specific sites in the body. The clearance rate of liposome-encased drugs is determined by both drug release and destruction of liposomes (uptake of liposomes by phagocyte immune cells, aggregation, pH-sensitive breakdown, etc.) (Ishida et al., "Liposome clearance," Biosci Rep 22: 197–224 (2002)).

One of more of these nanoparticulate formulations can be used to deliver the active agents described herein to the macrophages, across the blood brain barrier, and other locations as appropriate.

Controlled Release Formulations

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including but not limited to implants and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. For example, enterically coated compounds can be used to protect cleavage by stomach acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Suitable materials can also be obtained commercially.

Liposomal suspensions (including but not limited to liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in US Pat. No. 4,522,811 (incorporated by reference). For example, liposome formulations can be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

The terms used in describing the embodiments described herein are commonly used and known to those skilled in the art. As used herein, the following abbreviations have the indicated meanings:

DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
h	hour
Liq.	liquid
M	molar
MeOH	Methanol
min	minute
rt or RT	room temperature
TBAF	Tetrabutylammonium fluoride
THF	tetrahydrofuran

IX. General Methods for Preparing Active Compounds

Methods for the facile preparation of active compounds are known in the art and result from the selective combination known methods. The compounds disclosed herein can be prepared as described in detail below, or by other methods known to those skilled in the art. It will be understood by one of ordinary skill in the art that variations of detail can be made without departing from the spirit and in no way limiting the scope of the present disclosure.

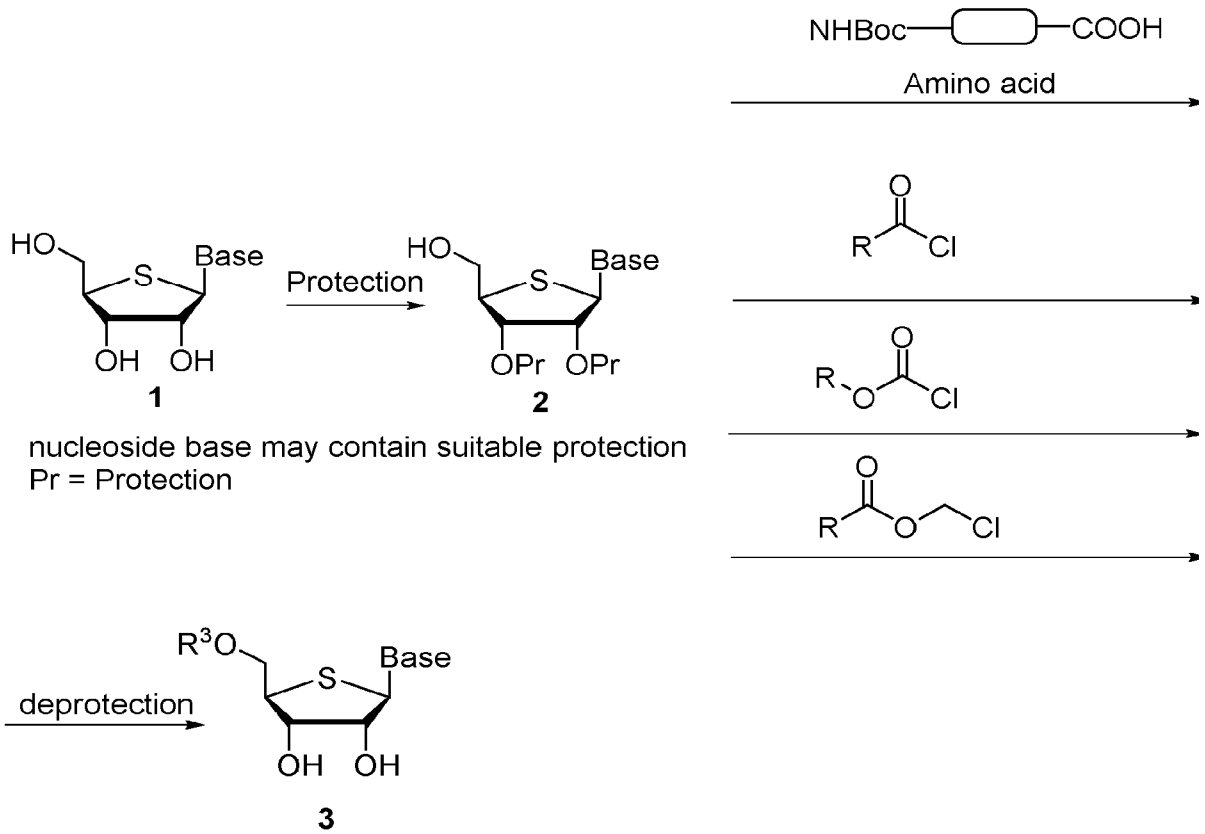
For some compounds, the syntheses described herein are exemplary and can be used as a starting point to prepare additional compounds of the formulas described herein. These compounds can be prepared in various ways, including those synthetic schemes shown and described herein. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

The various reaction schemes are summarized below.

Scheme 1 is a synthetic approach to nucleosides 3.

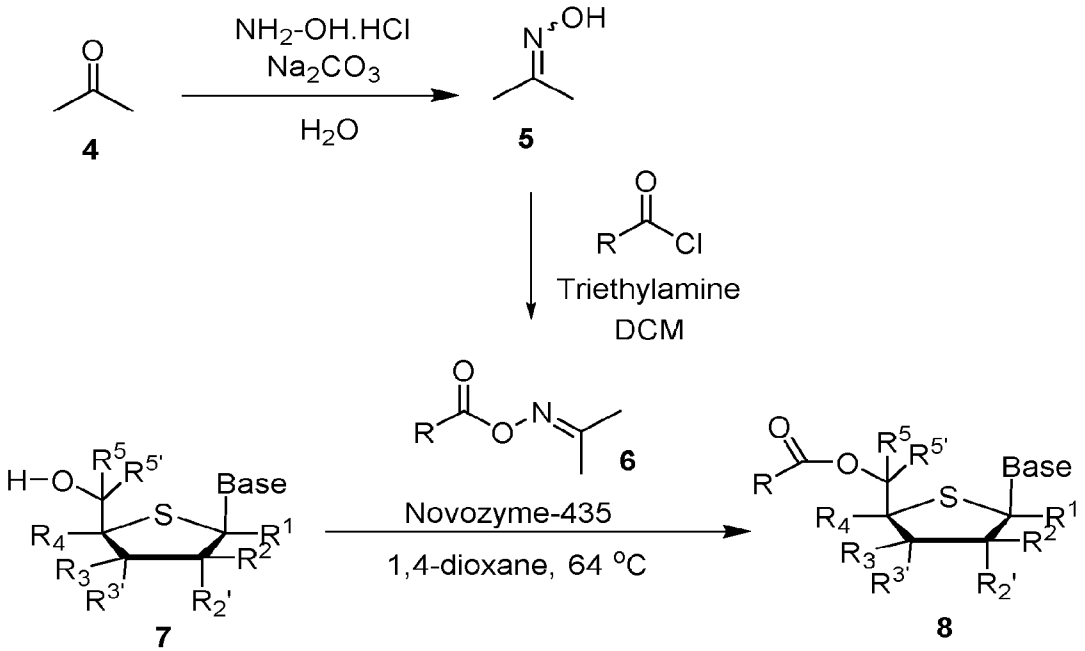
Scheme 2 is an enzymatic approach to the synthesis of compound **8**.)

In the schemes described herein, if a nucleoside base includes functional groups that might interfere with, or be decomposed or otherwise converted during the reaction steps, such functional groups can be protected using suitable protecting groups that can be removed. Protected functional groups, if any, can be deprotected later on.



Scheme 1: A synthetic approach to nucleosides **3**.

Compounds of general formula **3** can be prepared from nucleosides **1** by selective protection of the 2',3' hydroxyl groups, with for instance, acetone in presence of H_2SO_4, followed by coupling with a protected aninoacid in presence of a coupling agent, such as EDC, or with an acid chloride, a carbonate chloride or a chloromethylester derivative in presence of a base such as Et_3N or NaH followed by appropriate deprotection.



nucleoside base may contain suitable protection

Scheme 2. Enzymatic approach to the synthesis of compound **8**.

Compounds of general formula **8** can also be made by adapting the chemistry described in *ACS Omega* 2021, 6, 15, 10396–10402 and in Scheme 2.

Compounds of general Formula **A** and **B** can also be prepared by adapting the chemistry described in: *J. Am. Chem. Soc.* 2000, 122, 30, 7233–7243; *J. Med. Chem.* 2006, 49, 5, 1624–1634; Nucleosides, Nucleotides & Nucleic Acids (2001), 20(4-7), 743-746; European Journal of Organic Chemistry (1999), (3), 691-696; Journal of Organic Chemistry (1971), 36(1), 108-10; Nucleosides & Nucleotides (1992), 11(8), 1467-79; Journal of Medicinal Chemistry (1975), 18(8), 784-7; Tetrahedron Letters (2006), 47(4), 591-594.

Compounds of general Formula **C** and **F** can also be prepared by adapting the chemistry described in: Bioorganic & Medicinal Chemistry (2007), 15(16), 5519-5528; Chemistry & Biology (Oxford, United Kingdom) (2013), 20(3), 416-423; Nucleosides, Nucleotides & Nucleic Acids (2007), 26(6-7), 573-577; WO2004096286 A2; US20110288053 A1.

Compounds of general Formula **D** and **E** can also be prepared by adapting the chemistry described in: WO2021/159044 A1; Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1991), (1), 43-8; Bioorganic Chemistry (2015), 58, 18-25; Tetrahedron Letters (1985), 26(37), 4467-70; Journal of Medicinal Chemistry (2006), 49(22), 6614-6620; Collection of Czechoslovak Chemical Communications (1969), 34(12), 3755-68; Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1973), (7), 665-9; Organic & Biomolecular Chemistry (2011), 9(3), 676-678;

Monophosphate prodrugs of general Formula **A-F** can also be prepared by adapting the chemistry described in: *Chem Rev.* 2014;114(18):9154-9218.

Incorporation of Deuterium:

It is expected that single or multiple replacement of hydrogen with deuterium (carbon-hydrogen bonds to carbon-deuterium bond) at site(s) of metabolism in the sugar portion of a nucleoside antiviral agent will slow down the rate of metabolism. This can provide a relatively longer half-life, and slower clearance from the body. The slow metabolism of a therapeutic nucleoside is expected to add extra advantage to a therapeutic candidate, while other physical or biochemical properties are not affected. Intracellular hydrolysis or deuterium exchanges my result in liberation of deuterium oxide (D_2O).

Methods for incorporating deuterium into amino acids, phenol, sugars, and bases, are well known to those of skill in the art. Representative methods are disclosed in U.S. Patent No. 9,045,521.

A large variety of enzymatic and chemical methods have been developed for deuterium incorporation at both the sugar and nucleoside stages to provide high levels of deuterium incorporation (D/H ratio). The enzymatic method of deuterium exchange generally has low levels of incorporation. Enzymatic incorporation has further complications due to cumbersome isolation techniques which are required for isolation of deuterated mononucleotide blocks. Schmidt et al., Ann. Chem. 1974, 1856; Schmidt et al., Chem. Ber., 1968, 101, 590, describes synthesis of 5',5'-$^2H_2$-adenosine which was prepared from 2',3'-O-isopropylideneadenosine-5'-

carboxylic acid or from methyl-2,3-isopropylidene-beta-D-ribofuranosiduronic acid, Dupre, M. and Gaudemer, A., Tetrahedron Lett. 1978, 2783. Kintanar, et al., Am. Chem. Soc. 1998, 110, 6367 reported that diastereoisomeric mixtures of 5'-deuterioadenosine and 5'(R/S)-deuteratedthymidine can be obtained with reduction of the appropriate 5'-aldehydes using sodium borodeuteride or lithium aluminum deuteride (98 atom % ^2H incorporation). Berger et al., Nucleoside & Nucleotides 1987, 6, 395 described the conversion of the 5'-aldehyde derivative of 2'deoxyguanosine to 5' or 4'-deuterio-2'-deoxyguanosine by heating the aldehyde in ^2H_2O/pyridine mixture (1:1) followed by reduction of the aldehyde with $NaBD_4$.

Ajmera et al., Labelled Compd. 1986, 23, 963 described procedures to obtain 4'-deuterium labeled uridine and thymidine (98 atom % ^2H). Sinhababu, et al., J. Am. Chem. Soc. 1985, 107, 7628) demonstrated deuterium incorporation at the C3' (97 atom % ^2H) of adenosine during sugar synthesis upon stereoselective reduction of 1,2:5,6-di-O-isopropylidene-β-D-hexofuranos-3-ulose to 1,2:5,6-di-O-isopropylidene-3-deuterio-β-D-ribohexofuranose using sodium borodeuteride and subsequently proceeding further to the nucleoside synthesis. Robins, et al., Org. Chem. 1990, 55, 410 reported synthesis of more than 95% atom ^2H incorporation at C3' of adenosine with virtually complete stereoselectivity upon reduction of the 2'-O-tert-butyldimethylsilyl(TBDMS) 3-ketonucleoside by sodium borodeuteride in acetic acid. David, S. and Eustache, J., Carbohyd. Res. 1971, 16, 46 and David, S. and Eustache, J., Carbohyd. Res. 1971, 20, 319 described syntheses of 2'-deoxy-2'(S)-deuterio-uridine and cytidine. The synthesis was carried out by the use of 1-methyl-2-deoxy-2'-(S)-deuterio ribofuranoside.

Radatus, et al., J. Am. Chem. Soc. 1971, 93, 3086 described chemical procedures for synthesizing 2'-monodeuterated (R or S)-2'-deoxycytidines. These structures were synthesized from selective 2-monodeuterated-2-deoxy-D-riboses, which were obtained upon stereospecific reduction of a 2,3-dehydro-hexopyranose with lithium aluminum deuteride and oxidation of the resulting glycal. Wong et al. J. Am. Chem. Soc. 1978, 100, 3548 reported obtaining deoxy-1-deuterio-D-erythro-pentose, 2-deoxy-2(S)-deuterio-D-erythro-pentose and 2-deoxy-1,2(S)-dideuterio-D-erythro-pentose from D-arabinose by a reaction sequence involving the formation and $LiAlD_4$ reduction of ketene dithioacetal derivatives.

Pathak et al. J., Tetrahedron 1986, 42, 5427) reported stereospecific synthesis of all eight

2' or 2'-deuterio-2'-deoxynucleosides by reductive opening of appropriate methyl 2,3-anhydro-beta-D-ribo or beta-D-lyxofuranosides with $LiAlD_4$. Wu et al. J. Tetrahedron 1987, 43, 2355 described the synthesis of all 2',2"-dideuterio-2'-deoxynucleosides, for both deoxy and ribonucleosides, starting with oxidation of C2' of sugar and subsequent reduction with $NaBD_4$ or $LiAlD_4$ followed by deoxygenation by tributyltin deuteride. Roy et al. J. Am. Chem. Soc. 1986, 108, 1675, reported 2',2'-dideuterio-2'-deoxyguanosine and thymidine can be prepared from 2-deoxyribose 5-phosphate using 2-deoxyribose 5-phosphate aldolase enzyme in ^2H_2O achieving some 90 atom % deuteration. Similarly, the synthesis of 4',5',5'-$^2H_3$-guanosine can be carried out.

Therefore, it is clear that each position of the sugar residue can be selectively labeled.

A useful alternative method of stereospecific deuteration was developed to synthesize polydeuterated sugars. This method employed exchange of hydrogen with deuterium at the hydroxyl bearing carbon (i.e. methylene and methine protons of hydroxyl bearing carbon) using deuterated Raney nickel catalyst in ^2H_2O.

Various techniques are available to synthesize fully deuterated deoxy and ribonucleosides. Thus, in one method, exchange reaction of deuterated Raney nickel-^2H_2O with sugars, a number of deuterated nucleosides specifically labeled at 2', 3' and 4' positions were prepared. The procedure consisted of deuteration at 2', 3' and 4' positions of methyl beta-D-arabinopyranoside by Raney nickel-^2H_2O exchange reaction followed by reductive elimination of '2-hydroxyl group by tributyltin deuteride to give methyl beta-D-2',2',3',4'-$^2H_4$-2-deoxyribopyranoside, which was converted to methyl beta-D-2',2',3',4'-$^2H_4$-2'-deoxyribofuranoside and glycosylated to give various 2',2',3',4'-$^2H_4$-nucleosides (> 97 atom % ^2H incorporation for H3' & H4'.

The synthesis of deuterated phenols is described, for example, in Hoyer, H. (1950), Synthese des pan-Deutero-o-nitro-phenols. Chem. Ber., 83: 131–136. This chemistry can be adapted to prepare substituted phenols with deuterium labels. Deuterated phenols, and substituted analogs thereof, can be used, for example, to prepare phenoxy groups in phosphoramidate prodrugs.

The synthesis of deuterated amino acids is described, for example, in Matthews et al., Biochimica et Biophysica Acta (BBA) - General Subjects, Volume 497, Issue 1, 29 March 1977, Pages 1–13. These and similar techniques can be used to prepare deuterated amino acids, which can be used to prepare phosphoramidate prodrugs of the nucleosides described herein.

One method for synthesizing a deuterated analog of the compounds described herein involves synthesizing a deuterated ribofuranoside with a 1'-CN substitution; and attaching a nucleobase to the deuterated ribofuranoside to form a deuterated nucleoside. A prodrug, such as a phosphoramidate prodrug, can be formed by modifying the 5'-OH group on the nucleoside. Where a deuterated phenol and/or deuterated amino acid is used, one can prepare a deuterated phosphoramidate prodrug.

Another method involves synthesizing a ribofuranoside with 1'-CN substitution, and attaching a deuterated nucleobase to form a deuterated nucleoside. This method can optionally be performed using a deuterated furanoside to provide additional deuteration. As with the method described above, the nucleoside can be converted into a prodrug form, which prodrug form can optionally include additional deuteration.

A third method involves synthesizing a ribofuranoside with 1'-CN substitution, attaching a nucleobase to form a nucleoside, and converting the nucleoside to a phosphoramidate prodrug using one or both of a deuterated amino acid or phenol analog in the phosphoramidate synthesis.

Accordingly, using the techniques described above, one can provide one or more deuterium atoms in the sugar, base, and/or prodrug portion of the nucleoside compounds described herein.

Specific Examples

Specific representative compounds described herein were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the disclosure and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The present compounds can also be used as intermediates in

subsequent examples to produce additional compounds described herein. No attempt has necessarily been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

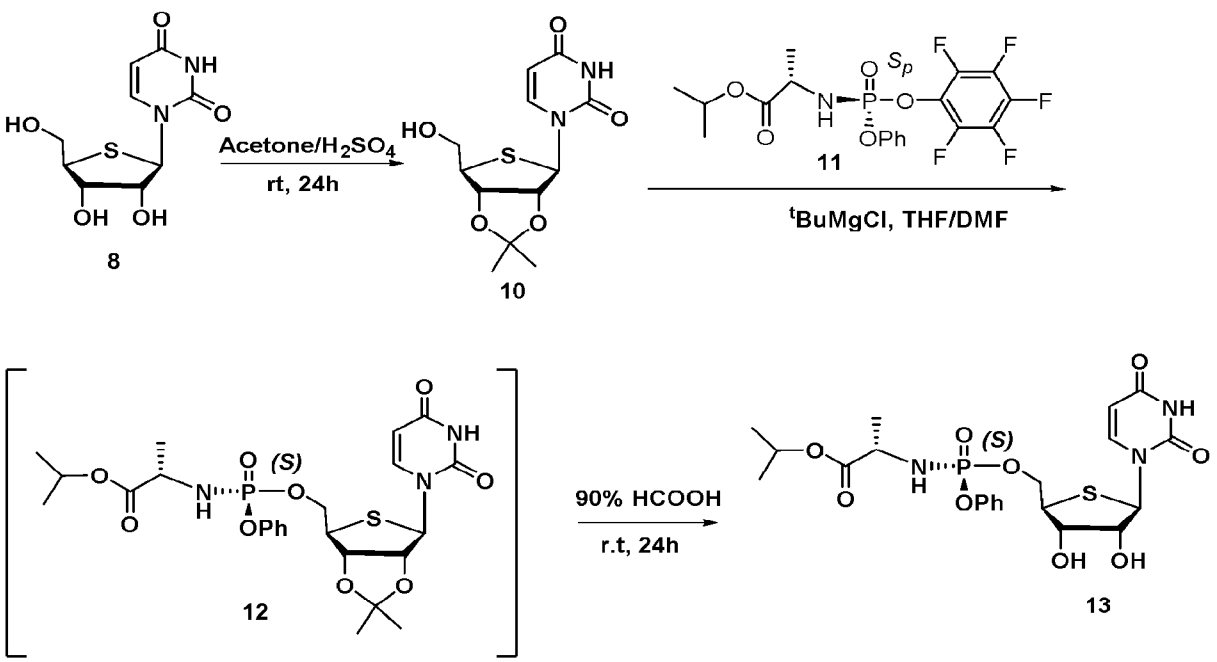
Anhydrous solvents were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI) and EMD Chemicals Inc. (Gibbstown, NJ). Reagents were purchased from commercial sources. Unless noted otherwise, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. Melting points (mp) were determined on an Electrothermal digit melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a Varian Unity Plus 400 spectrometer at room temperature and reported in ppm downfield from internal tetramethylsilane. Deuterium exchange, decoupling experiments or 2D-COSY were performed to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), bs (broad singlet), m (multiplet). All J- values are in Hz. Mass spectra were determined on a Micromass Platform LC spectrometer using electrospray techniques. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA). Analytic TLC was performed on Whatman LK6F silica gel plates, and preparative TLC on Whatman PK5F silica gel plates. Column chromatography was carried out on Silica Gel or via reverse-phase high performance liquid chromatography.

Experimental

1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)pyrimidine-2,4(1H,3H)-dione (8) and 4-amino-1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)pyrimidin-2(1H)-one (9) were synthesized by following procedures reported in Takashi Naka, Noriaki Minakawa, Hiroshi Abe, Daisuke Kaga, and Akira Matsuda The Stereoselective Synthesis of 4'-β-thioribonucleosides via the Pummerer Reaction J. Am. Chem. Soc. 2000, 122, 30, 7233–7243.

1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)pyrimidine-2,4(1H,3H)-dione (8): ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.44-3.41 (m, 1H), 3.82-3.80 (m, 2H), 4.18 (t, J = 3.8 Hz, 1H), 4.31-4.28 (m, 1H), 5.78 (d, J = 8.1 Hz, 1H), 6.07 (d, J = 6.3 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H); MS (ESI): m/z [M+H]$^+$ calcd for $C_9H_{13}N_2O_5S$: 261.3, found: 261.0.

4-amino-1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)pyrimidin-2(1H)-one (9): ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.84-3.43 (m, 1H), 3.84 (d, J = 4.84 Hz, 2H), 4.13-4.11(m, 1H), 4.23-4.21 (m, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.06 (d, J = 5.1 Hz, 1H), 8.29 (d, J = 7.6 Hz, 1H). MS (ESI): m/z [M+H]$^+$ calcd for $C_9H_{14}N_3O_4S$: 260.3, found: 260.0.



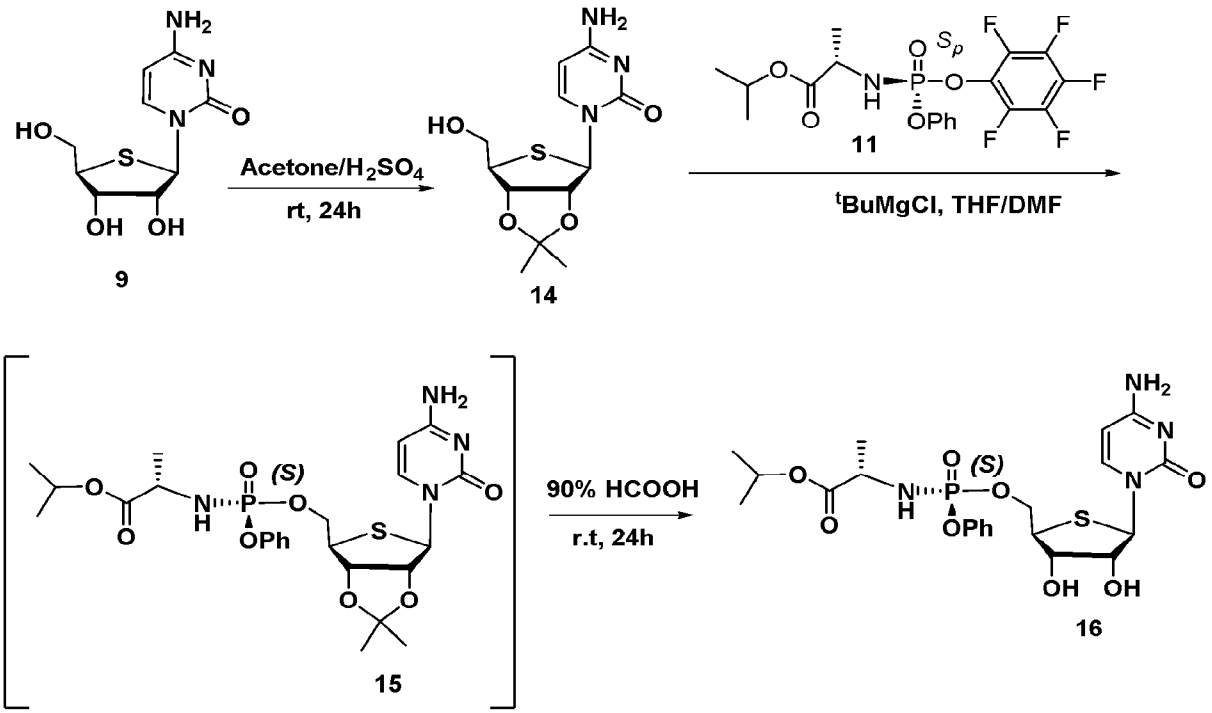
Scheme 3: Synthesis of compound **13**

1-((3aS,4R,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyl-tetrahydrothieno[3,4-d][1,3]dioxol-4-yl)pyrimidine-2,4(1H,3H)-dione (10): To a solution of compound **8** (30 mg, 0.115 mmol) in anhydrous acetone (5 mL) was added 2, 2-dimethoxypropane (1.0 ml) and a catalytic amount of cc H_2SO_4. The reaction mixture was stirred at room temperature for 16 h. Et_3N (0.5

ml) was added slowly to the mixture and the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM/MeOH = 30:1-5:1) to give **10** (35 mg, 82%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.34 (s, 3H), 1.57 (s, 3H), 3.71-3.69 (m, 1H), 3.83-3.81 (m, 2H), 4.90-4.87 (m, 1H), 4.96-4.94 (m, 1H), 5.74 (d, J = 8.1 Hz, 1H), 6.04 (d, J = 2.7 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H). MS (ESI): m/z [M+H]$^+$ calcd for $C_{12}H_{17}N_2O_5S$: 301.3, found: 301.0.

Isopropyl ((S)-(((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3,4-dihydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (13): To a stirred solution of **10** (15 mg, 0.050 mmol, 1.00 eq.) in anhydrous DMF (1 mL) and THF (1 mL), was added tert-butyl magnesium chloride (200 μL, 1 M solution in THF, 4.0 eq) slowly at 0°C. After addition, the mixture was stirred at 0 °C for 15 mins. To the above mixture was added isopropyl ((*S*)-(perfluorophenoxy)-(phenoxy)phosphoryl)-*L*-alaninate **11** (34 mg, 0.075 mmol, 1.5 eq) dropwise, and the resulting mixture was stirred at r.t for 24 h The mixture was quenched with cold water, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to provide the crude compound **12**. The crude compound **12** was dissolved in 2 mL of 90% HCOOH/H_2O (V: V) and stirred at r.t for 4 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM/MeOH = 30:1-10:1) to give **13** (9.0 mg, 50%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.27-1.24 (m, 6H), 1.38-1.36 (m, 3H), 3.59-3.58 (m, 1H), 3.96-3.91 (m, 1H), 4.18-4.17 (m, 1H), 4.28-4.26 (m, 1H), 4.38-4.32 (m, 2H), 5.03-4.97 (m, 1H), 5.72 (d, J = 8.1 Hz, 1H), 6.08 (d, J = 6.4 Hz, 1H), 7.30-7.23 (m, 3H), 7.42-7.38 (m, 2H), 8.05 (d, J = 8.1 Hz,

1H).^{31}P NMR (400 MHz, MeOH-d_4) δ 3.44; MS (ESI): m/z [M+Na]$^+$ calcd for $C_{21}H_{28}N_3NaO_9PS$: 552.4, found: 552.1.

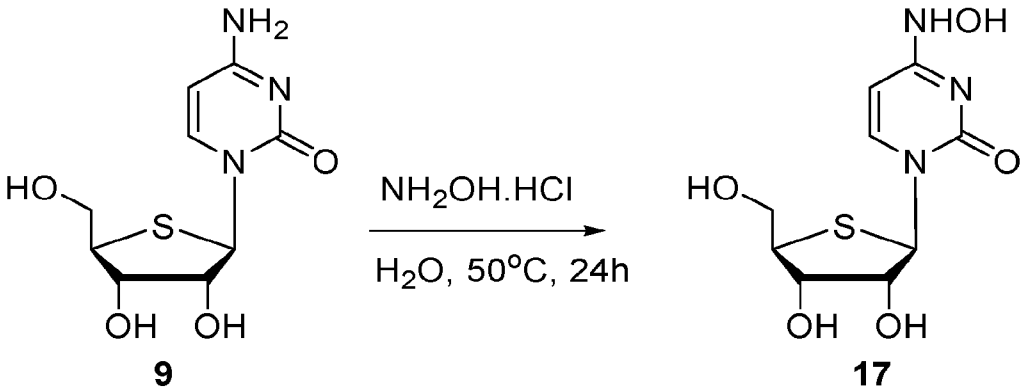


Scheme 4: Synthesis of compound **16**

4-Amino-1-((3a*S*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyl-tetrahydrothieno[3,4-d][1,3]dioxol-4-yl)pyrimidin-2(1H)-one (14): To a solution of compound **9** (45 mg, 0.174 mmol) in anhydrous acetone (5 mL) was added 2, 2-dimethoxypropane (1.0 ml) and a catalytic amount of cc H_2SO_4. The reaction mixture was stirred at room temperature for 16 h. Et_3N (0.5 ml) was added slowly to the mixture and the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM/MeOH = 30:1-5:1) to give **14** (34 mg, 65%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.34 (s, 3H), 1.57 (m, 3H), 3.70-3.68 (m,

1H), 3.82-3.80 (m, 2H), 4.90-4.88 (m, 1H), 4.94-4.92 (m, 1H), 5.97 (d, J = 7.5 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H).

Isopropyl ((*S*)-(((2*R*,3*S*,4*R*,5*R*)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3,4-dihydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (16): To a stirred solution of nucleoside **14** (30 mg, 0.100 mmol, 1.00 eq.) in anhydrous DMF (1 mL) and THF (2 mL), was added tert-butyl magnesium chloride (400 µL, 0.400 mmol, 4.0 eq., 1 M solution in THF) slowly at 0°C. After completion of the addition, the mixture was stirred at 0 °C for 15 mins. To the above mixture was added isopropyl ((*S*)-(perfluorophenoxy)-(phenoxy)phosphoryl)-*L*-alaninate **11** (68 mg, 0.150 mmol, 1.5 eq) dropwise, and the resulting mixture was stirred at r.t for 16 h. The mixture was quenched with cold water, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to provide the crude compound **15**. The crude compound **15** was dissolved in 4 mL of 90% HCOOH/H_2O (V: V) and stirred at r.t for 4 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM/MeOH = 30:1-10:1) to give **16** (9.1 mg, 59%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.26-1.24 (m, 6H), 1.38-1.36 (m, 3H), 3.64-3.60 (m, 1H), 3.96-3.92 (m, 1H), 4.16-4.14 (m, 1H), 4.26-4.24 (m, 1H), 4.40-4.33 (m, 2H), 5.03-4.97 (m, 1H), 5.97 (d, J = 7.5 Hz, 1H), 6.12 (d, J = 5.7 Hz, 1H), 7.30-7.21 (m, 3H), 7.38-7.42 (m, 2H), 8.13 (d, J = 8.0 Hz, 1H).^{31}P NMR (400 MHz, MeOH-d_4) δ 3.44; MS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{30}N_4O_8PS$: 529.5, found: 529.4.



9 17

Scheme 5: Synthesis of compound **17**

Synthesis of 1-((2*R*,3*S*,4*R*,5*R*)-3, 4-dihydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-4-(hydroxyamino) pyrimidin-2(1H)-one (17). To a solution of **9** (12 mg, 0.046 mmol, 1 eq) in H_2O (2 mL) was added $NH_2OH.HCl$ (64 mg, 0.93 mmol, 20 eq). The mixture was stirred at room temperature until TLC showed the complete conversion of **9** to compound **17** (24 h). The resulting mixture was concentrated under reduced pressure and the residue was purified using by flash chromatography (DCM/MeOH system) to afford 6.0 mg of compound **9** in 47% yield. Colorless powder. ^1H NMR (400 MHz, MeOH-d_4) δ 3.40 (s, 1H), 3.81-3.73 (m, 2H), 4.24-4.23 (m, 1H), 4.32-4.30 (m, 1H), 5.72 (d, J = 8.2 Hz, 1H), 6.11 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H). MS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{14}N_3O_5S$: 276.3, found: 276.0.

Example 2

Cellular Toxicity Assays

The toxicity of the compounds was assessed in Vero, human PBM, CEM (human lymphoblastoid), MT-2, and HepG2 cells, as described previously (see Schinazi R.F., Sommadossi J.-P., Saalmann V., Cannon D.L., Xie M.-Y., Hart G.C., Smith G.A. & Hahn E.F. *Antimicrob. Agents Chemother.* **1990**, 34, 1061-67). Cycloheximide was included as positive cytotoxic control, and untreated cells exposed to solvent were included as negative controls. The cytotoxicity IC_{50} or CC_{50} was obtained from the concentration-response curve using the median effective method described previously (see Chou T.-C. & Talalay P.

Adv. Enzyme Regul. **1984**, 22, 27-55; Belen'kii M.S. & Schinazi R.F. Antiviral Res. **1994**, 25, 1-11). The results are shown in Table 8 below:

Example 3

Mitochondrial Toxicity Assays in HepG2 Cells:

i) Effect of Compounds on Cell Growth and Lactic Acid Production: The effect on the growth of HepG2 cells can be determined by incubating cells in the presence of 0 μM, 0.1 μM, 1 μM, 10 μM and 100 μM drug. Cells (5 x 10^4 per well) can be plated into 12-well cell culture clusters in minimum essential medium with nonessential amino acids supplemented with 10% fetal bovine serum, 1% sodium pyruvate, and 1% penicillin/streptomycin and incubated for 4 days at 37°C. At the end of the incubation period the cell number can be determined using a hemocytometer. Also taught by Pan-Zhou X-R, Cui L, Zhou X-J, Sommadossi J-P, Darley-Usmer VM. "Differential effects of antiretroviral nucleoside analogs on mitochondrial function in HepG2 cells," Antimicrob. Agents Chemother. **2000**; 44: 496-503.

To measure the effects of the compounds on lactic acid production, HepG2 cells from a stock culture can be diluted and plated in 12-well culture plates at 2.5 x 10^4 cells per well. Various concentrations (0 μM, 0.1 μM, 1 μM, 10 μM and 100 μM) of compound can be added, and the cultures can be incubated at 37°C in a humidified 5% CO_2 atmosphere for 4 days. At day 4, the number of cells in each well can be determined and the culture medium collected. The culture medium can then be filtered, and the lactic acid content in the medium determined using a colorimetric lactic acid assay (Sigma-Aldrich). Since lactic acid product can be considered a marker for impaired mitochondrial function, elevated levels of lactic acid production detected in cells grown in the presence of test compounds indicates a drug-induced cytotoxic effect.

ii) Effect on Compounds on Mitochondrial DNA Synthesis: a real-time PCR assay to accurately quantify mitochondrial DNA content has been developed (see Stuyver LJ, Lostia S, Adams M, Mathew JS, Pai BS, Grier J, Tharnish PM, Choi Y, Chong Y, Choo H, Chu CK, Otto MJ, Schinazi RF. Antiviral activities and cellular toxicities of modified 2',3'-dideoxy-2',3'-didehydrocytidine analogs. Antimicrob. Agents Chemother. **2002**; 46: 3854-60). This assay can be used in all studies described in this application that determine the effect of

compounds on mitochondrial DNA content. In this assay, low-passage- number HepG2 cells are seeded at 5,000 cells/well in collagen-coated 96-well plates. Test compounds are added to the medium to obtain final concentrations of 0 μM, 0.1 μM, 10 μM and 100 μM. On culture day 7, cellular nucleic acids can be prepared by using commercially available columns (RNeasy 96 kit; Qiagen). These kits co-purify RNA and DNA, and hence, total nucleic acids are eluted from the columns. The mitochondrial cytochrome c oxidase subunit II (COXII) gene and the ß-actin or rRNA gene can be amplified from 5 μl of the eluted nucleic acids using a multiplex Q-PCR protocol with suitable primers and probes for both target and reference amplifications. For COXII the following sense, probe and antisense primers can be used, respectively: 5'- TGCCCGCCATCATCCTA-3', 5'-tetrachloro-6-carboxyfluorescein-TCCTCATCGCCCTCCCATCCC-TAMRA-3' and 5'-CGTCTGTTATGTAAAGGATGCGT-3'. For exon 3 of the ß-actin gene (GenBank accession number E01094) the sense, probe, and antisense primers are 5'- GCGCGGCTACAGCTTCA-3', 5'-6-FAMCACCACGGCCGAGCGGGATAMRA-3' and 5'-TCTCCTTAATGTCACGCACGAT-3', respectively. The primers and probes for the rRNA gene are commercially available from Applied Biosystems. Since equal amplification efficiencies are obtained for all genes, the comparative CT method can be used to investigate potential inhibition of mitochondrial DNA synthesis. The comparative CT method uses arithmetic formulas in which the amount of target (COXII gene) is normalized to the amount of an endogenous reference (the ß-actin or rRNA gene) and is relative to a calibrator (a control with no drug at day 7). The arithmetic formula for this approach is given by $2^{-\Delta\Delta CT}$, where ΔΔCT is (CT for average target test sample - CT for target control) - (CT for average reference test -CT for reference control) (see Johnson MR, K Wang, JB Smith, MJ Heslin, RB Diasio. Quantitation of dihydropyrimidine dehydrogenase expression by real-time reverse transcription polymerase chain reaction. Anal. Biochem. 2000; 278:175-184). A decrease in mitochondrial DNA content in cells grown in the presence of drug indicates mitochondrial toxicity.

Example 4

Mitochondrial Toxicity- Glu/Gal

Protocol Summary

HepG2 cells are plated on 96 or 384 well tissue culture polystyrene plates. After 24 hr the cells are dosed with test compound at a range of concentrations and incubated for 72 hr in medium supplemented with either galactose or glucose. Test compounds are said to cause mitochondrial toxicity if the cells grown in galactose-containing medium are more sensitive to the test compound than the cells grown in glucose-containing medium.

Objective: To measure the sensitivity of HepG2 cells grown in medium containing either galactose or glucose to the test compound.

Experimental Procedure

HepG2 human hepatocellular carcinoma cells are plated on 96 or 384-well tissue culture polystyrene plates containing either galactose or glucose containing medium supplemented with 10 % fetal bovine serum and antibiotics and incubated overnight. The cells are dosed with increasing concentrations of the test compound (final DMSO concentration 0.5 %; typical final test compound concentrations of 100, 30, 10, 3, 1, 0.3, 0.1, 0.03 μM for an eight point dose response curve; n = 3 replicates per concentration) and the cells are incubated for 72 hr. Appropriate controls are simultaneously used as quality controls. Cell viability is measured using Hoechst staining and cell counting by a HCS reader.

Example 5

Mitochondrial Toxicity Assays in Neuro2A Cells

To estimate the potential of the compounds described herein to cause neuronal toxicity, mouse Neuro2A cells (American Type Culture Collection 131) can be used as a model system (see Ray AS, Hernandez-Santiago BI, Mathew JS, Murakami E, Bozeman C, Xie MY, Dutschman GE, Gullen E, Yang Z, Hurwitz S, Cheng YC, Chu CK, McClure H, Schinazi RF, Anderson KS. Mechanism of anti-human immunodeficiency virus activity of beta-D-6-cyclopropylamino-2',3'-didehydro-2',3'-dideoxyguanosine. *Antimicrob. Agents Chemother.* **2005**, 49, 1994-2001). The concentrations necessary to inhibit cell growth by 50% (CC50) can be measured using the 3-(4,5-dimethyl-thiazol-2-yl)-2,5- diphenyltetrazolium bromide dye-based assay, as described. Perturbations in cellular lactic acid and mitochondrial DNA levels at defined concentrations of drug can be carried out as described above. ddC and AZT can be used as control nucleoside analogs.

Example 6

Assay for Bone Marrow Cytotoxicity

Primary human bone marrow mononuclear cells can be obtained commercially from Cambrex Bioscience (Walkersville, MD). CFU-GM assays is carried out using a bilayer soft agar in the presence of 50 units/mL human recombinant granulocyte/macrophage colony-stimulating factor, while BFU-E assays used a ethylcellulose matrix containing 1 unit/mL erythropoietin (see Sommadossi JP, Carlisle R. Toxicity of 3'-azido-3'-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl) guanine for normal human hepatopoietic progenitor cells *in vitro*. Antimicrob. Agents Chemother. 1987; 31: 452-454; Sommadossi, JP, Schinazi, RF, Chu, CK, and Xie, MY. Comparison of cytotoxicity of the (-) and (+) enantiomer of 2',3'-dideoxy-3'-thiacytidine in normal human bone marrow progenitor cells. Biochem. Pharmacol. 1992; 44:1921- 1925). Each experiment can be performed in duplicate in cells from three different donors. AZT is used as a positive control. Cells can be incubated in the presence of the compound for 14-18 days at 37°C with 5% CO_2, and colonies of greater than 50 cells can be counted using an inverted microscope to determine the IC_{50}. The 50% inhibitory concentration (IC_{50}) can be obtained by least-squares linear regression analysis of the logarithm of drug concentration versus BFU-E survival fractions. Statistical analysis can be performed with Student's t test for independent non-paired samples.

Example 7

In vitro human mitochondrial RNA polymerase (POLRMT) assay

In vitro RNA nucleotide incorporation assays with POLRMT (INDIGO Biosciences) can be performed as previously described (Arnold *et al.* 2012). Briefly, ^{32}P-radiolabeled RNA primer (5'-UUUUGCCGCGCC) can be hybridized to 3 molar excess of the appropriate DNA template (5'-GGGAATGCANGGCGCGGC where position N can be replaced by A, T, or C). 125 nM of POLRMT can be incubated with 500 nM of 5'-radiolabled RNA/DNA hybrid, 10 mM $MgCl_2$ and 100 μM of the corresponding nucleoside triphosphate. For non-nucleoside analogs, 100 μM of inhibitor can be added at the same time as 100 μM UTP. Incorporation can be allowed to proceed for 2 h at 30°C and reactions are stopped by the addition of 10 mM EDTA and formamide. Samples are visualized on 20% denaturing polyacrylamide gel. Data can be analyzed by normalizing the product fraction for each nucleoside triphosphate analog to that of the corresponding natural nucleoside triphosphate.

Example 8

Effect of Nucleotide Analogs on the DNA Polymerase and Exonuclease Activities of Mitochondrial DNA Polymerase γ

i) Purification of Human Polymerase γ: The recombinant large and small subunits of polymerase γ can be purified as described previously (see Graves SW, Johnson AA, Johnson KA. Expression, purification, and initial kinetic characterization of the large subunit of the human mitochondrial DNA polymerase. *Biochemistry*. **1998**, 37, 6050-8; Johnson AA, Tsai Y, Graves SW, Johnson KA. Human mitochondrial DNA polymerase holoenzyme: reconstitution and characterization. Biochemistry **2000**; 39: 1702-8). The protein concentration can be determined spectrophotometrically at 280 nm, with extinction coefficients of 234,420, and 71,894 M-1 cm-1 for the large and the small subunits of polymerase γ, respectively.

ii) Kinetic Analyses of Nucleotide Incorporation: Pre-steady-state kinetic analyses can be performed to determine the catalytic efficiency of incorporation (k/K) for DNA polymerase γ for nucleoside-TP and natural dNTP substrates. This allowed determination of the relative ability of this enzyme to incorporate modified analogs and predict toxicity. Pre-steady-state kinetic analyses of incorporation of nucleotide analogs by DNA polymerase γ would be carried out essentially as described previously (see Murakami E, Ray AS, Schinazi RF, Anderson KS. Investigating the effects of stereochemistry on incorporation and removal of 5-fluorocytidine analogs by mitochondrial DNA polymerase gamma: comparison of D- and L-D4FC-TP. *Antiviral Res.* **2004**, *62*, 57-64; Feng JY, Murakami E, Zorca SM, Johnson AA, Johnson KA, Schinazi RF, Furman PA, Anderson KS. Relationship between antiviral activity and host toxicity: comparison of the incorporation efficiencies of 2',3'-didcoxy-5-fluoro-3'-thiacytidine-triphosphate analogs by human immunodeficiency virus type 1 reverse transcriptase and human mitochondrial DNA polymerase. *Antimicrob Agents Chemother.* **2004**, 48, 1300-6). Briefly, a pre-incubated mixture of large (250 nM) and small (1.25 mM) subunits of polymerase γ and 60nM DNA template/primer in 50mM Tris-HCl, 100 mM NaCl, pH 7.8, can be added to a solution containing $MgCl_2$ (2.5 mM) and various concentrations of nucleotide analogs. Reactions can be quenched and analyzed as described previously. Data can be fit to the same equations as described above.

iii) Assay for Human Polymerase γ 3' 5' Exonuclease Activity: The human polymerase γ exonuclease activity can be studied by measuring the rate of formation of the cleavage products in the absence of dNTP. The reaction can be initiated by adding $MgCl_2$ (2.5mM) to a pre-incubated mixture of polymerase γ large subunit (40nM), small subunit (270nM), and 1,500nM chain-terminated template/primer in 50mM Tris-HCl, 100mM NaCl, pH 7.8, and quenched with 0.3M EDTA at the designated time points. All reaction mixtures would be analyzed on 20% denaturing polyacrylamide sequencing gels (8M urea), imaged on a Bio-Rad GS-525 molecular image system, and quantified with Molecular Analyst (Bio- Rad). Products formed from the early time points would be plotted as a function of time. Data would be fitted by linear regression with Sigma Plot (Jandel Scientific). The slope of the line can be divided by the active enzyme concentration in the reaction to calculate the kexo for exonuclease activity (see Murakami E, Ray AS, Schinazi RF, Anderson KS. Investigating the effects of stereochemistry on incorporation and removal of 5- fluorocytidine analogs by mitochondrial DNA polymerase gamma: comparison of D- and L-D4FC-TP. Antiviral Res. 2004; 62: 57-64; Feng JY, Murakami E, Zorca SM, Johnson AA, Johnson KA, Schinazi RF, Furman PA, Anderson KS. Relationship between antiviral activity and host toxicity: comparison of the incorporation efficiencies of 2',3'-dideoxy-5-fluoro-3'-thiacytidine-triphosphate analogs by human immunodeficiency virus type 1 reverse transcriptase and human mitochondrial DNA polymerase. Antimicrob Agents Chemother. 2004; 48: 1300-6).

Example 9

Inhibition of Human DNA Polymerases by NTP's

Study Objectives

To determine whether a nucleoside-triphosphate analog inhibits human DNA polymerases Alpha, Beta and Gamma and to calculate IC_{50} values.

Materials and Methods

Human DNA Polymerase Alpha – Enzyme can be purchased from Chimerx (cat#1075) and assayed based on their recommendations with some modifications. The 2'-Me-UTP was treated with Inorganic Pyrophosphatase (Sigma) to remove any pyrophosphate contamination. A final concentration of 500 μM 2'-Me-UTP can be incubated with 1 mM DTT, 50 mM Tris, 50 mM NaCl, 6 mM $MgCl_2$, and 1 unit of pyrophosphatase for 1 hour at 37°C followed by

inactivation at 95°C for 10 minutes. A mixture of 0.05 units of Human DNA Polymerase Alpha and a 5'end radiolabeled 24nt DNA primer (5'-TCAGGTCCCTGTTCGGGCGCCACT) anneal to a 48nt DNA template (5'-CAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACCTGAAAGC) can be mixed with increasing concentrations of compound from 0 to 100 µM in 60 mM Tris-HCl (pH 8.0), 5 mM magnesium acetate, 0.3 mg/ml bovine serum albumin, 1 mM dithiothreitol, 0.1 mM spermine, 0.05 mM of each dCTP, dGTP, dTTP, dATP in a final reaction volume of 20 µl for 5 min at 37°C (all concentrations represent final concentrations after mixing). The reactions can be stopped by mixing with 0.3 M (final) EDTA. Products are separated on a 20% polyacrylamide gel and quantitated on a Bio-Rad Molecular Imager FX. Results from the experiments can be fit to a dose response equation, (y min +((y max)-(y min)))/(1+(compound concentration)/IC_{50})^slope) to determine IC_{50} values using Graphpad Prism or SynergySoftware Kaleidagraph. Data can be normalized to controls.

Human DNA Polymerase Beta – Enzyme can be purchased from Chimerx (cat#1077) and assayed based on their recommendations with some modifications. A mixture of 0.1 units of Human DNA Polymerase Beta and a 5'end radiolabeled 24nt DNA primer (5'-TCAGGTCCCTGTTCGGGCGCCACT) anneal to a 48nt DNA template (5'-CAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACCTGAAAGC) can be mixed with increasing concentrations of compound from 0 to 100 µM in 50 mM Tris-HCl (pH 8.7), 10 mM KCl, 10 mM $MgCl_2$, 0.4 mg/ml bovine serum albumin, 1 mM dithiothreitol, 15% (v/v) glycerol, and 0.05 mM of each dCTP, dGTP, dTTP, dATP in a final reaction volume of 20 µl for 5 min at 37°C (all concentrations represent final concentrations after mixing). The reactions can be stopped by mixing with 0.3 M (final) EDTA. Products can be separated on a 20% polyacrylamide gel and quantitated on a Bio-Rad Molecular Imager FX. Results from the experiments can be fit to a dose response equation, (y min +((y max)-(y min)))/(1+(compound concentration)/IC_{50})^slope) to determine IC_{50} values using Graphpad Prism or SynergySoftware Kaleidagraph. Data can be normalized to controls..

Human DNA Polymerase Gamma – Enzyme can be purchased from Chimerx (cat#1076) and assayed based on their recommendations with some modifications. A mixture of 0.625 units of Human DNA Polymerase Gamma and a 5'end radiolabeled 24nt DNA primer (5'-TCAGGTCCCTGTTCGGGCGCCACT) anneal to a 36nt DNA template (5'-

TCTCTAGAAGTGGCGCCCGAACAGGGACCTGAAAGC) can be mixed with increasing concentrations of compound from 0 to 100 μM in 50 mM Tris-HCl (pH 7.8), 100 mM NaCl, 5 mM $MgCl_2$, and 0.05 mM of each dCTP, dGTP, dTTP, dATP in a final reaction volume of 20 μl for 200 min at 37°C (all concentrations represent final concentrations after mixing). The reactions can be stopped by mixing with 0.3 M (final) EDTA. Products can be separated on a 20% polyacrylamide gel and quantitated on a Bio-Rad Molecular Imager FX. Results from the experiments can be fit to a dose response equation, (y min +((y max)-(y min)))/(1+(compound concentration)/IC_{50})^slope) to determine IC_{50} values using Graphpad Prism or SynergySoftware Kaleidograph. Data can be normalized to controls.

Example 10

Cellular Pharmacology in HepG2 cells

HepG2 cells are obtained from the American Type Culture Collection (Rockville, MD), and are grown in 225 cm^2 tissue culture flasks in minimal essential medium supplemented with non-essential amino acids, 1% penicillin-streptomycin. The medium is renewed every three days, and the cells are subcultured once a week. After detachment of the adherent monolayer with a 10 minute exposure to 30 mL of trypsin-EDTA and three consecutive washes with medium, confluent HepG2 cells are seeded at a density of 2.5 x 10^6 cells per well in a 6-well plate and exposed to 10 μM of [^{3}H] labeled active compound (500 dpm/pmol) for the specified time periods.

The cells are maintained at 37°C under a 5% CO_2 atmosphere. At the selected time points, the cells are washed three times with ice-cold phosphate-buffered saline (PBS).

Intracellular active compound and its respective metabolites are extracted by incubating the cell pellet overnight at -20°C with 60% methanol followed by extraction with an additional 20 pal of cold methanol for one hour in an ice bath. The extracts are then combined, dried under gentle filtered air flow and stored at -20°C until HPLC analysis.

Example 11

Cellular Pharmacology in Vero, Calu-3 and Caco-2 cells

The Vero, Calu-3 and Caco-2 cells were seeded at 1x106 per well in 12-well plates and incubated in a cell culture incubator at 37 °C with a humidified atmosphere of 5% CO2. Adherent cells were subsequently exposed to 10 μM of RS-3995. At 4 h, drug-containing

medium was removed, and cells were washed twice with ice-cold phosphate buffered saline (PBS). Cells were resuspended in 70% ice-cold methanol containing 20 nM ddATP overnight at -20 °C. The supernatants were then dried under a flow of air and dried samples stored at -20 °C until analyzed by LC-MS/MS. Prior to analysis, each sample was reconstituted in 200 µL mobile phase.

Chromatographic separation and detection were performed on a Vanquish Flex system (Thermo Scientific, Waltham, MA) coupled with a TSQ Quantiva triple quadrupole mass spectrometer (Thermo Scientific, Waltham, MA). Analytes were separated using a Kinetex EVO-C18 column (100 X 2.1 mm, 2.6 µm) (Phenomenex, Torrance, CA) at a flow rate of 250 µL/min. The mobile phase A consisted of 2 mM of ammonium phosphate monobasic and 3 mM of hexylamine in water and the mobile phase B consisted of acetonitrile. The LC gradient increased from 2% to 60% of mobile phase B in 7 min, and then returned to the initial condition. Selected reaction monitoring in both positive and negative modes (spray voltage: 3200 V (pos) or 2500 V (neg); sheath gas: 35 Arb; Auxiliary gas: 20 Arb; Ion transfer tube temperature: 350 °C; vaporizer temperature: 380 °C) was used to detect the targets.

Table 1: Levels of compound 8 monophosphate (MP), diphosphate (DP) and triphosphate (TP) in Vero, Calu-3 and Caco-2 cells after 4 h.

Metabolites at 4 hr (pmol/million cells)	**Vero cells**	**Calu3 cells**	**Caco2 cells**
8-MP	0.23 ± 0.002	BLOQ	BLOQ
8-DP	9.89 ± 0.29	10.4 ± 0.6	1.76 ± 0.26
8-TP	**307 ± 2**	**257 ± 4**	**41.2 ± 5.1**

BLOQ: Below level of quantification

Example 12

MERS Assay

Cells and Virus:

Human lung carcinoma cells (A-549) can be used for the primary antiviral assays and can be obtained from American Type Culture Collection (ATCC, Rockville, Md., USA). The cells can be passed in minimal essential medium (MEM with 0.15% $NaCHO_3$, Hyclone Laboratories, Logan, Utah, USA) supplemented with 10% fetal bovine serum. When evaluating compounds for efficacy, the serum can be reduced to a final concentration of 2% and the medium can contain gentamicin (Sigma-Aldrich, St. Louis, Mo.) at 50 μg/mL. Since the MERS-Co virus did not produce detectable virus cytopathic effects, virus replication in A549 cells can be detected by titering virus supernatant fluids from infected, compound-treated A549 cells in Vero 76 cells.

Vero 76 cells can be obtained from ATCC and can be routinely passed in MEM with 0.15% $NaCHO_3$ supplemented with 5% fetal bovine serum. When evaluating compounds, the serum can be reduced to a final concentration of 2% and supplemented with 50 μg/mL of gentamicin.

The Middle Eastern coronavirus strain EMC (MERS-CoV) was an original isolate from humans that was amplified in cell culture by Ron Fouchier (Erasmus Medical Center, Rotterdam, the Netherlands) and was obtained from the Centers for Disease Control (Atlanta, Ga.).

Controls:

Infergen® (interferon alfacon-1, a recombinant non-naturally occurring type-I interferon (Blatt, L., et al., J. Interferon Cytokine Res. (1996) 16(7):489-499 and Alberti, A., BioDrugs (1999) 12(5):343-357) can be used as the positive control drug in all antiviral assays. Infergen=0.03 ng/mL.

Antiviral Assay:

Virus can be diluted in MEM to a multiplicity of infection=0.001 and each compound can be diluted in MEM+2% FBS using a half-log 8 dilution series. Compound can be added first to 96 well plates of confluent A549 cells followed within 5 mins by virus. Each test compound dilution can be evaluated for inhibition in triplicate. After plating, the plates can be incubated at 37° C. for 4 d. The plates can then be frozen at -80° C.

Virus Yield Reduction Assay:

Infectious virus yields from each well from the antiviral assay can be determined. Each plate from an antiviral assay can be thawed. Samples wells at each compound concentration tested can be pooled and titered for infectious virus by CPE assay in Vero 76 cells. The wells can be scored for CPE and virus titers calculated. A 90% reduction in virus yield can then be calculated by regression analysis. This represented a one log_10 inhibition in titer when compared to untreated virus controls.

Example 13

Determining the Efficacy of the Compounds against HCoV-OC43 and SARS-CoV-2 Infections

Viruses

HCoV-OC43 was obtained from ATCC (Manasas, VA) and SARS-CoV-2 was provided by BEI Resources (NR-52281: USA-WA/2020). HCoV-OC43 and SARS-CoV-2 were propagated in appropriate cells, respectively and titrated by $TCID_{50}$ method followed by storage of aliquots at -80°C until further use.

Cells and Media:

For cytotoxicity and antiviral studies, the following immortalized/transformed cell lines were used: human colon epithelial cells (Caco-2; ATCC® HTB-37™, Manassas, VA, USA), human bronchial epithelial cells (Calu-3; ATCC® HTB-55™, Manassas, VA, USA), human small alveolar cells expressing the human ACE-2 receptor via lentivirus transduction ($A549^{hACE2}$; kind gift from Dr. Susan Weiss (Lei et al 2021)), and African Green Monkey kidney cells (Vero; ATCC® CCL-81™, Manassas, VA, USA). Media compositions were (1) Caco-2 and Calu-3: Eagle's minimum essential medium (EMEM), 10% fetal bovine serum (FBS), 100 U/mL penicillin-streptomycin (pen-strep), and 2 μM L-glutamine (L-glut), (2) $A549^{hACE2}$ and Vero: Dulbecco's modified eagle medium (DMEM), 10% FBS, 100 U/mL pen-strep. Additional studies were performed in differentiated primary normal human bronchial/tracheal cells (NHBEs) derived from a single donor per culture (Lonza Biosciences CC-2540s, Basal, Switzerland) cultivated in 3D via standard air-liquid interface (ALI;

StemCell Technologies 2021) or as custom apical-out lung organoids (HBO; Lee and LeCher et al unpublished). HBTECs were expanded in custom Pneuma-Cult™ Ex Plus medium (Stem Cell Technologies, Vancouver, B.C.) and differentiated in either custom Pneuma-Cult™ ALI medium (ALI; Stem Cell Technologies, Vancouver, B.C.) or Pneuma-Cult™ Organoid Apical-out medium (HBO; Stem Cell Technologies, Vancouver, B.C.) supplemented with hydrocortisone and heparin sulfate. For all experiments, cells were grown at 37 °C in a 95% O_2, 5% CO_2 incubator.

Antiviral Screening Assays:

For standard antiviral screening, cells (Caco-2, Calu-3 monolayer, Ace-2^{h549}, and Vero) were grown to confluency (1 x 10^5 cells) in 96-well plates. Dose-response curves were performed by treating cells with 2-fold serial dilutions (0 – 10 μM) of compounds of interest in respective base media containing 2% heat-inactivated FBS (ΔFBS) then infected with SARS-CoV2 at an MOI of 0.1 (Vero) or 1.0 (Caco2, Calu-3, $A549^{hACE2}$) for 48 (Vero) or 72 hr (Caco2, Calu-3, $A549^{hACE2}$). Cells/supernatants were collected in 150 μL RLT Buffer (Qiagen©, Hilden, Germany) for downstream RNA extraction (RNeasy 96 extraction kit; Qiagen©, Hilden, Germany) and subsequent qRT-PCR to detect viral load.

Advanced antiviral assays were also performed by dose-response assay with lead compounds in ALI-Calu-3s, ALI-NHBEs, and HBO-NHBEs with the following modifications: ALI-Calu3 – 1.8 x 10^4 cells were seeded onto a 96-well 1.0 μm pore transwell insert (Corning, USA). After 3 days, media was removed from the apical chamber and cells were cultured for an additional week at ALI. ALI-NHBEs - 1.5 x10^5 cells were seeded onto a 24-well collagen-coated 0.4 μm pore transwell insert (Corning, USA) After 3 days, media was removed from the apical chamber and cells were cultured for an additional 3 weeks at ALI. For both ALI cultures, compounds were added at indicated dilutions to the basolateral chamber. Cells were washed 3x with HEPES-buffered salt solution (HBSS) on apical surface to remove excess mucus then infected by adding 50 μL of SARS-CoV-2 (MOI 1.0) to the apical chamber for a 5 hr adsorption after which virus was removed and cells retained in ALI for an additional 3 days. For HBO cultures, 3 x 10^3 cells were seeded in hanging-drop suspension with Matrigel® Basement Membrane Matrix (Corning, USA) to generate a single organoid per well and cultured for 21 days. Serially diluted compounds and virus (MOI 1.0)

were added directly to the wells for a period of 3 days. Calu3-ALI and HBO infected cultures were collected in 150 µL RLT Buffer (Qiagen©, Hilden, Germany) while NHBE-ALI cultures were collected in 300 µL of Trizol™ Reagent and RNA extracted by phenyl-chloroform method according to manufactures' protocol (ThermoFisher Scientific, USA). All infections were carried out in a BSL-3 level laboratory at Emory University in accordance with the guidelines of the 5th edition of Biosafety in Microbiological and Biomedical Laboratories. All experiments were performed three independent times in duplicate or triplicate.

SARS-CoV-2-yield inhibition assay by qRT-PCR assay:

Virus yield inhibition assays were performed as previously described (Zandi et al 2020). In brief, viral RNA was detected by real-time PCR using a 6-carboxyfluorescein (FAM)-labeled probe with primers against SARS-CoV2 non-structural protein 3 (nsp3). (SARS-CoV-2 FWD: AGA AGA TTG GTT AGA TGA TGA TAG T; SARS-CoV-2 REV:TTC CAT CTC TAA TTG AGG TTG AAC C; SARS-CoV-2 Probe: 56-FAM/TC CTC ACT GCC GTC TTG TTG ACC A/3BHQ_1) RNA isolated from uninfected cells was used as a negative control for virus detection. RNA was added to optimized 10 µM primer/probe mix in Mastermix (qScript™ XLT One-Step RT-qPCR ToughMix®; Quantabio, USA) and run on StepOne Plus real-time PCR (Roche, Germany) according to the manufacturer's protocol. C_T values were calculated from replicate groups then virus yield quantified via standard curve. Median effective concentration of compounds (EC_{50}) and concentrations with a 90% inhibitory effect (EC_{90}) were calculated using GraphPad Prism, version 7 (GraphPad Software Inc., San Diego, CA) and reported as the mean ± standard deviation.

SARS-CoV-2-yield inhibition by neon-green reporter assay:

Virus yield inhibition assays via neon-green reporter were performed as previously described (Tao et al 2021). In brief, cells were infected in the presence or absence of compounds as described above but with a neon green-expressing icSARS-CoV-2-mNG infectious clone (Xie et al 2020) at MOI 0.1 (Vero). Cultures were monitored daily for the neon green expression in control wells. After 48 (Vero), 72 (Caco-2, Calu-3, $A549^{hACE2}$, ALI-NHBE, & HBO-NHBE), or 96 (ALI-NHBE, & HBO-NHBE) hr post infection, all wells were

imaged and antiviral activity of compounds was determined as percent reduction in mean relative fluorescence from controls.

One of two methods was employed to obtain images: (1) Living cells were imaged on Leica FC 7000 GT microscope with pE-300 fluorescent light housing using LAX software (Leica Biosystems), images processed with Image J software, and cells collected in RLT Buffer for downstream qRT-PCR, or (2) cells were directly fixed in 4% paraformaldehyde for 30 min for removal from the BSL3, permeabilized in 1% ND-40-PBS buffer, DAPI counterstained, and imaged on a Cytation 5 cell imaging multi-mode reader and quantified on Gen5 software (Biotek, Winooski, VT). Uninfected wells served as a negative control measure for background fluorescence.

The anti-SARS-CoV-2 activity is shown in Tables 2-5 below, and toxicity data is shown in Table 6 below:

Table 2

Compound	Anti-SARS-CoV-2 Activity (Vero) (μM)		Anti-SARS-CoV-2 Activity (Calu3) (μM)		Anti-SARS-CoV-2 Activity (Caco2) (μM)		Cytotoxicity CC_{50} (μM)			
	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}	PBM	CEM	Vero	Huh7
9	0.2	4.5	1.9	3.9	4.9	>10	>100	28.0	71.8	93.1
8	0.4	0.8	1.7	3.5	1.1	2.8	>100	20.5	68.3	>100
16	>10						>100	>100	>100	>100
13	>10						>100	>100	>100	>100
17	<10		<10				>100		>100	>100
NHC	0.2	0.42	0.6	2.0	1.0	>10	49.2	2.6	16.5	80.3
Remdesivir	1.0	3.5	0.1	0.6	0.004	0.04	6.4	12	>100	1.5

ND: Not determined

Table 3

Compound	3D Primary Culture Systems			
	Anti-SARS-CoV-2 Activity (HAE-ALI) (μM)		Anti-SARS-CoV-2 Activity (Organoids) (μM)	
	EC_{50}	EC_{90}	EC_{50}	EC_{90}
8	**0.04**	**0.1**	**0.7**	**2.5**
Remdesivir	0.6	1.2	0.7	1.5

Table 4

	Antiviral Activity Against SARS-CoV-2 Variants in Vero (μM)				Antiviral Activity Against SARS-CoV-2 Variants in Calu3 (μM)			
	8		**Remdesivir**		**8**		**Remdesivir**	
	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}
Alpha	**0.3**	**1.4**	0.4	1.6	**0.3**	**1.2**	0.3	0.4
Beta	**0.8**	**1.0**	1.1	2.2	**1.1**	**1.2**	ND	ND
Gamma	**0.2**	**0.3**	0.3	2.1	**0.04**	**0.1**	0.26	0.3
Delta	**ND**	**ND**	ND	ND	**1.8**	**3.6**	0.3	2.3
Lineage A (Eng)	**0.2**	**0.4**	0.3	2.9	**1.7**	**4.5**	0.02	0.3
Lineage A (Wa)	**0.8**	**1.2**	0.2	0.6	**0.1**	**0.4**	0.1	0.4

Table 4

Compound	Anti-HCoV-OC43 Activity (μM)	
	EC_{50}	EC_{90}
8	**2.2 – 2.5**	**6.1 – 7.3**
Remdesivir	0.007-0.03	0.03-0.08

Table 5

Compounds	Anti-Omicron Activity (Calu-3)		Anti-Omicron Activity (Caco-2)	
	EC_{50} (μM)	EC_{90} (μM)	EC_{50} (μM)	EC_{90} (μM)
Remdesivir	0.2 – 0.3	0.6 – 0.7	0.05	0.4
NHC	0.4	1.2	>10 (13.3)	>10
8	0.9 - 1.3	2.7 - 4.4	8.2	>10

Table 6: Toxicity of Compound 8 in Caco2 and Calu3 cells

	Cytotoxicity CC_{50} (μM)	
	Calu3	**Caco2**
8	**>100**	**>100**
cyclohexamide	**10**	**10**

Quantification and Non-compartment PK Analysis of compound 8 in Mouse Plasma Samples:

Methods:

- CD-1 mice were administered compound 8 by PO (30 mg/kg, 3 mice) or IV (15 mg/kg, 3 mice). Plasma samples were collected at 30 min, 2 h, 4 h, and 7 h.

Sample preparation:

- 20 μL mice plasma was mixed with 100 μL MeOH.
- The supernatant was air-dried, then reconstituted in 200 μL of H2O.
- Subjected to LC-MS analysis.
- Calibration curve range: 50 nM to 100 μM.

LC-MS/MS condition:

- Instrument: TSQ Quantiva, Column: Kinetex XB-C8 (50X2.1 mm, 2.6 μm)
- LC buffers: A): 0.1% formic acid, and B): Acetonitrile
- LC gradients: 0 – 0.3 min, 2% B; 0.3 – 3 min, 2% - 80% B; 3 – 3.2 min, 80% B; 3.2 – 3.5 min, 80% – 2% B; 3.5 – 8 min, 2% B

Compound 8 mitochondrial toxicity in HepG2 cells:

- CC_{50} for MtDNA >100 μM (<1% inhibition at 100 μM)
- CC_{50} rDNA > 100 μM (36.32% inhibition at 100 μM)

References:

Li, Y., Renner, D. M., Comar, C. E., Whelan, J. N., Reyes, H. M., Cardenas-Diaz, F. L., and Weiss, S. R. (2021). SARS-CoV-2 induces double-stranded RNA-mediated innate immune responses in respiratory epithelial-derived cells and cardiomyocytes. *Proceedings of the National Academy of Sciences, 118*(16).

Stem Cell Technologies. Model the human airway in vitro as ALI cultures or airway organoids.

Lee, J. H. and LeCher, J. C., et al (2021). Apical-out human bronchial organoid models for SARS-CoV-2 infection studies. Unpublished Study.

Zandi, K., Amblard, F., Musall, K., Downs-Bowen, J., Kleinbard, R., Oo, A., and Schinazi, R. F. (2020). Repurposing nucleoside analogs for human coronaviruses. *Antimicrobial agents and chemotherapy*, *65*(1), e01652-20.

Tao, S., Zandi, K., Bassit, L., Ong, Y. T., Verma, K., Liu, P., and Schinazi, R. F. (2021). Comparison of anti-SARS-CoV-2 activity and intracellular metabolism of remdesivir and its parent nucleoside. *Current Research in Pharmacology and Drug Discovery*, *2*, 100045.

Xie, X., Muruato, A., Lokugamage, K. G., Narayanan, K., Zhang, X., Zou, J., and Shi, P. Y. (2020). An infectious cDNA clone of SARS-CoV-2. *Cell host & microbe*, *27*(5), 841-848.

Evaluation in a model of SARS-CoV-2 infection of human lung epithelium and monocytes system:

In vitro transmigration experiments and infection with virus. The H441 Club cell line was grown on Alvetex scaffolds (ReproCELL, Glasgow, UK) coated with rat-tail collagen (Sigma) for 2 weeks at air liquid interface with 2% v/v Ultroser G (Crescent Chemical, Islandia, NY) in 50/50 DMEM/F12. The filters were then flipped and placed into fresh media in the bottom of the well. Virus (PR8: A/Puerto Rico/8/1934; OC43; or NR-52281, SARS-CoV-2 Isolate USA-WA1/2020) is added to the media such that that the multiplicity of infection (MOI) is 0.1 and incubated for 24 hours. This setup requires manual flipping of filters prior to transmigration, a delicate process to perform in BSL3 conditions. Thus, the epithelial cells must be infected while the cells are submerged and no longer at ALI, which may introduce artifacts reminiscent of pneumonia. The filters were transferred to RPMI media with LTB4 (100 nM) and CCL2 (250 pg/mL) with or without additional drugs. Drugs were used at a final concentration of 1 or 10 uM. The untreated condition contained 0.01% v/v DMSO as a vehicle control. Blood monocytes were purified using RosetteSep (StemCell). A total of around 10^6 cells was loaded onto the Alvetex scaffold for transmigration, which was allowed to occur for 24 hours. After transmigration, TriPure (Roche) was added to epithelial cells and frozen at -80 °C.

Plasma stability:

450 µL of human, mouse or hamster plasma were exposed to 10 µM of compound and incubated at 37 °C. At 0, 5, 15, 30, 60, 90 and 120 min, 50 µL of plasma sample was mixed with 200 µL of ice-cold methanol (70%). 50 µL supernatant was dried and reconstituted in 100 µL H_2O. Propantheline bromide was used as positive control. The supernatant was then subjected to LC-MS analysis (LC-MS condition: Instrument: Thermo TSQ Quantiva. Column: Kinetex C88 (50 x 2.1 mm, 2.6 µm). LC buffers: A): 0.1% formic acid, and B): acetonitrile.

Cellular pharmacology:

The uptake and egress of Compounds is measured in cell culture in HAE cells, as well as a variety of other cells. The cell culture involved HAE cells seeded at a density of 0.15×10^6/well, and other cells were seeded at a density of 1×10^6/well. To measure uptake, the compound is incubated in cells for 4 hours at a concentration of 10 µM. To measure egress of the compound from the cells, the cells are pre-treated for 24 hr at a concentration of 10 µM, at which time the media was replaced, then cells are harvested at 0, 2, 4, 6, 8, 12, 24, and 32 hours.

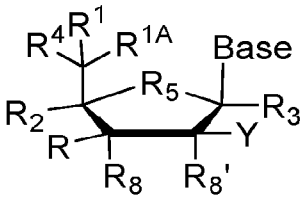
LC-MS/MS: TSQ Quantiva. Buffer A: 2 mM $NH_3H_2PO_4$ with 3 mM Hexylamine; Buffer B: Acetonitrile; flow rate: 250 µL/min. HPLC column: Kinetex EVO C18 100 X 2.1 mm, 2.6 µm. MS detection: SRM mode.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

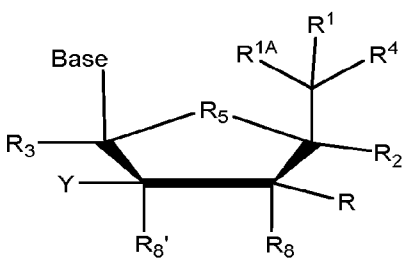
Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

We claim:

1. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**A**) or Formula (**A1**) to a patient in need of treatment or prevention thereof:



Formula A



Formula A1

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Y and R are, independently, selected from the group consisting of H, OH, halo, an optionally substituted O-linked amino acid, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR', SR', wherein each R' is independently a -C(O)-C_{1-12} alkyl, -C(O)-C_{2-12} alkenyl, -C(O)-C_{2-12} alkynyl, -C(O)-C_{3-6} cycloalkyl, -C(O)O-C_{1-12} alkyl, -C(O)O-C_{2-12} alkenyl, -C(O)O-C_{2-12} alkynyl, -C(O)O-C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-6} cycloalkyl, wherein the groups can be substituted with one or more

substituents selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), hydroxyl, amino, alkylamino, arylamino, alkoxy, nitro, and cyano,

R^1 is and R^{1A} are, independently, H, CH_3, CH_2F, CHF_2, or CF_3, wherein, when R^1 is Me, the carbon to which it is attached may be wholly or partially *R* or *S* or any mixture thereof, or R^1 and R^{1A} can combine to form a C_{3-7} cycloalkyl ring;

R^2 is H, CN, N_3, F, CH_2-halogen, CH_2-N_3, O-CH_2-P-$(OH)_3$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl or substituted or unsubstituted C_{2-8} alkynyl;

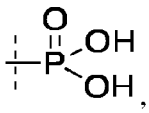
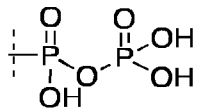
R^3 is selected from the group consisting of H, F, N_3, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, O-(C_{1-8}) alkyl and N_3,

R^5 is S,

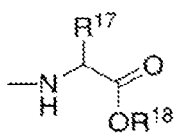
R^8 and $R^{8'}$ are independently selected from the group consisting of H, OH, halo, an optionally substituted O-linked amino acid, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR', SR', wherein each R' is independently a -C(O)-C_{1-12} alkyl, -C(O)-C_{2-12} alkenyl, -C(O)-C_{2-12} alkynyl, -C(O)-C_{3-6} cycloalkyl, -C(O)O-C_{1-12} alkyl, -C(O)O-C_{2-12} alkenyl, -C(O)O-C_{2-12} alkynyl, -C(O)O-C_{3-6} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, wherein the groups can be substituted with one or more substituents selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), hydroxyl, amino, alkylamino, arylamino, alkoxy, nitro, and cyano,

R^4 is OH, an optionally substituted O-linked amino acid, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, -O-C(O)O-C_{3-6} cycloalkyl, OC_{1-6} alkyl, OC_{1-6} haloalkyl, OC_{1-6} alkoxy, OC_{2-6} alkenyl, OC_{2-6} alkynyl, OC_{3-6} cycloalkyl, O-P(O)R^6R^7, O-CH_2-P-$(OH)_3$, O-CH_2-P-$(OH)_3$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center of R^4, it may be wholly or partially R_p or S_p or any mixture thereof,

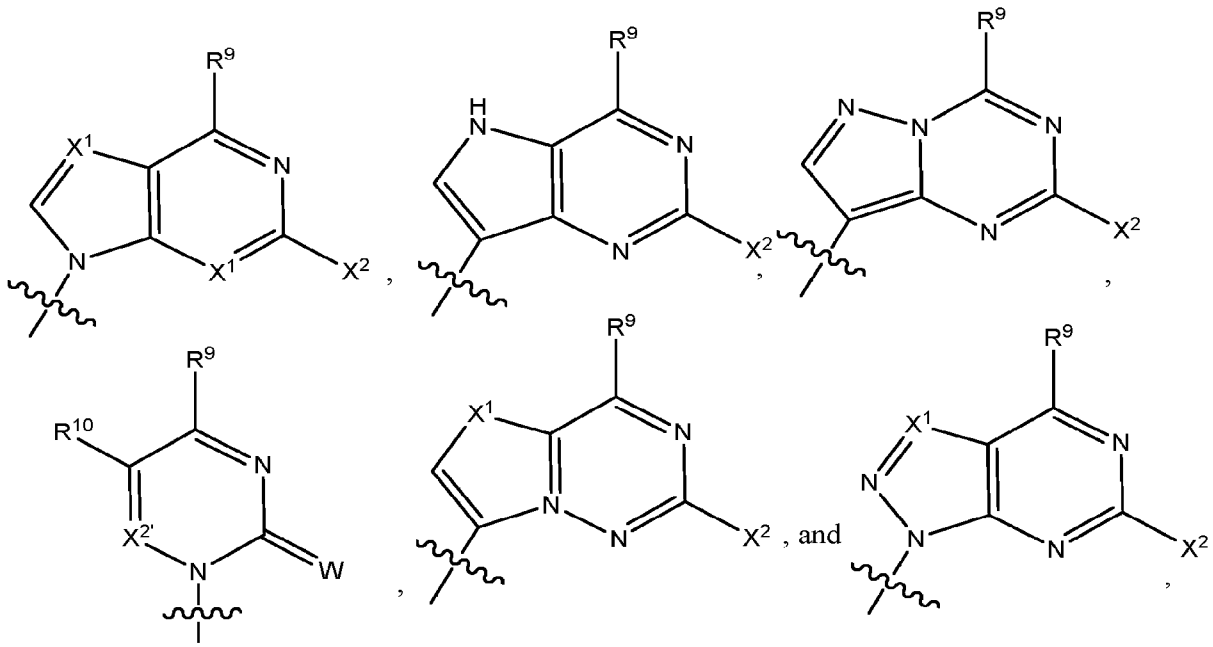
R^6 and R^7 are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, aryl, and heteroaryl, such as phenyl and pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl- C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl;

(*b*) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl;

Base is selected from the group consisting of:



X^1 is CH, C-(C_{1-6})alkyl, C-(C_{2-6})alkenyl, C-(C_{2-6})alkynyl, C-(C_{3-7})cycloalkyl, C-(C_{1-6}) haloalkyl, C-(C_{1-6})hydroxyalkyl, C-OR^{22}, C-$N(R^{22})_2$, C-halo, C-CN or N,

$X^{1'}$ is CH, C-(C_{1-6})alkyl, C-(C_{2-6})alkenyl, C-(C_{2-6})alkynyl, C-halo, C-CN or N

R^9 and X^2 are independently H, OH, NH_2, halo (i.e., F, Cl, Br, or I), SH, NHOH, O(C_{1-10})alkyl, O(C_{2-10})alkene, O(C_{2-10})alkyne, O(C_{3-7})cycloalkyl, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, -O-C(O)O-C_{3-6} cycloalkyl, S(C_{1-10})alkyl, S(C_{2-10})alkene, S(C_{2-10})alkyne, S(C_{3-7})cycloalkyl, an optionally unsaturated NH(C_{1-10})alkyl, an optionally unsaturated N((C_{1-10})alkyl)$_2$, NH(C_{3-7})cycloalkyl, an optionally unsaturated NH(CO)(C_{1-20})alkyl, an optionally unsaturated NH(CO)O(C_{1-20})alkyl, NHOH, an optionally unsaturated NHO(CO)(C_{1-20})alkyl, or an optionally unsaturated NHO(CO)NH(C_{1-20})alkyl, (C_{1-3})alkyl,

$R^{9'}$ is OH, NH_2, SH, NHOH, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, or -O-C(O)O-C_{3-6} cycloalkyl,

R^{10} is H or F,

$X^{2'}$ is N or CH, and

W is O or S.

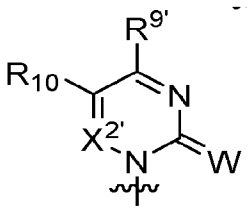
2. The method of Claim 1, wherein R^2 is H or substituted or unsubstituted C_{2-8} alkynyl.

3. The method of Claim 1, wherein R^3 is H.

4. The method of Claim 1, wherein R^1 is and R^{1A} are H.

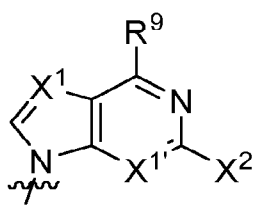
5. The method of Claim 1, wherein R^8 and $R^{8'}$ are OH.

6. The method of Claim 1, wherein R^4 is OH or O-P(O)R^6R^7.



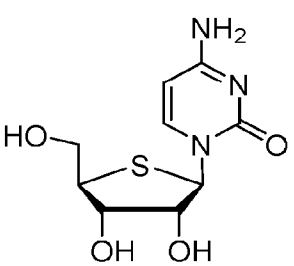
7. The method of Claim 1, wherein Base is .

8. The method of Claim 8, wherein $R^{9'}$ is OH, NH_2, or NHOH

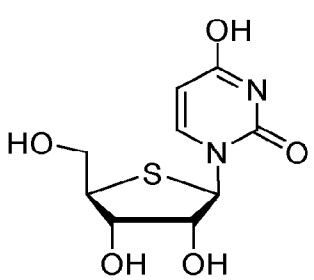


9. The method of Claim 1, wherein Base is .

10. The method of Claim 10, wherein X^2 is NH_2, OH or SH.

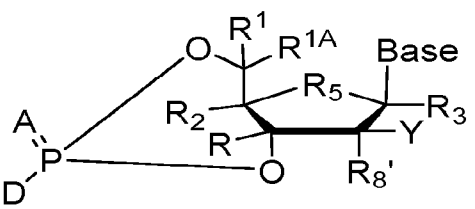


11. The method of Claim 1, wherein the compound is or

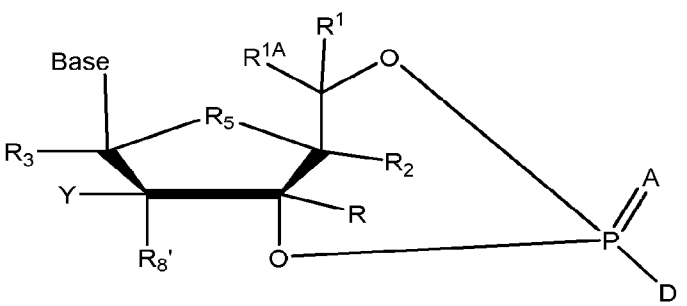


.

12. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**B**) or (**B1**) to a patient in need of treatment or prevention thereof:



Formula B



Formula B1

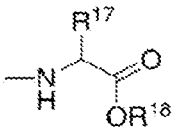
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

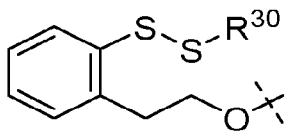
Base, Y, R, R^1, R^{1A}, R^2, R^3, R^5, and $R^{8'}$ are as defined in Formula A,

A is O or S, and

D is selected from the group consisting of:

(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, and heteroaryl, such as phenyl and pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

13. The method of Claim 12, wherein R^2 is H or substituted or unsubstituted C_{2-8} alkynyl.

14. The method of Claim 12, wherein R^3 is H.

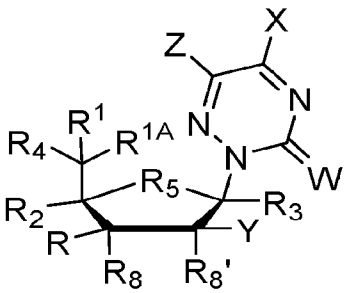
15. The method of Claim 12, wherein $R^{8'}$ is OH.

16. The method of Claim 12, wherein Y is H.

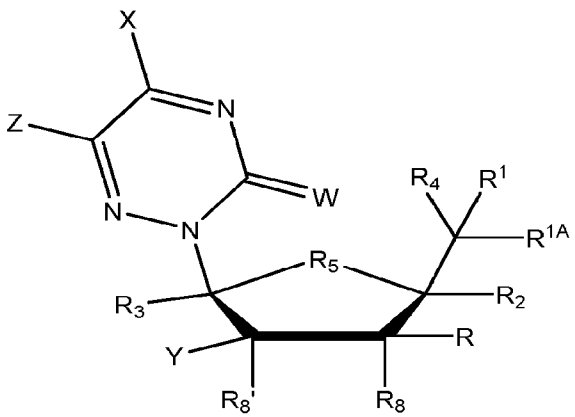
17. The method of Claim 12, wherein R^1 and R^{1A} are H.

18. The method of Claim 12, wherein A is O.

19. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula **(C)** or **(C1)** to a patient in need of treatment or prevention thereof:



Formula C



Formula C1

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R, R^1, R^{1A}, R^2, R^3, R^5, R^8, $R^{8'}$ and Y are as defined in Formula A,

X is OH, NH_2, SH, NHOH, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, or -O-C(O)O-C_{3-6} cycloalkyl,

Z is H or F, and

W is O or S.

20. The method of Claim 19, wherein R^2 is H or substituted or unsubstituted C_{2-8} alkynyl.

21. The method of Claim 19, wherein R^3 is H.

22. The method of Claim 19, wherein R^8 and $R^{8'}$ are OH.

23. The method of Claim 19, wherein Y is H.

24. The method of Claim 19, wherein R is H.

25. The method of Claim 19, wherein Z is H.

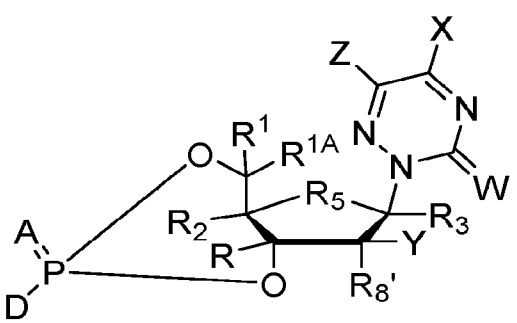
26. The method of Claim 19, wherein X is OH, NH_2 or NHOH.

27. The method of Claim 19, wherein W is O.

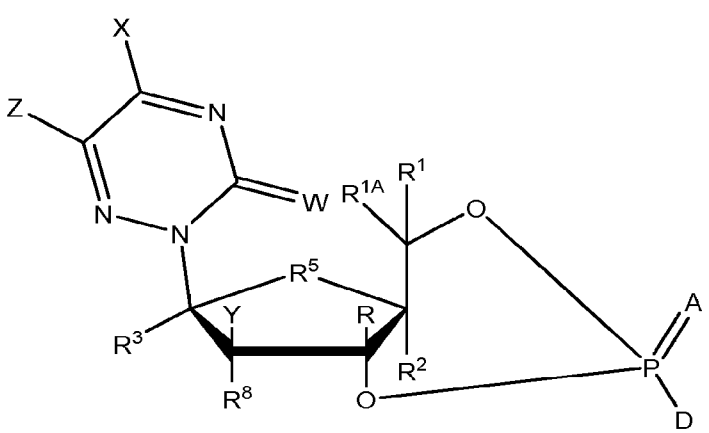
28. The method of Claim 19, wherein R^1 and R^{1A} are H.

29. The method of Claim 19, wherein R^4 is OH or O-P(O)R^6R^7.

30. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**D**) or (**D1**) to a patient in need of treatment or prevention thereof:



Formula D



Formula D1

or a pharmaceutically acceptable salt or prodrug thereof, wherein R, R^1, R^{1A}, R^2, R^3, R^5, $R^{8'}$ and Y are as defined in Formula A, and A and D are as defined in Formula C.

31. The method of Claim 30, wherein R^2 is H or substituted or unsubstituted C_{2-8} alkynyl.

32. The method of Claim 30, wherein R^3 is H.

33. The method of Claim 30, wherein $R^{8'}$ is OH.

34. The method of Claim 30, wherein Y is H.

35. The method of Claim 30, wherein R is H.

36. The method of Claim 30, wherein Z is H.

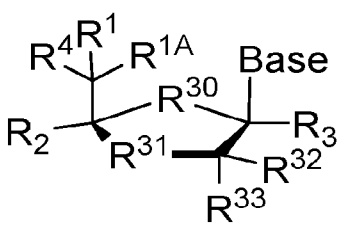
37. The method of Claim 30, wherein X is OH, NH_2 or NHOH.

38. The method of Claim 30, wherein W is O.

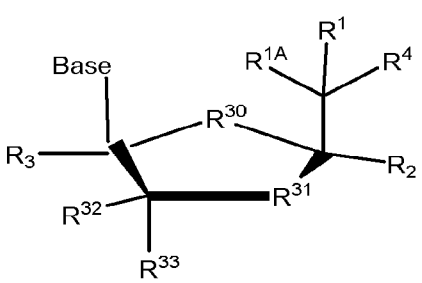
39. The method of Claim 30, wherein R^1 and R^{1A} are H.

40. The method of Claim 30, wherein R^4 is OH or $O\text{-}P(O)R^6R^7$.

41. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**E**) or (**E1**) to a patient in need of treatment or prevention thereof:



Formula E



Formula E1

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base, R^1, R^{1A}, R^2, R^3, and R^4 are as defined in Formula A,

R^{30} is S,

R^{31} is O or S,

R^{31} is O when R^{30} is S, and

R^{32} and R^{33} are independently H, F, C_1-C_3 alkyl, C_2-C_3 alkene, or C_2-C_3 alkyne.

42. The method of Claim 41, wherein R^{31} is O.

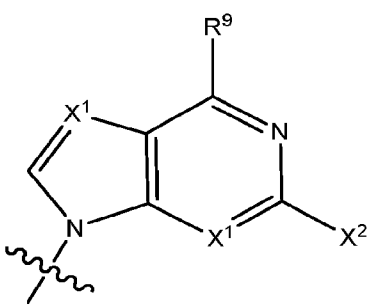
43. The method of Claim 41, wherein R^{32} and R^{33} are, independently, H or F.

44. The method of Claim 41, wherein R^3 is H.

45. The method of Claim 41, wherein R^2 is N_3 or substituted or unsubstituted C_{2-8} alkynyl.

46. The method of Claim 41, wherein R^1 and R^{1A} are H.

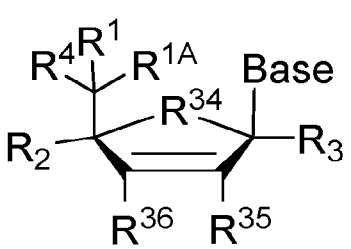
47. The method of Claim 41, wherein R^4 is OH or O-P(O)R^6R^7.

48. The method of Claim 41, wherein Base is 

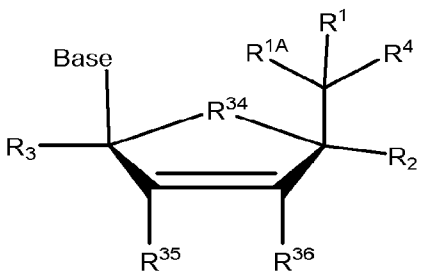
.

49. The method of Claim 41, wherein X^1 is N.

50. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**F**) or (**F1**) to a patient in need of treatment or prevention thereof:



Formula F



Formula F1

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base, R^1, R^{1A}, R^2, R^3, and R^4 are as defined in Formula A,

R^{34} is S, and

R^{35} and R^{36} are independently H, F or CH_3.

51. The method of Claim 50, wherein R^{35} and R^{36} are H.

52. The method of Claim 50, wherein R^{34} is CH_2.

53. The method of Claim 50, wherein R^4 is OH or or O-P(O)R^6R^7.

54. The method of Claim 50, wherein wherein R^3 is H.

55. The method of Claim 50, wherein R^2 is H or substituted or unsubstituted C_{2-8} alkynyl.

56. The method of Claim 50, wherein R^1 and R^{1A} are H.

57. The method of any of Claims 1-56, wherein the compounds can be present in the β-D or β-L configuration.

58. The method of any of Claims 1-56, wherein the virus is a Coronavirus.

59. The method of Claim 58, wherein the Coronavirus is SARS-CoV2, MERS, SARS, or OC-43.

60. The method of Claim 58, wherein the Coronavirus is SARS-CoV2.

61. The method of any of Claims 1-61, wherein the compound is co-administered with one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2

(ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

62. The method of Claim 61, wherein the compound is administered with remdesivir, N-hydroxy cytidine, or a pharmaceutically-acceptable salt or prodrug thereof.

63. The method of Claim 61, wherein the additional active compound is a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

64. The method of Claim 61, wherein the one or more additional active agents comprise an anticoagulant or a platelet aggregation inhibitor.

65. The method of Claim 61, wherein the one or more additional active agents comprise an ACE-2 inhibitor, a CYP-450 inhibitor, or NOX inhibitor.

66. The use of a compound of any of Claims 1-56 in the preparation of a medicament for use in treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection.

67. The use of Claim 66, wherein the infection is a Coronaviridae infection.

68. The use of Claim 67, wherein the Coronavirus is SARS-CoV2, MERS, SARS, or OC-43.

69. The use of Claim 67, wherein the Coronavirus is SARS-CoV2.

70. The use of Claim 66, wherein the medicament further comprises one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

71. The use of Claim 66, wherein the medicament further comprises remdesivir, N-hydroxy cytidine, or a pharmaceutically-acceptable salt or prodrug thereof.

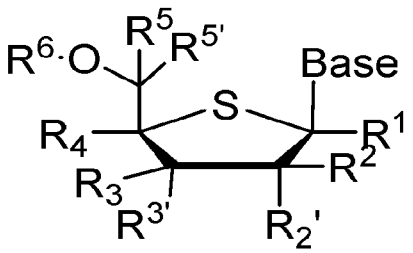
72. The use of Claim 66, wherein the medicament further comprises a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

73. The use of Claim 66, wherein the medicament further comprises an anticoagulant or a platelet aggregation inhibitor.

74. The use of Claim 66, wherein the medicament further comprises an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

75. The use of Claim 66, wherein the medicament is is a transdermal composition or a nanoparticulate composition.

76. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**A**) to a patient in need of treatment or prevention thereof:



Formula A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is H, deuterium, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl or N_3,

R^2 and $R^{2'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7,

each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally

substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

with the proviso that R^2 and $R^{2'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7.

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

R^3 and $R^{3'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7, wherein each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

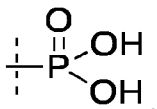
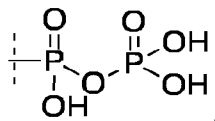
with the proviso that R^3 and $R^{3'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7,

R^4 is selected from the group consisting of H, deuterium, CN, halo, N_3, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, substituted or unsubstituted (C_{1-8}) haloalkyl and N_3,

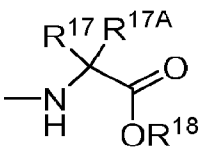
R^5 is and $R^{5'}$ are, independently, H, CH_3, CH_2F, CHF_2, or CF_3, wherein, when R^5 is CH_3, the carbon to which it is attached may be wholly or partially *R* or *S* or any mixture thereof, or R^5 and $R^{5'}$ can combine to form a C_{3-7} cycloalkyl ring;

R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted $-CH_2$-O-C(O)-R', an optionally substituted $-CH_2$-O-C(O)O-R', an optionally substituted $-CH_2-CH_2$-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

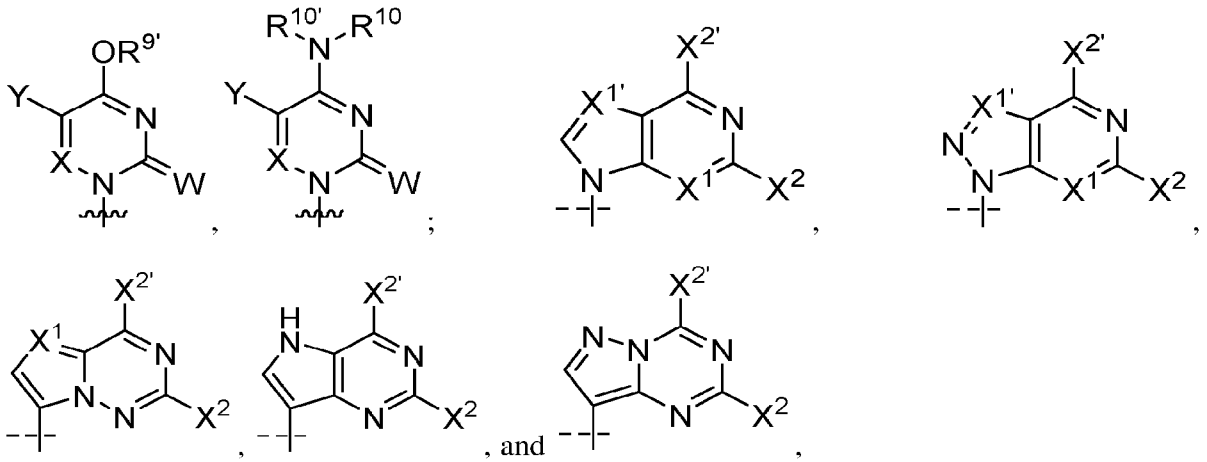
R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl;

Base is selected from the group consisting of:



Y is H or halo,

X is N or CH,

W is O or S,

X^1 and $X^{1'}$ are, independently, CH, C-(C_{1-6})alkyl, C-(C_{2-6})alkenyl, C-(C_{2-6})alkynyl, C-(C_{3-7})cycloalkyl, C-(C_{1-6}) haloalkyl, C-(C_{1-6})hydroxyalkyl, C-OR^{22}, C-$N(R^{22})_2$, C-halo, C-CN or N,

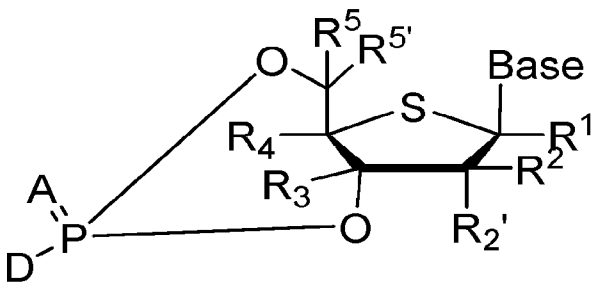
X^2 and $X^{2'}$ are independently H, halo, $OR^{9'}$ or $NR^{10}R^{10'}$,

$R^{9'}$ is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, an (acyloxybenzyl)ester, an (acyloxybenzyl)ether, an optionally substituted bis-acyloxybenzyl)ester, an optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12}-alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, (acyloxybenzyl)amide, (acyloxybenzyl)amine, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, PEG amide, PEG carbamate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid amide, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, or a lipid carbamate, wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), with the proviso that R^{10} and $R^{10'}$ cannot both be OH.

77. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**B**) to a patient in need of treatment or prevention thereof:



Formula B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base, R^1, R^2, $R^{2'}$, R^3, R^4, R^5 $R^{5'}$, R^7 and R^8 are as defined in Formula A,

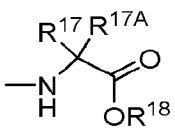
A is O or S, and

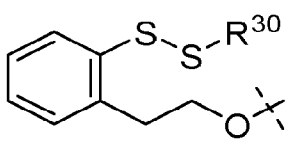
D is selected from the group consisting of:

(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as

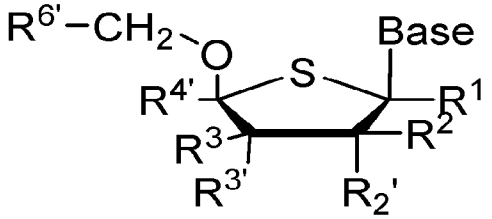
pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

78. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**C**) to a patient in need of treatment or prevention thereof:



Formula C

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base, R^1, R^2, $R^{2'}$, R^3 and $R^{3'}$ are as defined in Formula A,

$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

$R^{6'}$ is selected from the group consisting of $-OR^6$, $-P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted $-CH_2$-O-C(O)-R', an optionally substituted $-CH_2$-O-C(O)O-R', an optionally substituted $-CH_2-CH_2$-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted $-C(NR')N(R')_2$, an optionally substituted $-O-C(O)N(R')_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), $O-P(O)R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

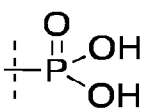
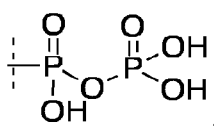
R^7 is an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-

disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')$N(R')_2$, and an optionally substituted –O-C(O)$N(R')_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

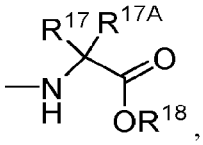
wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl, and

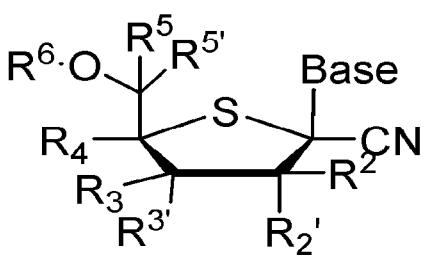
R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')$N(R')_2$, optionally substituted –O-C(O)$N(R')_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

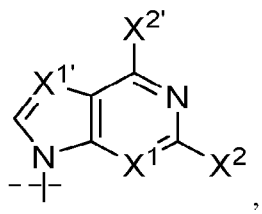
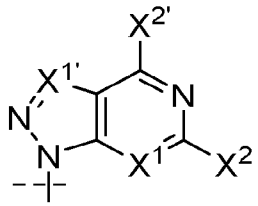
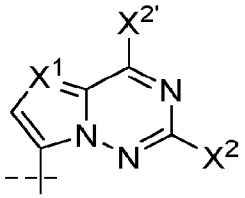
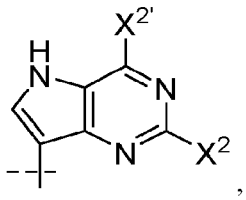
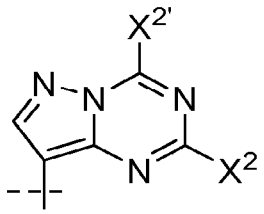
79. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**D**) to a patient in need of treatment or prevention thereof:



Formula D

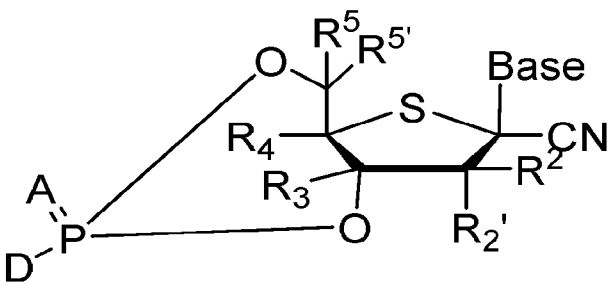
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is selected from the group consisting of:


,

,

,

, and

, and

X^1, $X^{1'}$, $X^{2'}$, X^2, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, R^5, $R^{5'}$ and R^6 are as defined in Formula A.

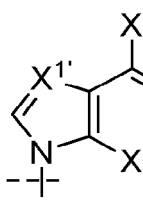
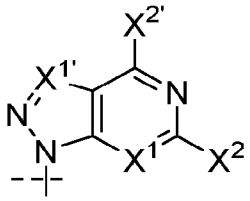
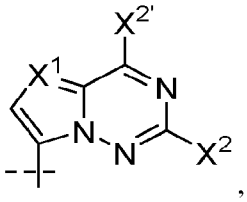
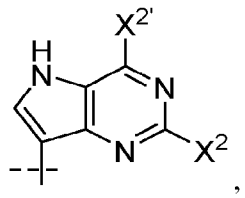
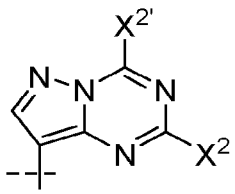
80. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**E**) to a patient in need of treatment or prevention thereof:



Formula E

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is selected from the group consisting of:

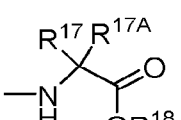




, and

, X^1, $X^{1'}$, $X^{2'}$, X^2 R^2, $R^{2'}$, R^3, R^4, R^5 and $R^{5'}$are as defined in Formula A,

A is O or S, and

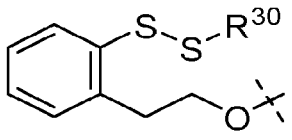
D is selected from the group consisting of:

(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

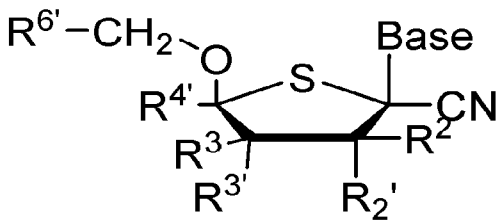
where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-

C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

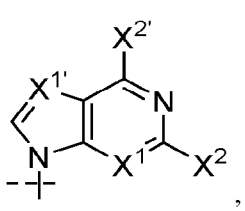
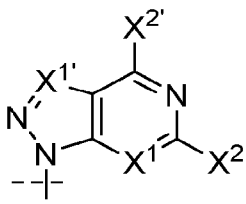
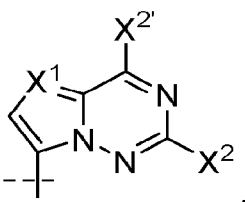
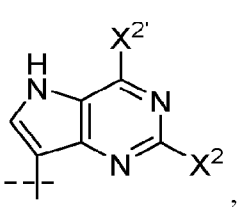
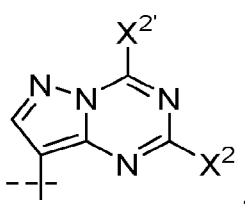
81. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**F**) to a patient in need of treatment or prevention thereof:



Formula F

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is selected from the group consisting of:

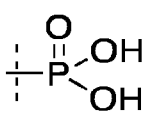
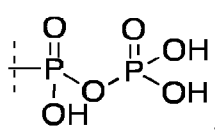
 ,  ,  ,  , and  , X^1, $X^{1'}$, $X^{2'}$, X^2 R^2, $R^{2'}$, R^3 and $R^{3'}$are as defined in Formula A,

$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

$R^{6'}$ is selected from the group consisting of $-OR^6$, $-P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

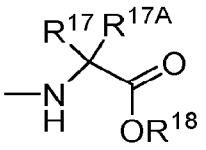
R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted $-CH_2$-O-C(O)-R', an optionally substituted $-CH_2$-O-C(O)O-R', an optionally substituted $-CH_2-CH_2$-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')$N(R')_2$, an optionally substituted –O-C(O)$N(R')_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')$N(R')_2$, optionally substituted –O-C(O)$N(R')_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and

heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

82. The method of Claim 76, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

83. The method of Claim 77, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

84. The method of Claim 78, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H.

85. The method of Claim 79, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

86. The method of Claim 80, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

87. The method of Claim 81, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H.

88. The method of Claim 76, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

89. The method of Claim 77, wherein $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

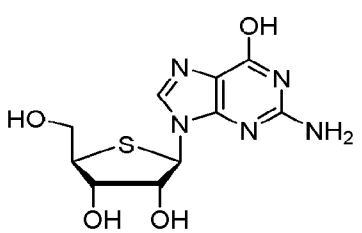
90. The method of Claim 78, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

91. The method of Claim 79, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

92. The method of Claim 80, wherein $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

93. The method of Claim 81, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

94. The method of Claim 76, wherein the compound is one of the following compounds: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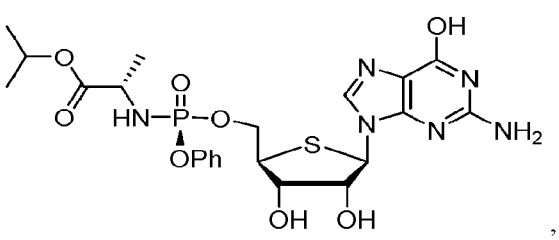
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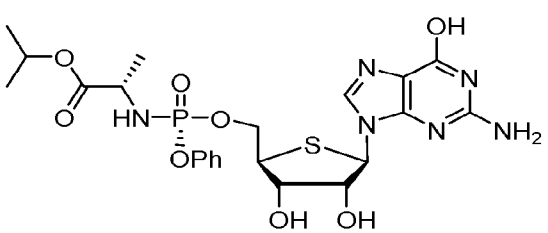
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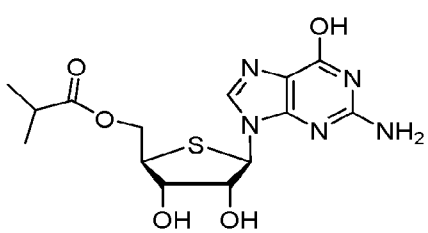
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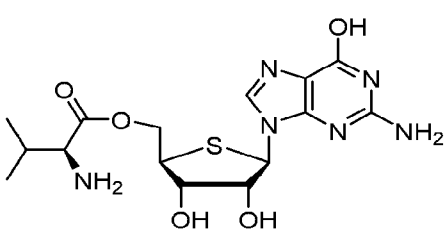
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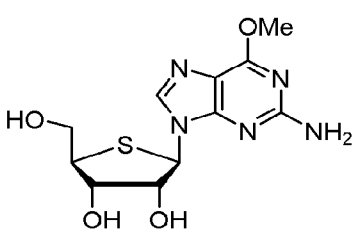
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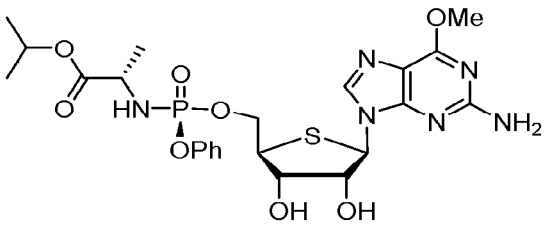
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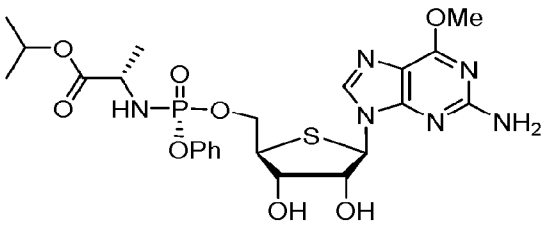
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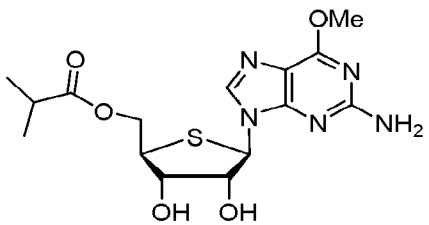
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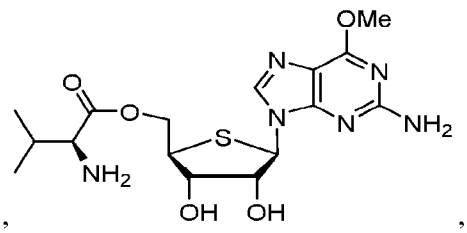
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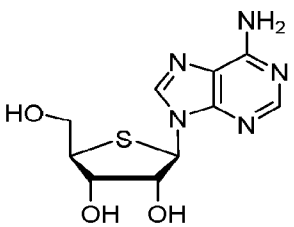
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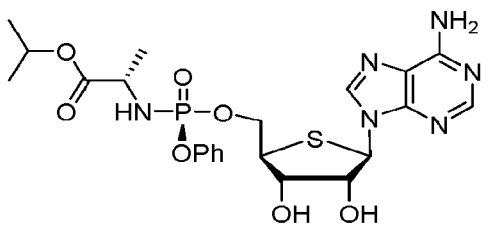
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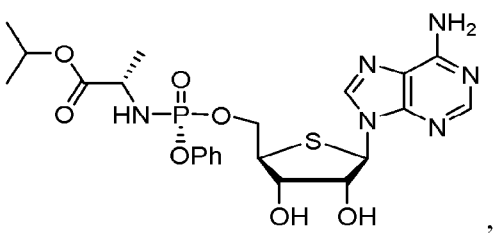
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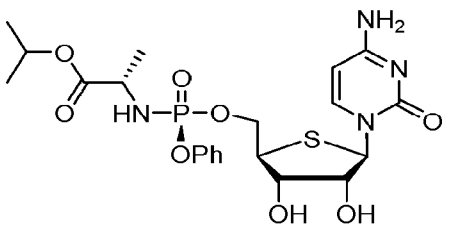
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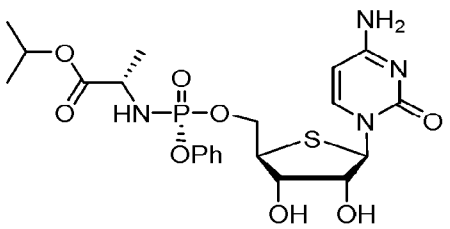
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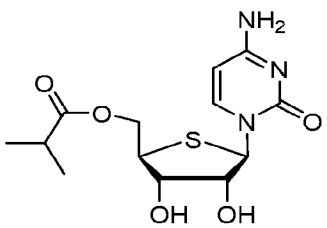
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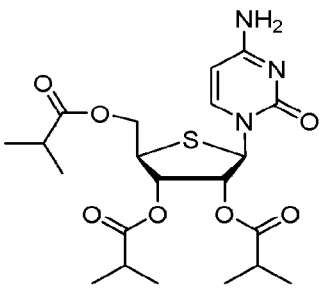
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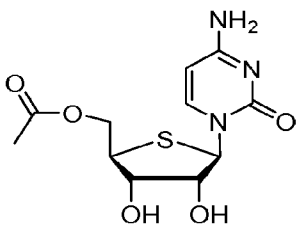
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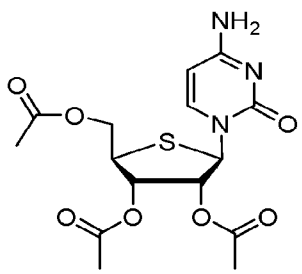
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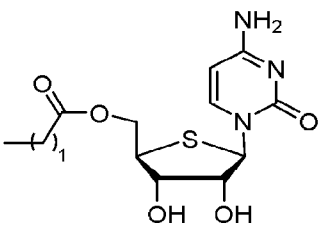
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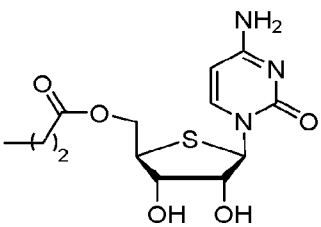
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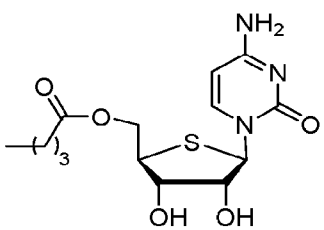
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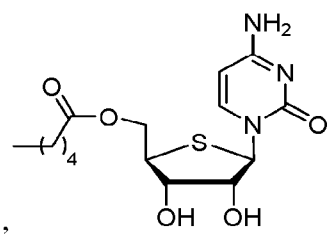
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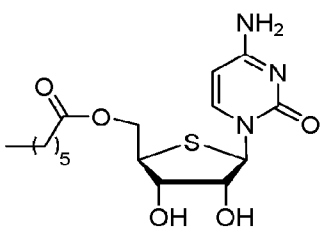
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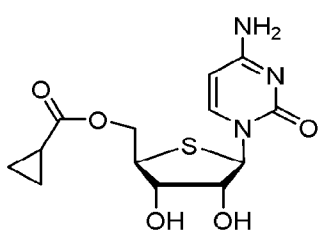
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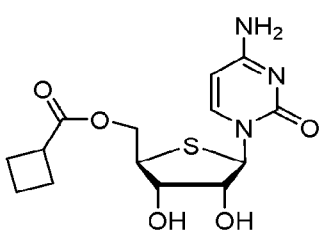
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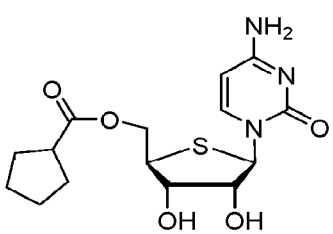
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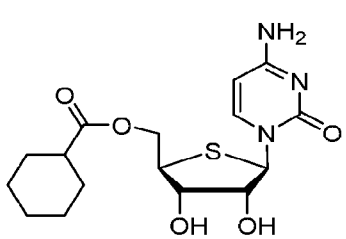
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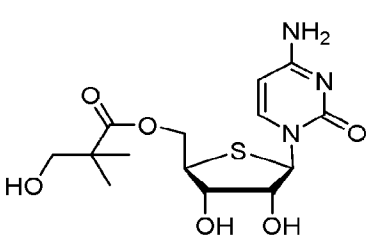
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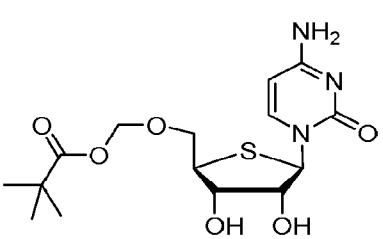
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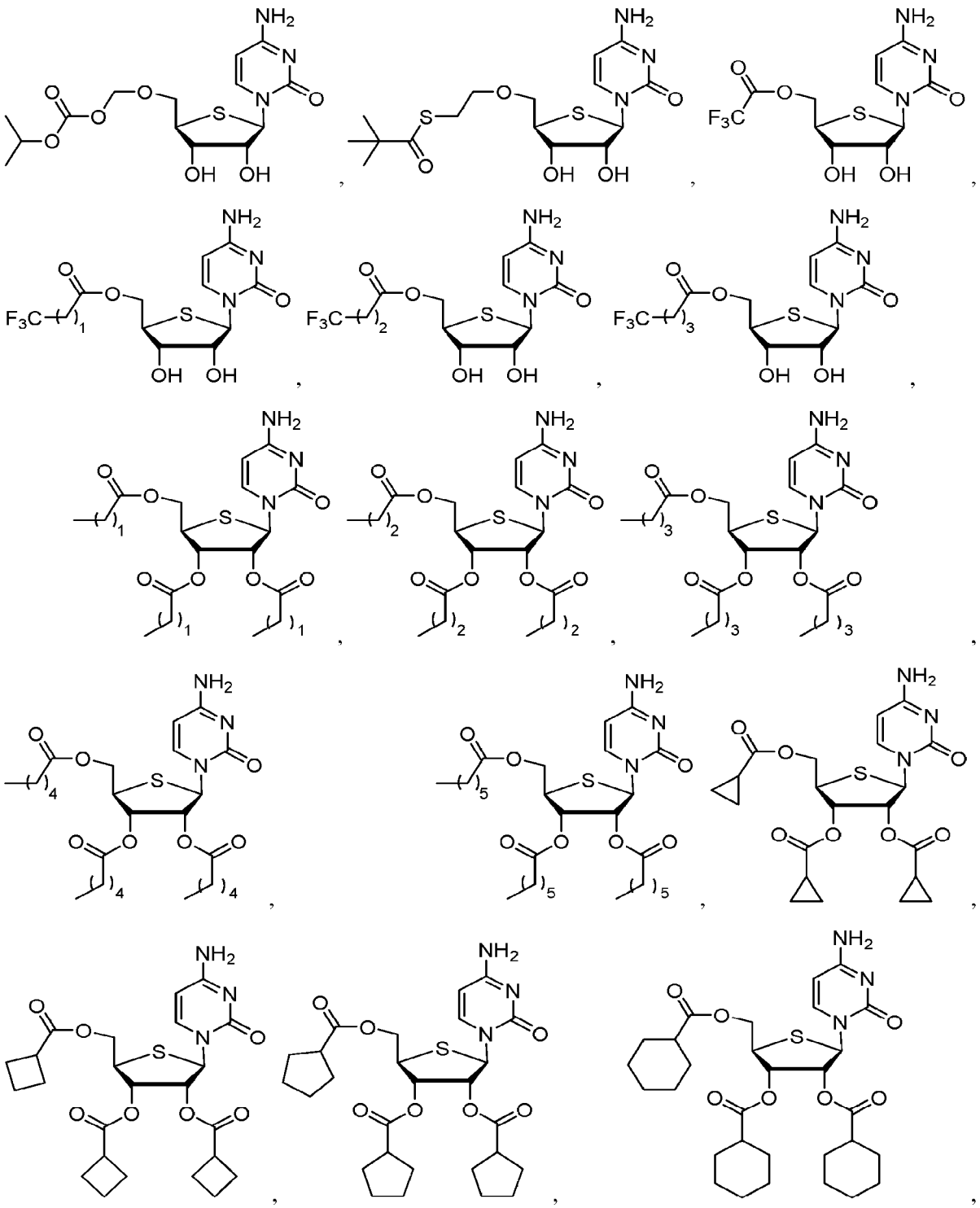

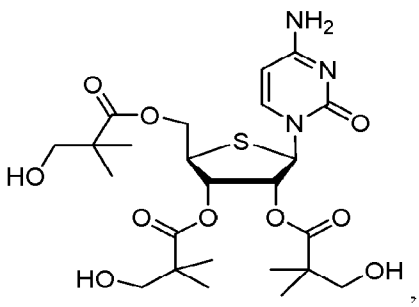
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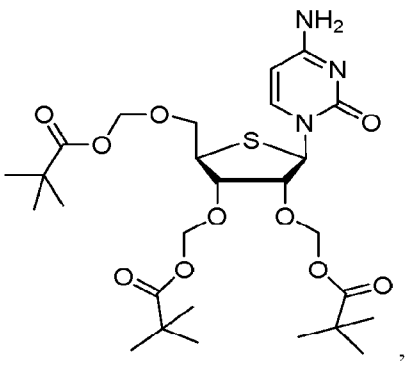
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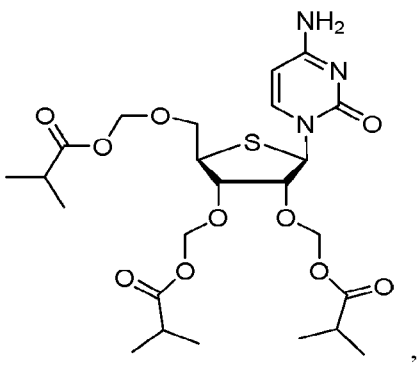
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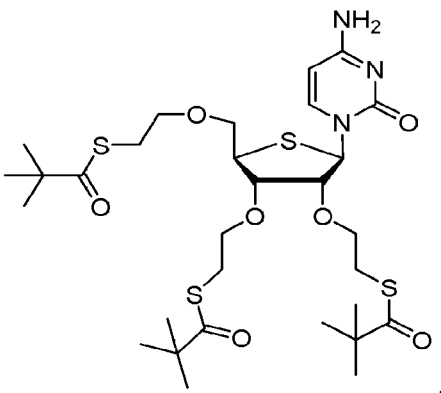
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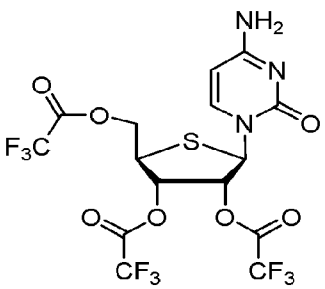
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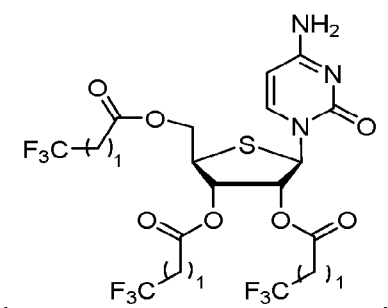
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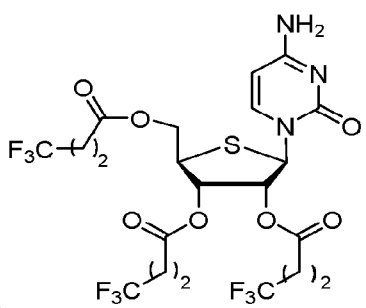
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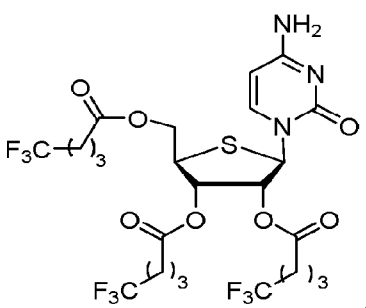
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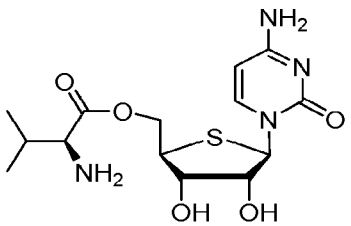
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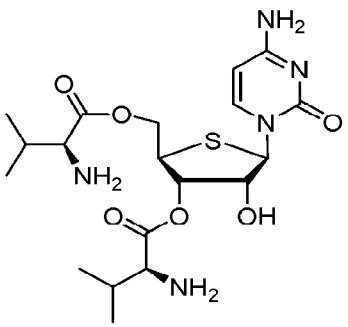
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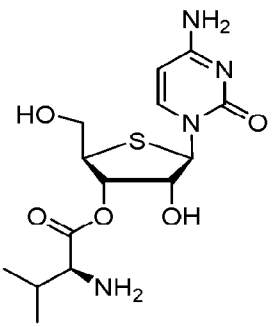
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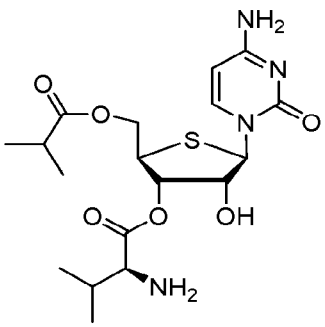
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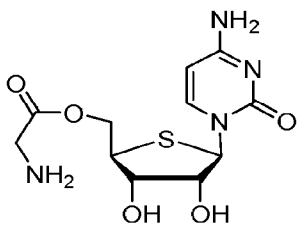
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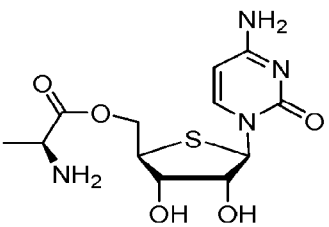
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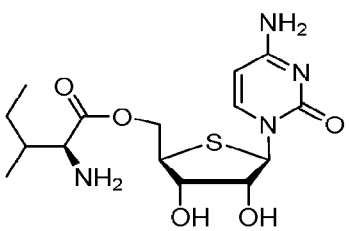
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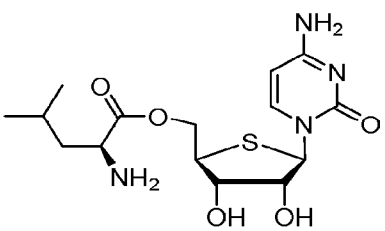
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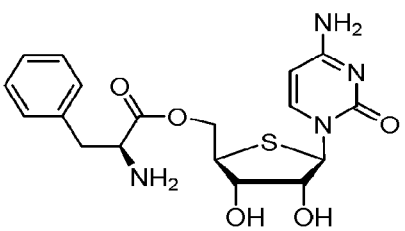
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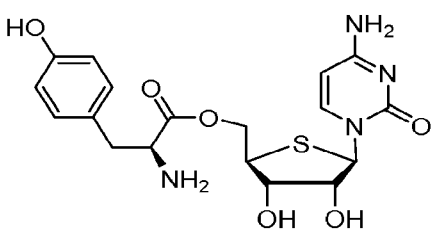
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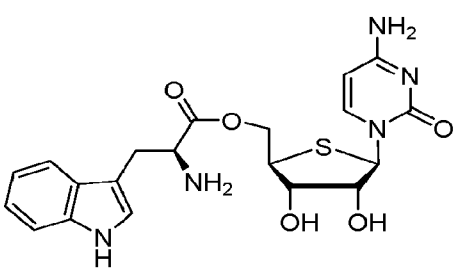
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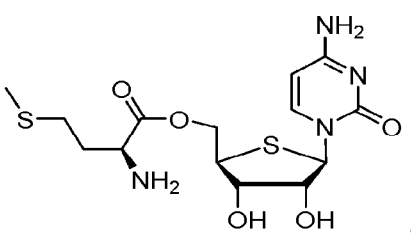
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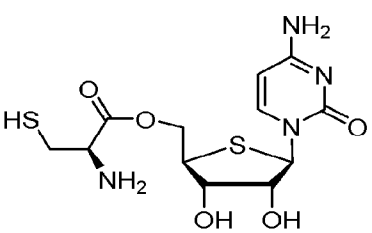
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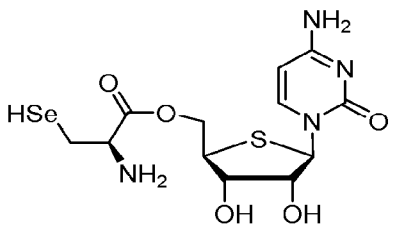
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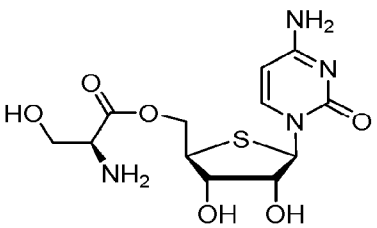
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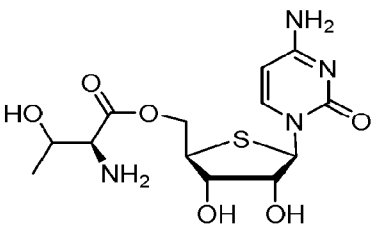
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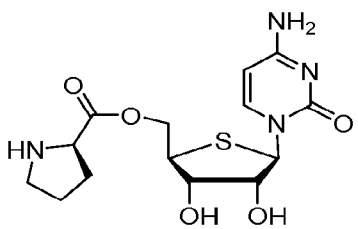
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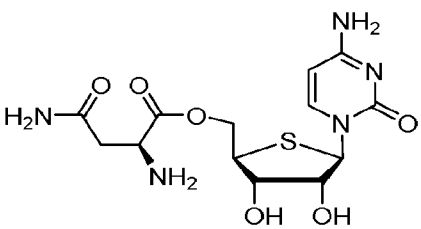
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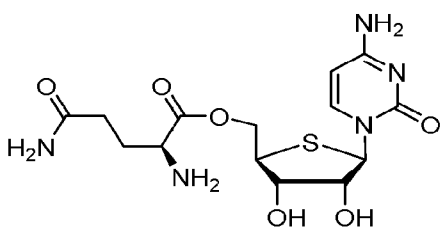
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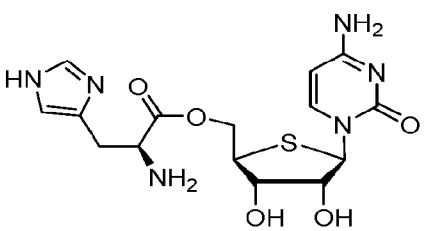
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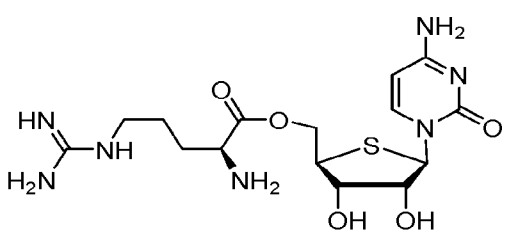
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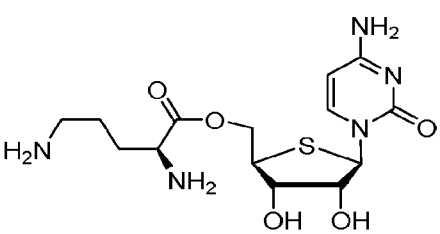
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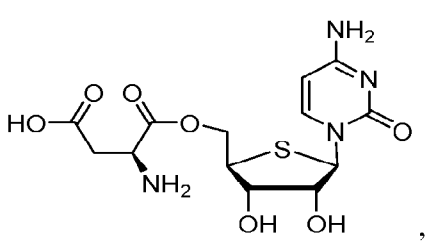
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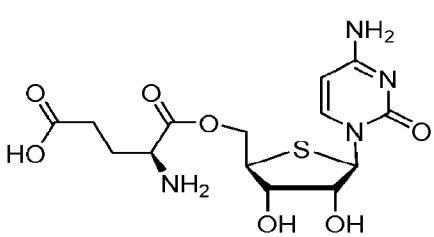
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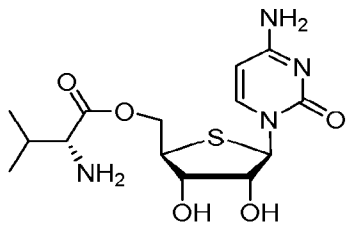
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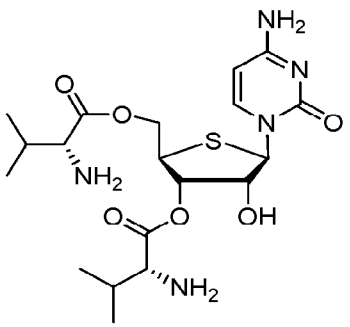
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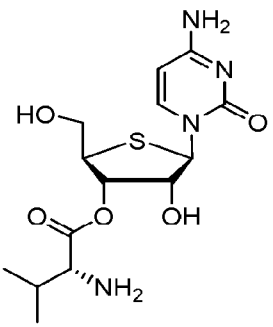
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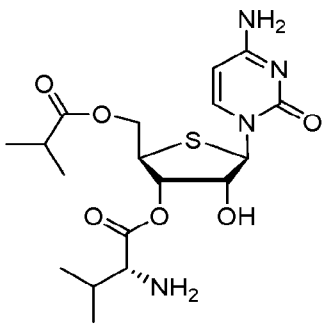
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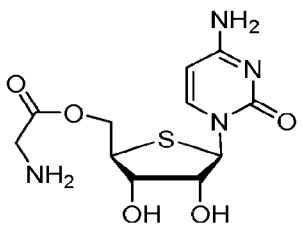
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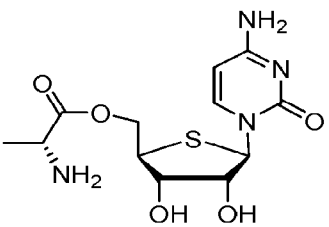
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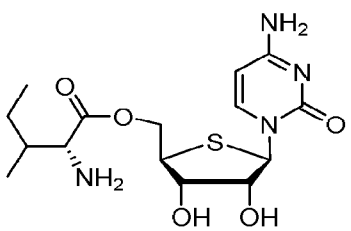
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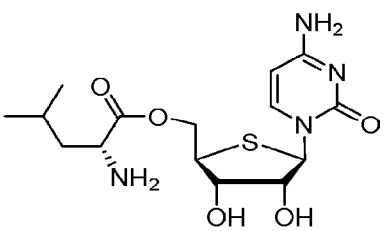
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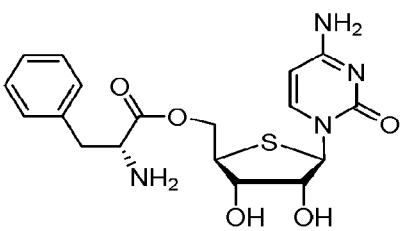
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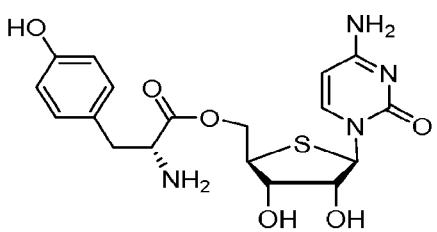
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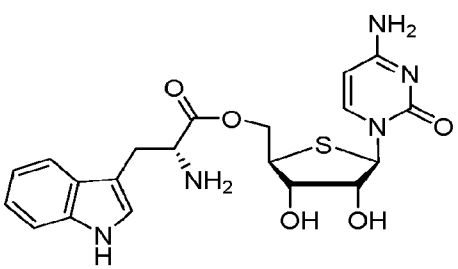
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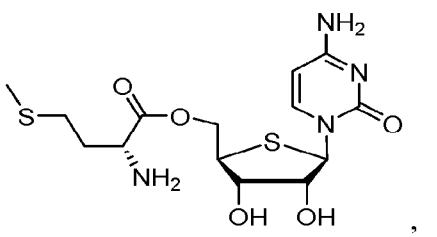
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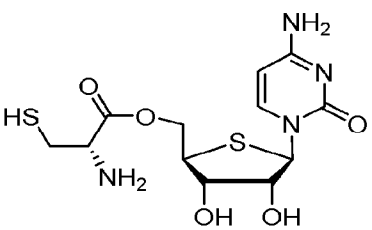
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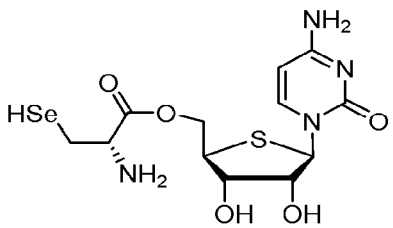
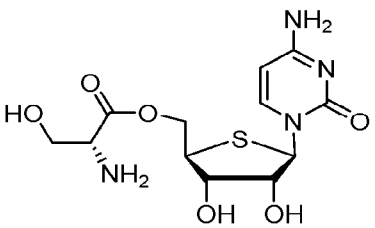
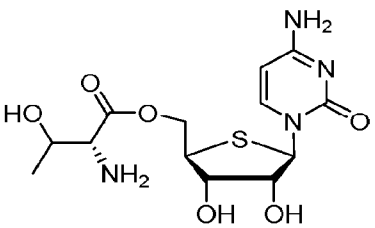
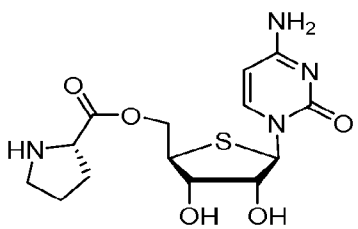
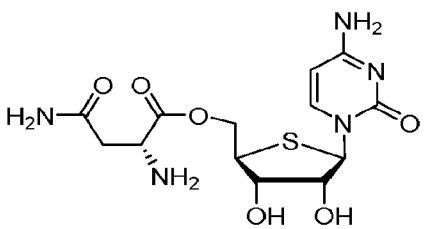
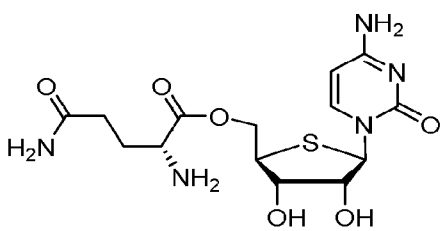
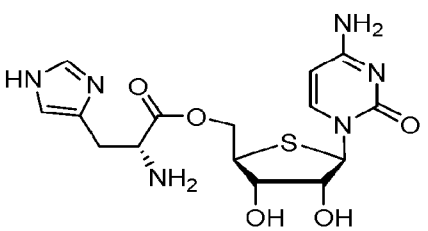
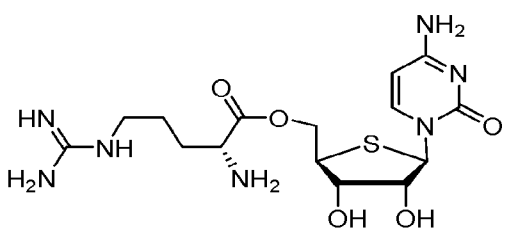
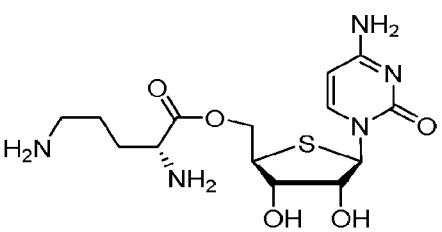
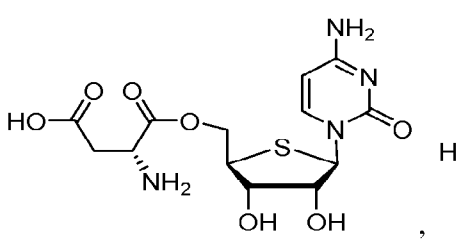


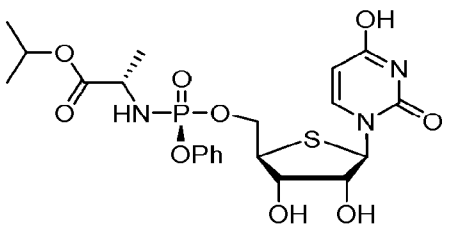
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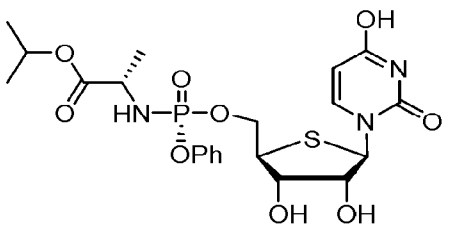
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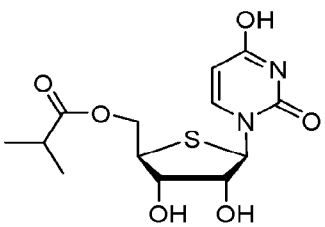
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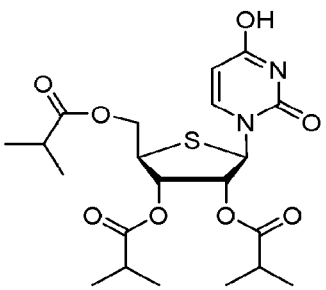
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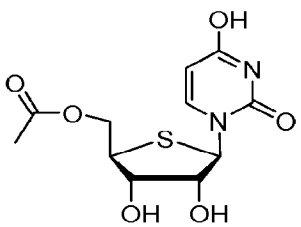
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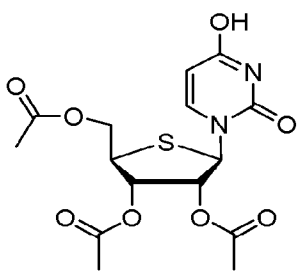
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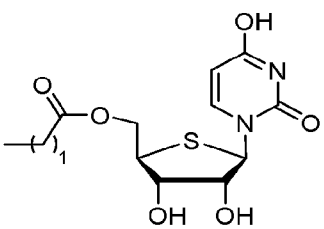
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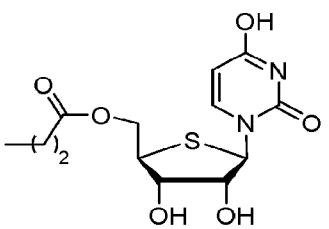
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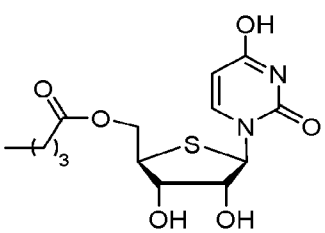
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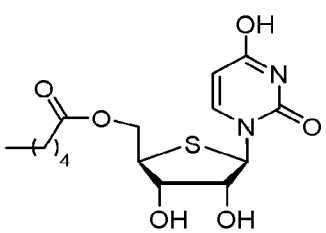
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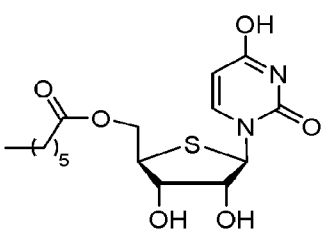
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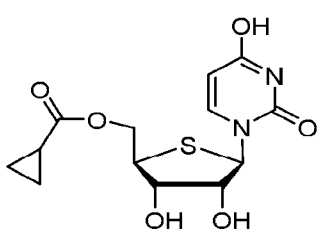
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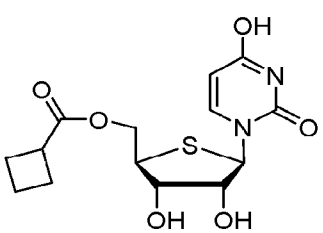
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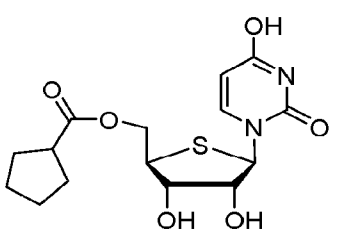
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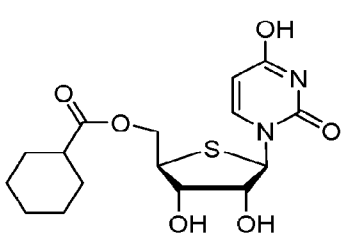
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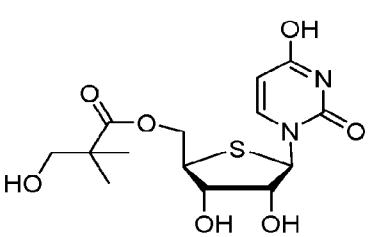
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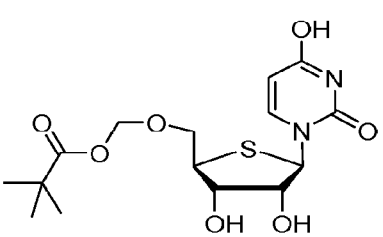
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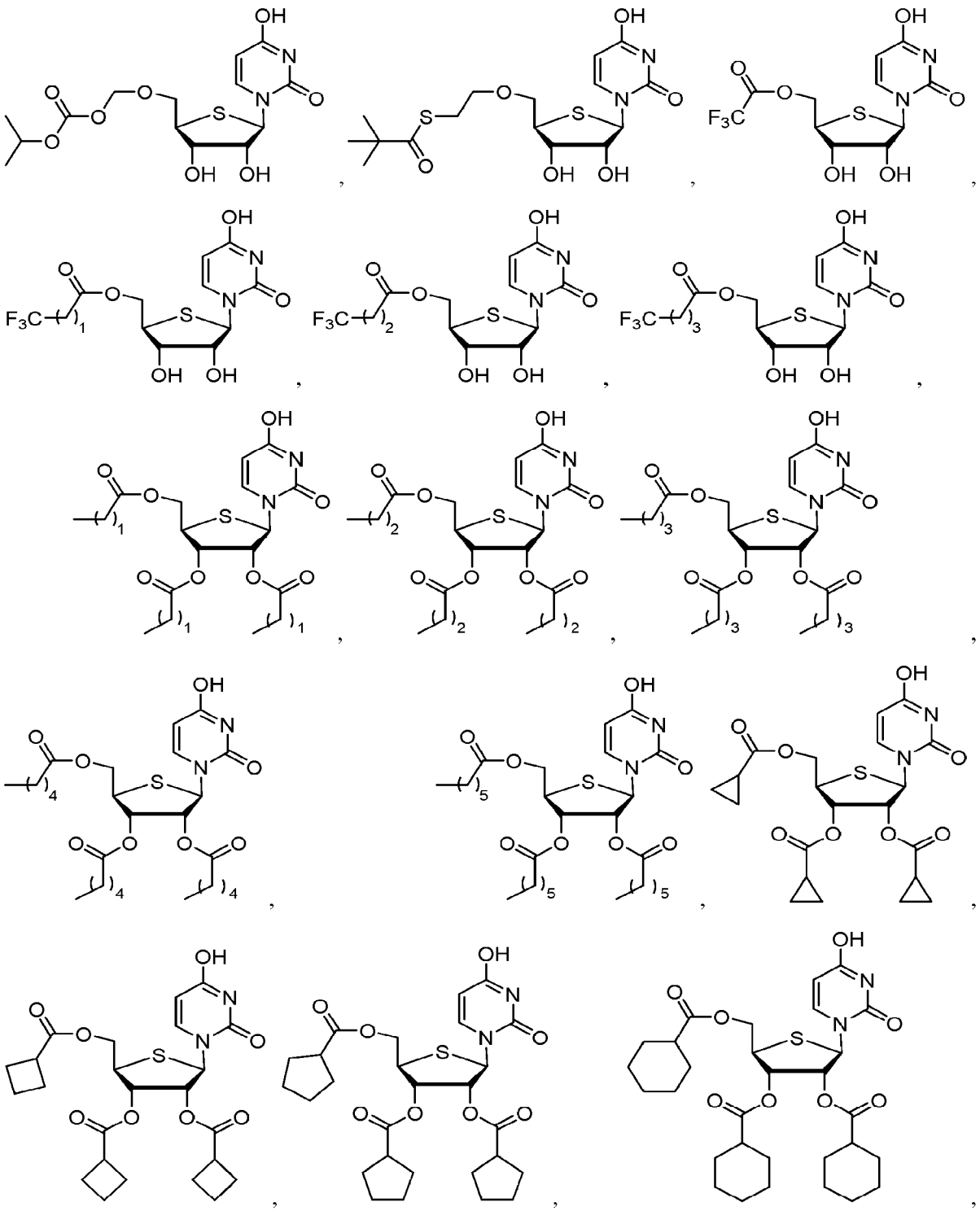

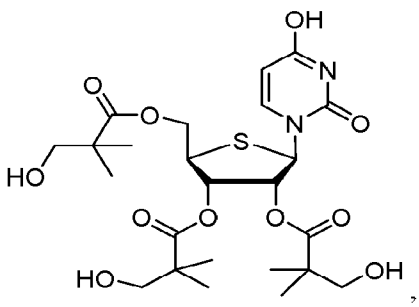
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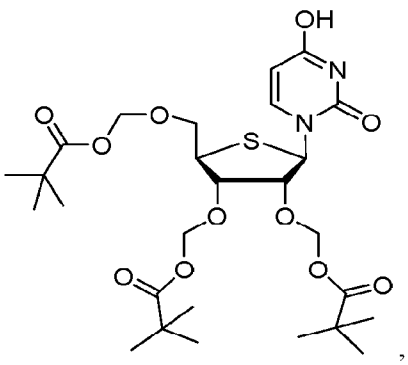
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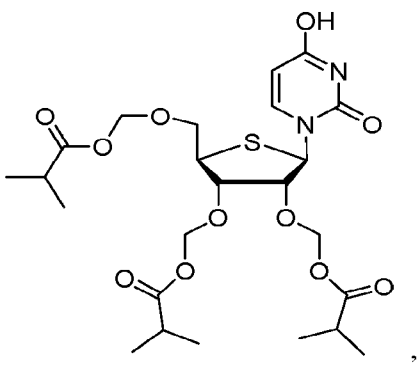
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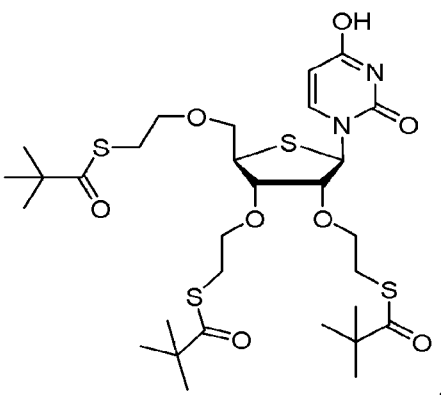
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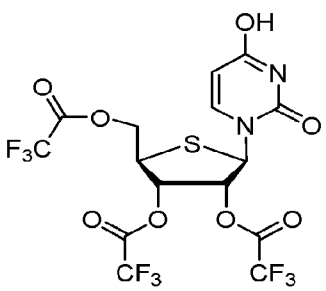
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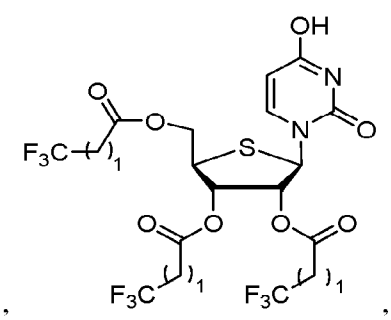
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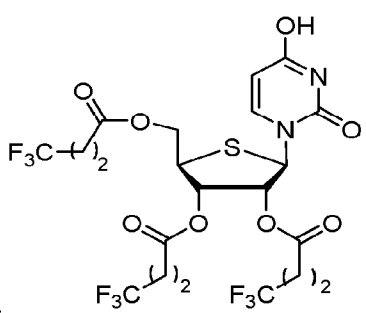
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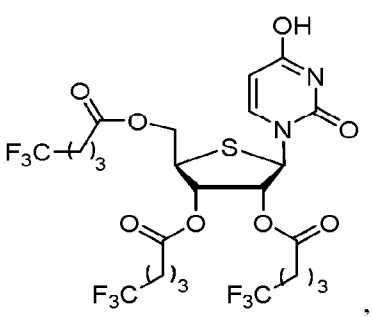
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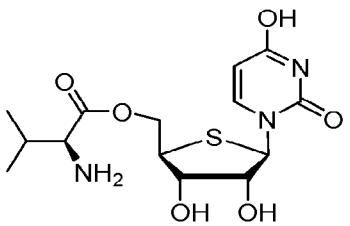
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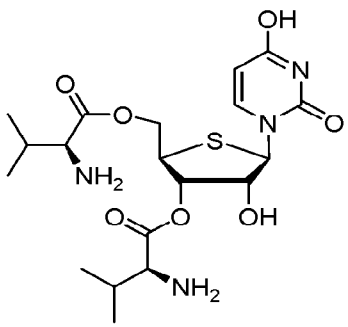
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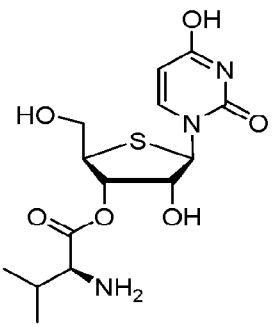
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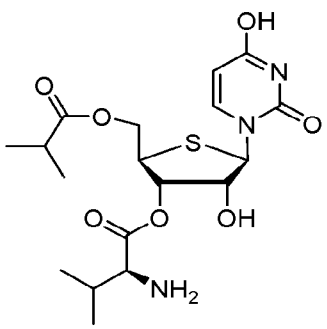
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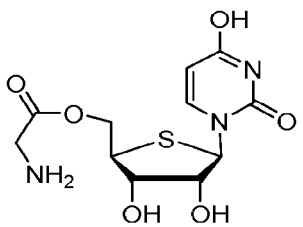
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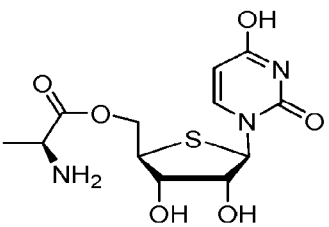
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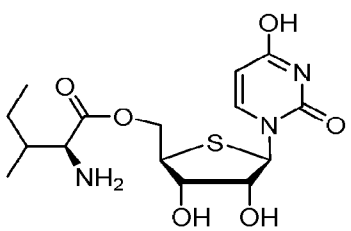
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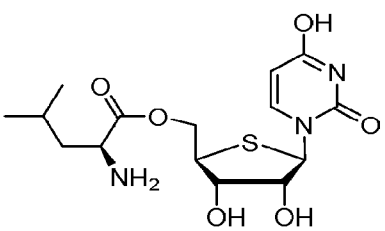
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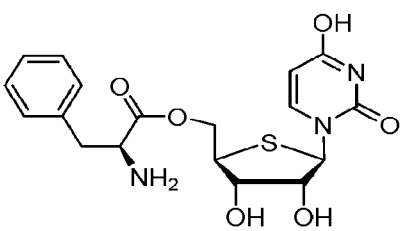
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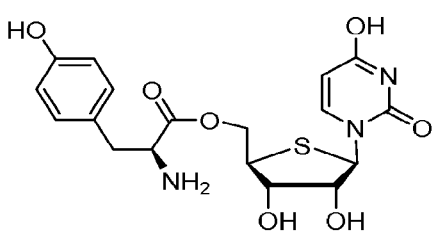
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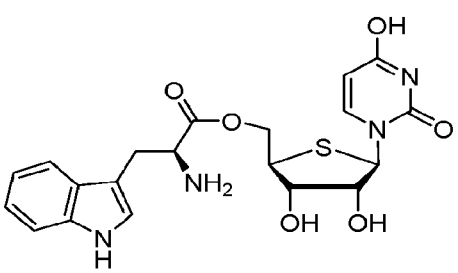
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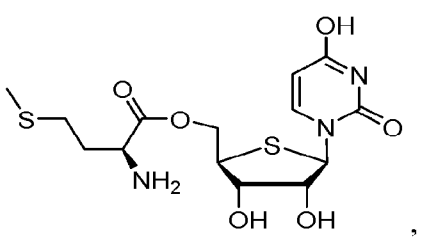
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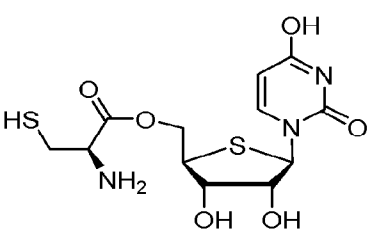
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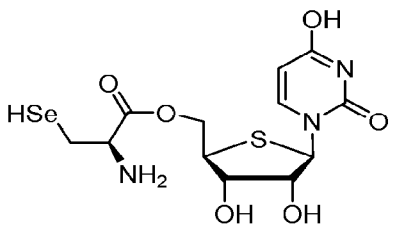
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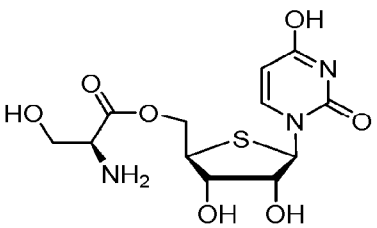
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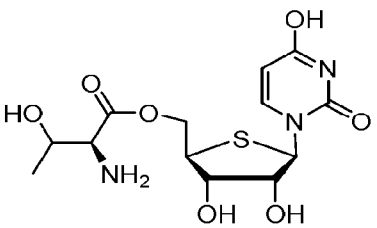
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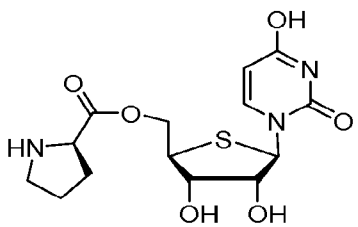
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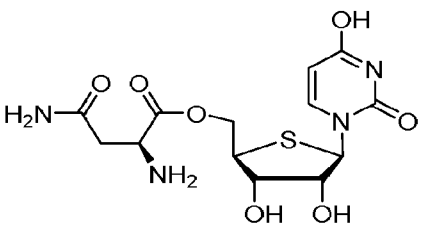
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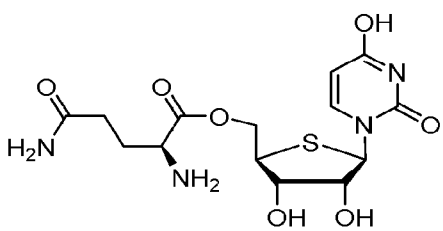
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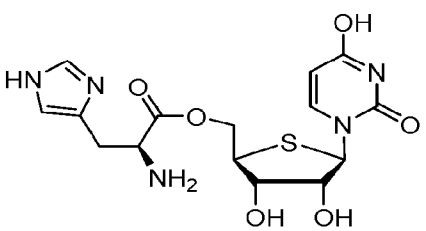
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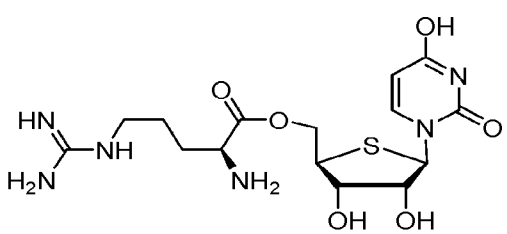
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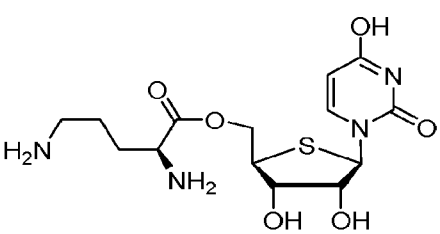
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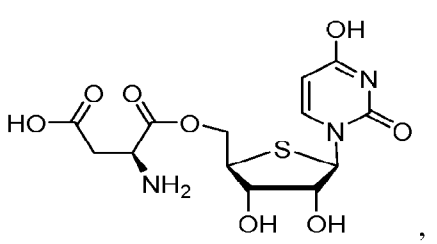
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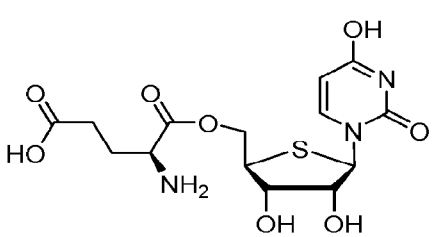
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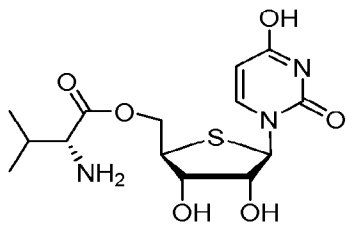
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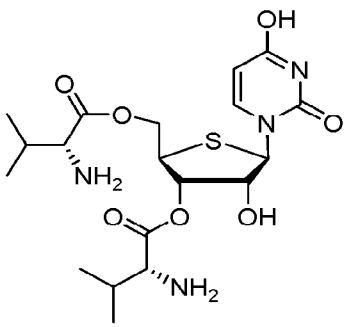
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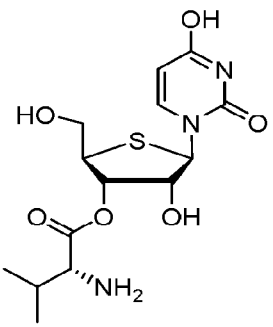
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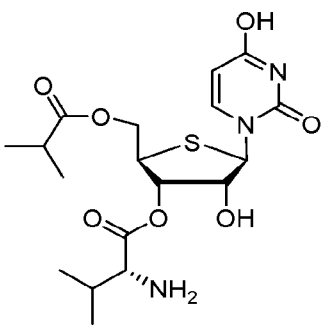
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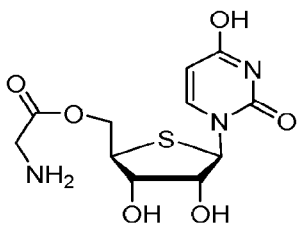
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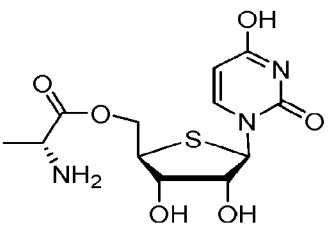
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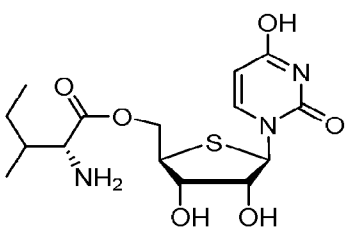
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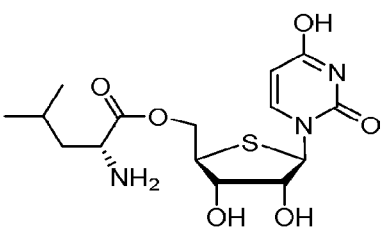
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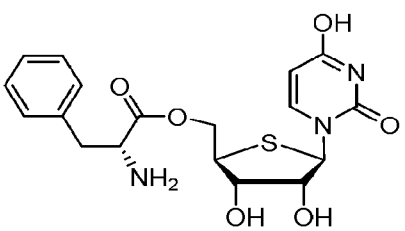
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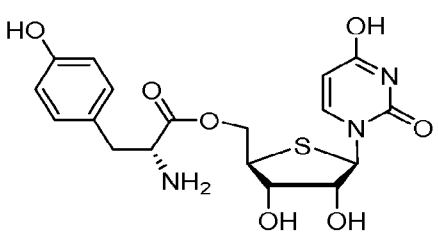
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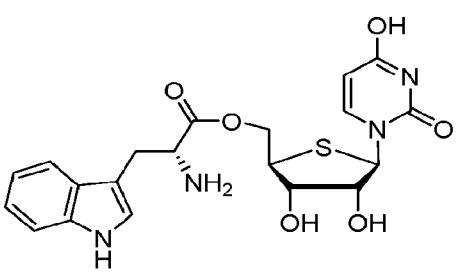
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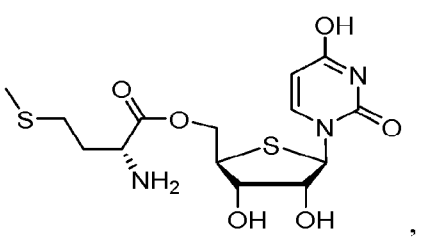
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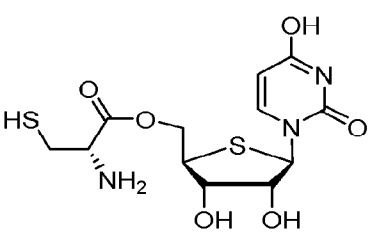
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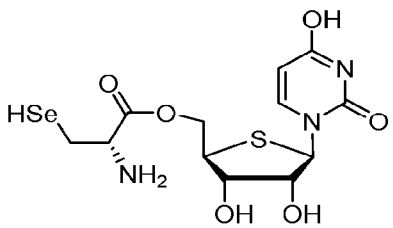
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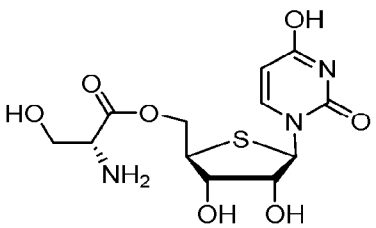
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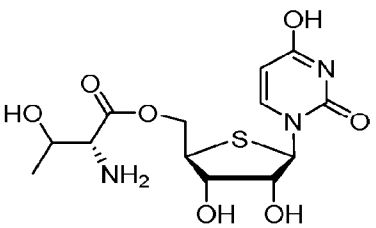
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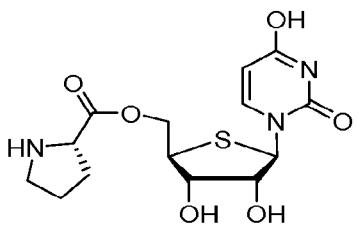
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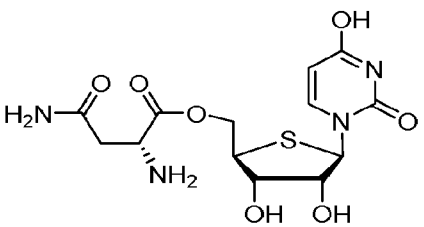
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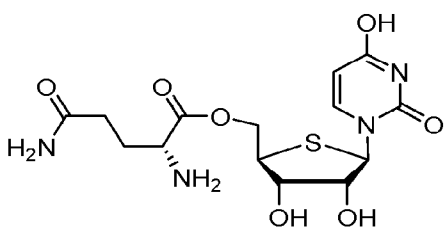
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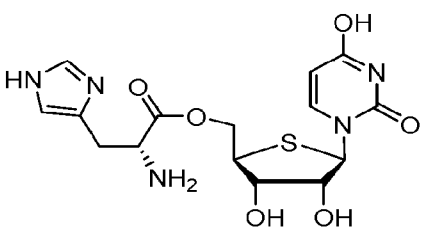
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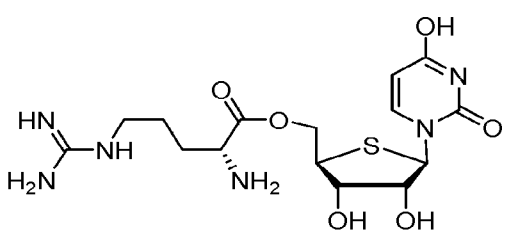
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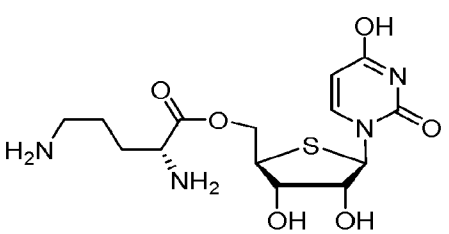
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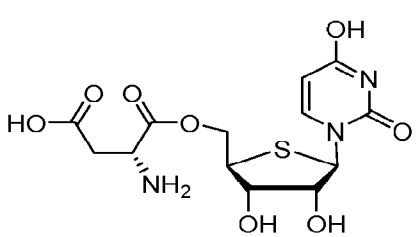
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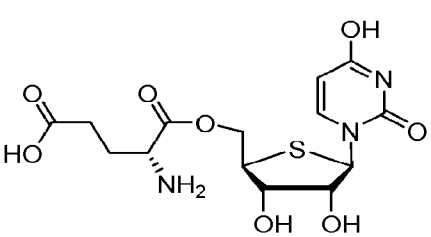
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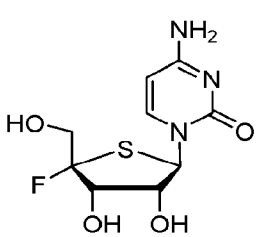
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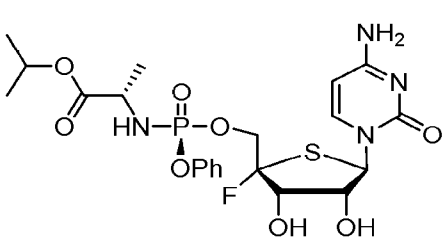
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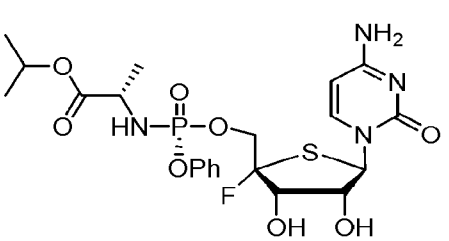
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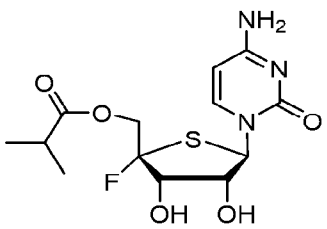
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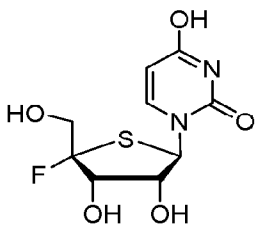
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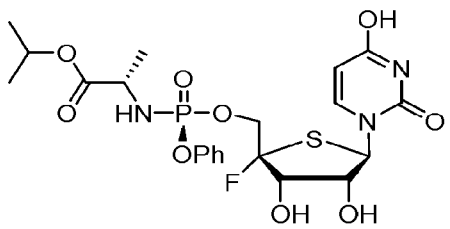
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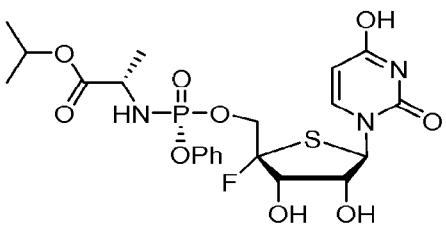
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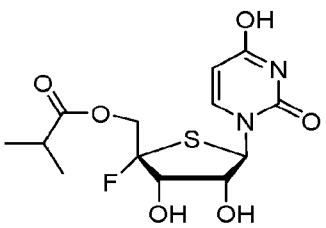
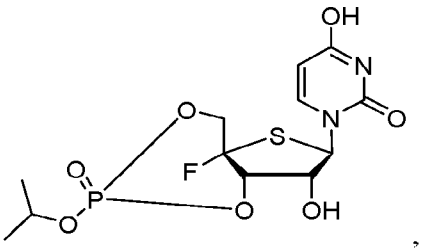

,

or a pharmaceutically acceptable salt or prodrug thereof.

95. The method of Claim 77, wherein the compound is one of the following compounds:



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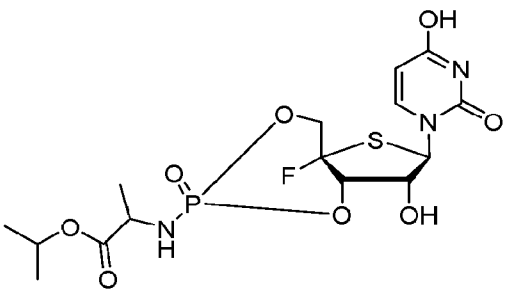

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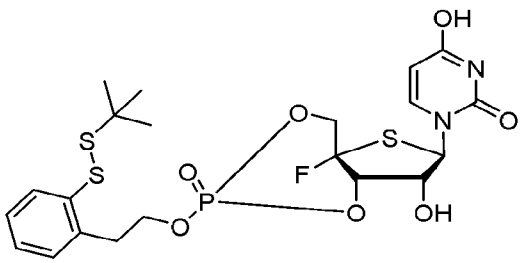

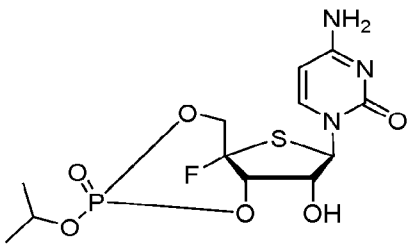

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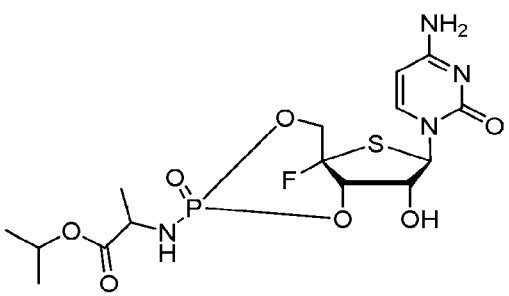

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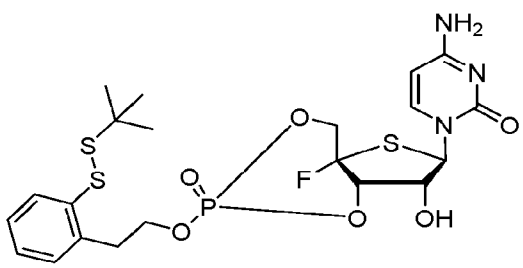

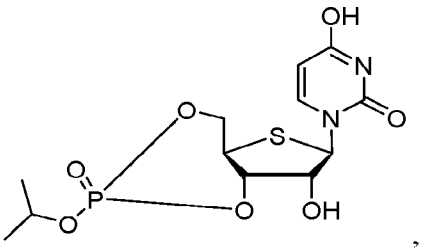

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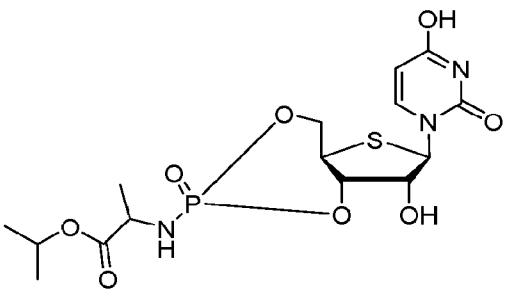

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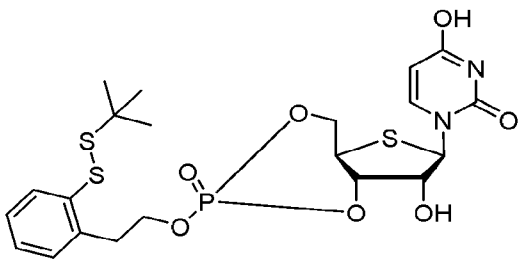

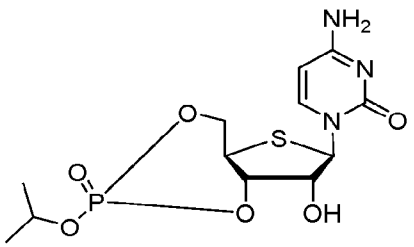

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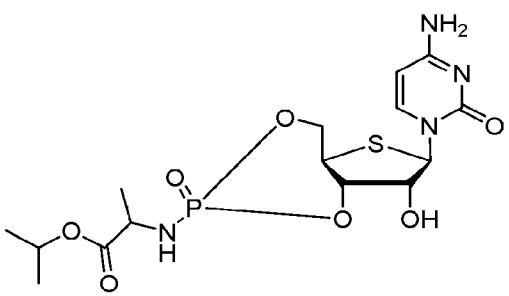

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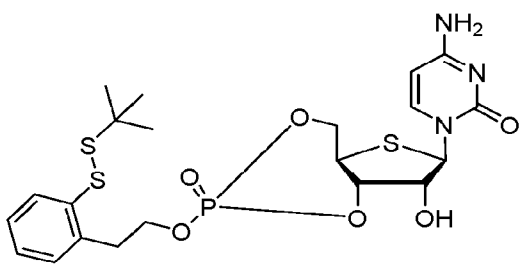

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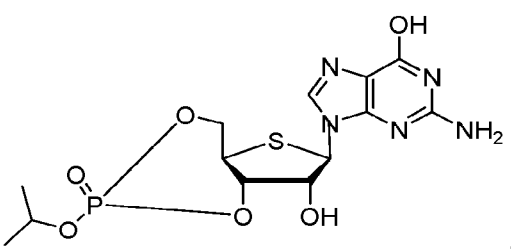

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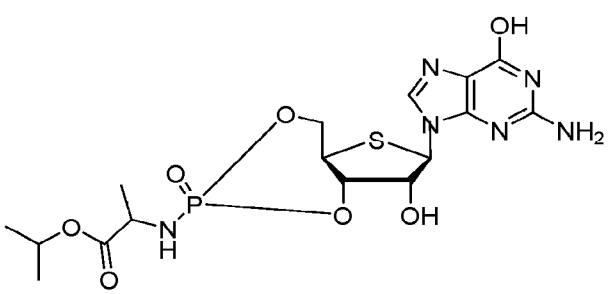

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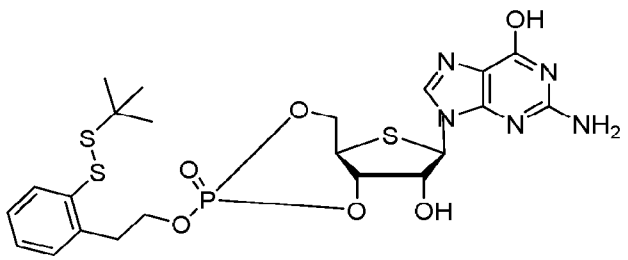
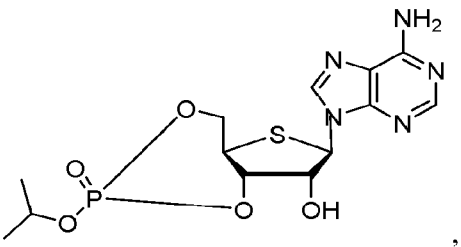
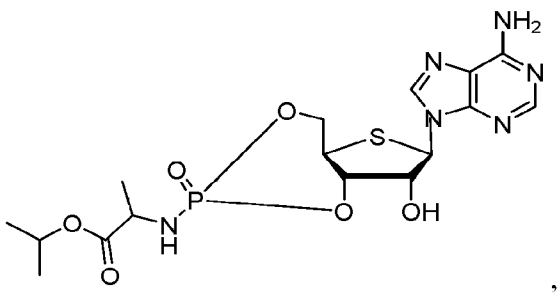
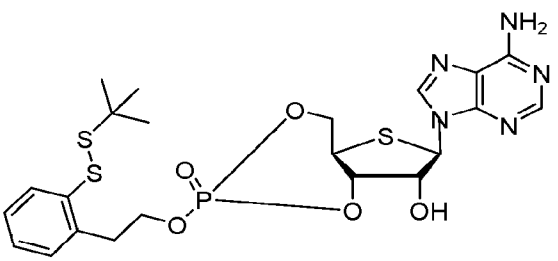
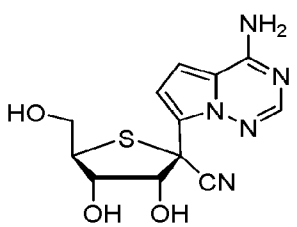
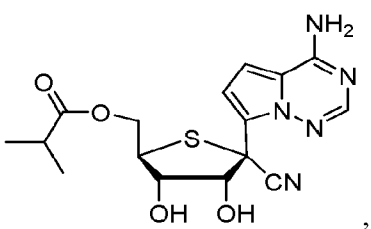
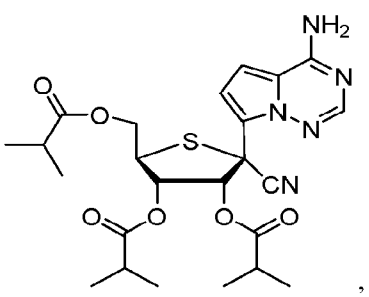
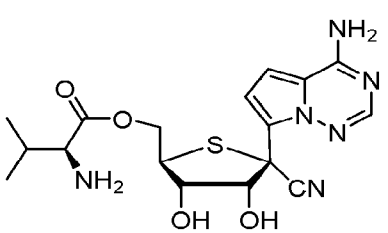
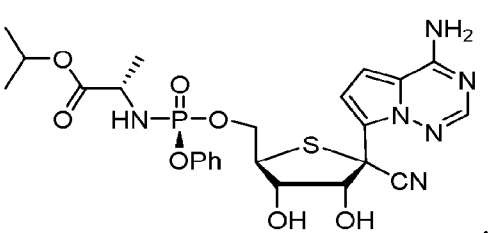
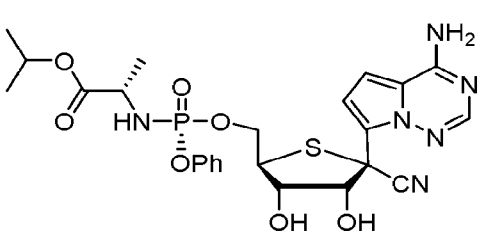





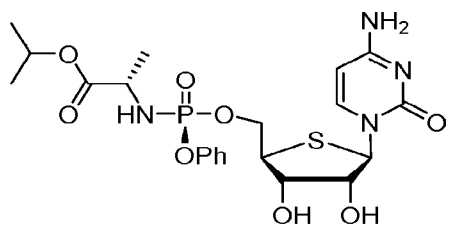
or a pharmaceutically acceptable salt or prodrug thereof.

96. The method of Claim 76, wherein the compound is one of the following compounds:

or a pharmaceutically acceptable salt or prodrug thereof.

97. The method of Claim 94, wherein the compound is one of the following compounds: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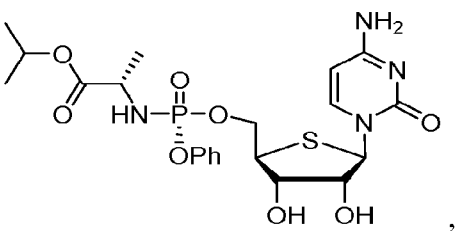
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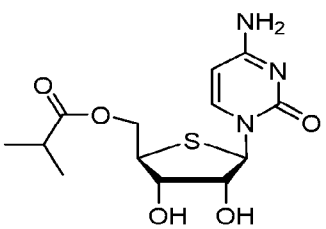
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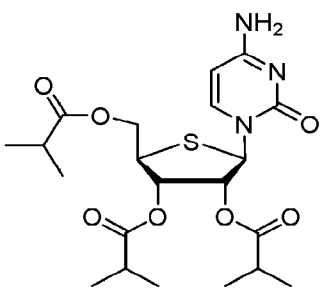
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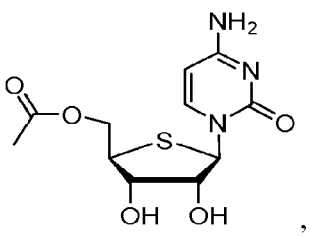
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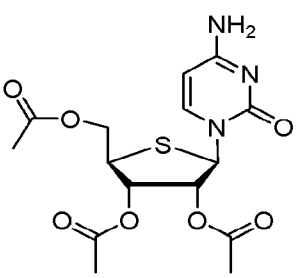
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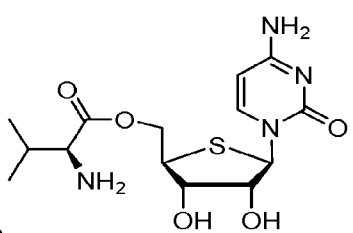
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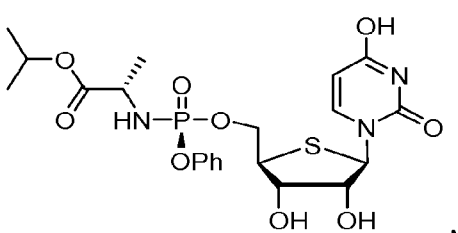
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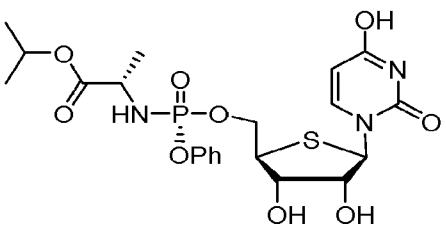
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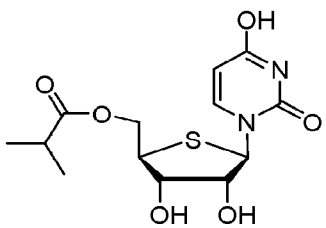
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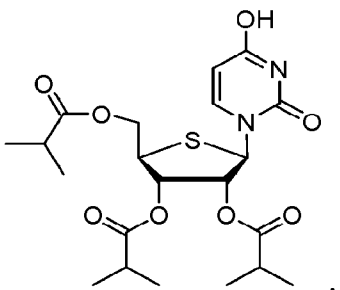
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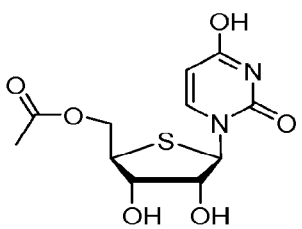
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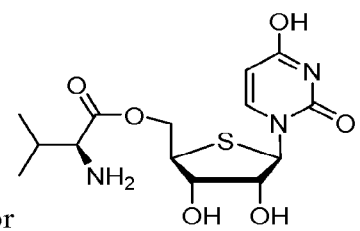
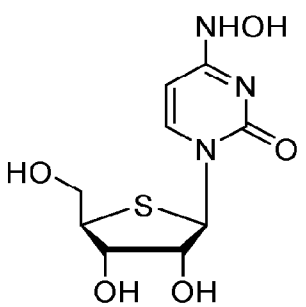


or a pharmaceutically acceptable salt or prodrug thereof.

98. The method of Claim 76, wherein the compound is  , or a pharmaceutically-acceptable salt or prodrug thereof.

99. The method of any of Claims 76-98, wherein the compounds can be present in the β-D or β-L configuration.

100. The method of any of Claims 76-98, wherein the virus is a Coronavirus.

101. The method of Claim 100, wherein the Coronavirus is human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2.

102. The method of Claim 100, wherein the Coronavirus is SARS-CoV2.

103. The method of any of Claims 76-98, wherein the compound is co-administered with one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

104. The method of Claim 103, wherein the compound is administered with remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814, or a pharmaceutically-acceptable salt or prodrug thereof.

105. The method of Claim 103, wherein the additional active compound is a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

106. The method of Claim 103, wherein the one or more additional active agents comprise an anticoagulant or a platelet aggregation inhibitor.

107. The method of Claim 103, wherein the one or more additional active agents comprise an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

108. The use of a compound of any of Claims 76-98 in the preparation of a medicament for use in treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection.

109. The use of Claim 108, wherein the infection is a Coronaviridae infection.

110. The use of Claim 109, wherein the Coronavirus is human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2.

111. The use of Claim 109, wherein the Coronavirus is SARS-CoV2.

112. The use of Claim 108, wherein the medicament further comprises one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

113. The use of Claim 108, wherein the medicament further comprises remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814 or a pharmaceutically-acceptable salt or prodrug thereof.

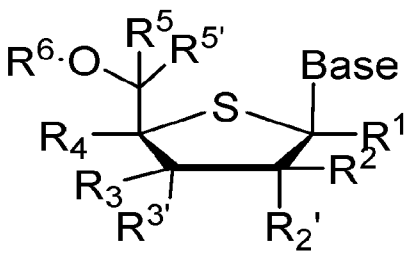
114. The use of Claim 108, wherein the medicament further comprises a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

115. The use of Claim 108, wherein the medicament further comprises an anticoagulant or a platelet aggregation inhibitor.

116. The use of Claim 108, wherein the medicament further comprises an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

117. The use of Claim 108, wherein the medicament is a transdermal composition or a nanoparticulate composition.

118. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**A**) to a patient in need of treatment or prevention thereof:



Formula A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is H, deuterium, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl or N_3,

R^2 and $R^{2'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7,

each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally

substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

with the proviso that R^2 and $R^{2'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7.

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

R^3 and $R^{3'}$ are, independently, selected from the group consisting of H, deuterium, OH, SH, NH_2, halo, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} cycloalkyl, cyano, cyanoalkyl, azido, azidoalkyl, OR^7, and SR^7, wherein each R^7 is, independently, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

wherein optional substituents are selected from the group consisting of halo, C_{1-12} haloalkyl, C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, C_{3-7} cycloalkyl, hydroxyl, carboxyl, C_{1-12} acyl, aryl, heteroaryl, C_{1-6} acyloxy, amino, amido, carboxyl derivatives, alkylamino, di-C_{1-12}-alkylamino, arylamino, C_{1-12} alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, boronic acid and boronic ester;

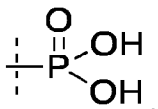
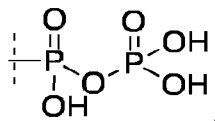
with the proviso that R^3 and $R^{3'}$ cannot both be OH, SH, NH_2, OR^7 or SR^7,

R^4 is selected from the group consisting of H, deuterium, CN, halo, N_3, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, substituted or unsubstituted (C_{1-8}) haloalkyl and N_3,

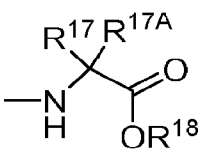
R^5 is and $R^{5'}$ are, independently, H, CH_3, CH_2F, CHF_2, or CF_3, wherein, when R^5 is CH_3, the carbon to which it is attached may be wholly or partially *R* or *S* or any mixture thereof, or R^5 and $R^{5'}$ can combine to form a C_{3-7} cycloalkyl ring;

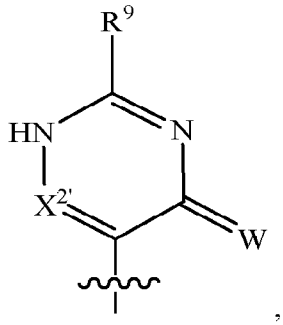
R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted $-CH_2$-O-C(O)-R', an optionally substituted $-CH_2$-O-C(O)O-R', an optionally substituted $-CH_2-CH_2$-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl;

Base is 

,

Y is H or halo,

X is N or CH,

W is O or S,

X^1 and $X^{1'}$ are, independently, CH, C-(C_{1-6})alkyl, C-(C_{2-6})alkenyl, C-(C_{2-6})alkynyl, C-(C_{3-7})cycloalkyl, C-(C_{1-6}) haloalkyl, C-(C_{1-6})hydroxyalkyl, C-OR^{22}, C-$N(R^{22})_2$, C-halo, C-CN or N,

X^2 and $X^{2'}$ are independently H, halo, $OR^{9'}$ or $NR^{10}R^{10'}$,

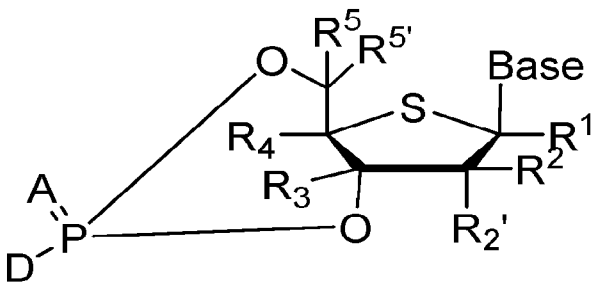
$R^{9'}$ is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, an (acyloxybenzyl)ester, an (acyloxybenzyl)ether, an optionally substituted bis-acyloxybenzyl)ester, an optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12}-alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, (acyloxybenzyl)amide, (acyloxybenzyl)amine, optionally substituted (acyloxybenzyl)esters,

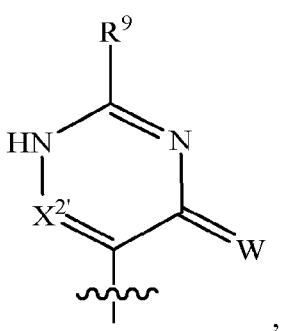
an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, PEG amide, PEG carbamate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid amide, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, or a lipid carbamate, wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), with the proviso that R^{10} and $R^{10'}$ cannot both be OH.

119. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**B**) to a patient in need of treatment or prevention thereof:



Formula B

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is 

,

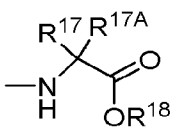
R^1, R^2, $R^{2'}$, R^3, R^4, R^5 $R^{5'}$, R^7 and R^8 are as defined in Formula A,

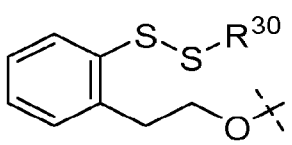
A is O or S, and

D is selected from the group consisting of:

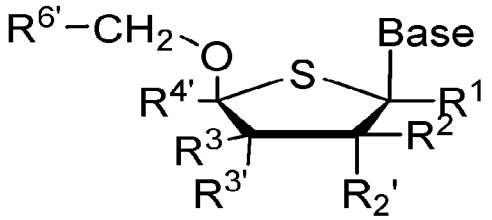
(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

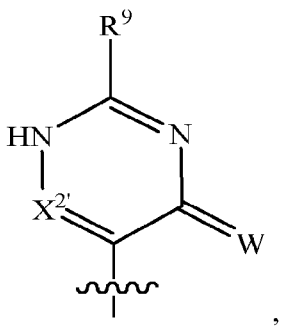
(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

120. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (C) to a patient in need of treatment or prevention thereof:



Formula C

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is 

,

R^1, R^2, $R^{2'}$, R^3 and $R^{3'}$are as defined in Formula A,

$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

$R^{6'}$ is selected from the group consisting of $-OR^6$, $-P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR',

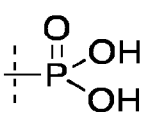
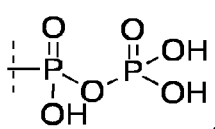
an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^7 is an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)esters, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-C_{1-12}R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, a PEG ester, a PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', a lipid ester, or a lipid carbonate,

wherein the lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

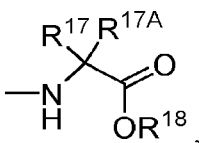
R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl, and

R^8 and $R^{8'}$ are independently selected from the group consisting of:

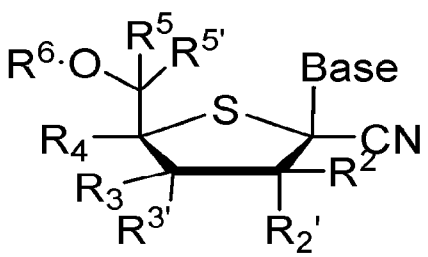
(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-}

$_{20}$alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

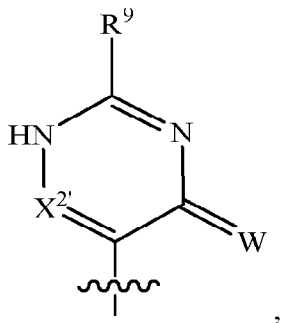
(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

121. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**D**) to a patient in need of treatment or prevention thereof:



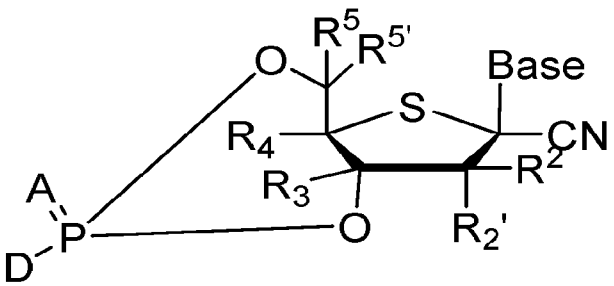
Formula D

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is  ,

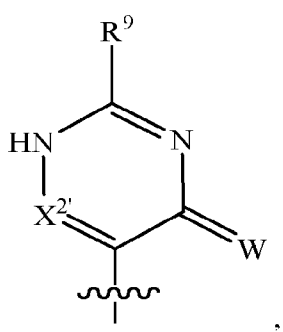
X^1, $X^{1'}$, $X^{2'}$, X^2, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, R^5, $R^{5'}$ and R^6 are as defined in Formula A.

122. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**E**) to a patient in need of treatment or prevention thereof:



Formula E

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is  ,

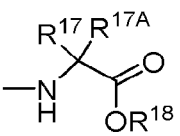
X^1, $X^{1'}$, $X^{2'}$, X^2 R^2, $R^{2'}$, R^3, R^4, R^5 and $R^{5'}$are as defined in Formula A,

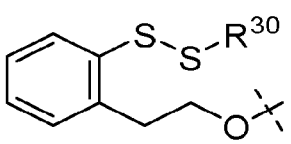
A is O or S, and

D is selected from the group consisting of:

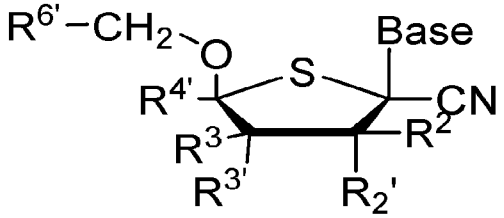
(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl, and

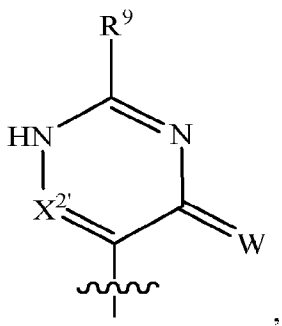
(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

123. A method for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, comprising administering a treatment or preventative amount of a compound of Formula (**F**) to a patient in need of treatment or prevention thereof:



Formula F

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Base is 

,

X^1, $X^{1'}$, $X^{2'}$, X^2 R^2, $R^{2'}$, R^3 and $R^{3'}$are as defined in Formula A,

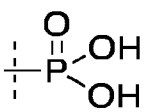
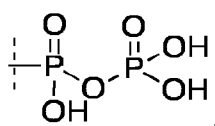
$R^{4'}$ is selected from the group consisting of H, deuterium, CN, substituted or unsubstituted (C_{1-8})alkyl, substituted or unsubstituted (C_{2-8})alkenyl, substituted or unsubstituted (C_{2-8})alkynyl, and substituted or unsubstituted (C_{1-8}) haloalkyl,

$R^{6'}$ is selected from the group consisting of $-OR^6$, $-P(O)R^7R^8$, and a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

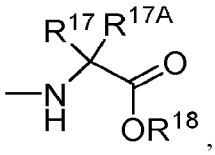
R^6 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR',

an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, an optionally substituted –O-C(O)N(R')$_2$, a lipid ester, a lipid carbonate (in which a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy), O-P(O)$R^8R^{8'}$, or a mono-, di-, or triphosphate, wherein, when chirality exists at the phosphorous center, it may be wholly or partially R_p or S_p or any mixture thereof,

R^8 and $R^{8'}$ are independently selected from the group consisting of:

(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')N(R')$_2$, optionally substituted –O-C(O)N(R')$_2$, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, such as phenyl, and heteroaryl, such as pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting of $(CH_2)_{0-6}CO_2R^{16}$ and $(CH_2)_{0-6}$ $CON(R^{16})_2$;

where R^{16} is independently H, substituted or unsubstituted C_{1-20} alkyl, substituted or unsubstituted C_{1-20} alkene, substituted or unsubstituted C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, C_{1-5} alkene, C_{1-5} alkyne, C_{3-7} cycloalkyl or C_{1-5} alkyl substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6} alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and

(*b*) the ester of a D- or L-amino acid  , wherein R^{17} and R^{18} are, independently, H, C_{1-20} alkyl, C_{1-20} alkene, C_{1-20} alkyne, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl, or substituted heteroaryl; wherein the substituents are C_{1-5} alkyl, or C_{1-5} alkyl substituted with a C_{1-6}alkyl, alkoxy, di(C_{1-6}alkyl)-amino, fluoro, C_{3-10} cycloalkyl, or cycloalkyl; and R^{17A} is H or C_{1-2}alkyl.

124. The method of Claim 118, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

125. The method of Claim 119, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

126. The method of Claim 120, wherein R^1 is H, R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H.

127. The method of Claim 121, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

128. The method of Claim 122, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7, R^4 is H, R^5 and $R^{5'}$ are H or Me.

129. The method of Claim 123, wherein R^2 is H, $R^{2'}$ is OH or OR^7, R^3 is H, $R^{3'}$ is OH or OR^7 and R^4 is H

130. The method of Claim 118, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

131. The method of Claim 119, wherein $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

132. The method of Claim 120, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

133. The method of Claim 121, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl and R^6 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl.

134. The method of Claim 122, wherein $R^{2'}$ is OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

135. The method of Claim 123, wherein $R^{2'}$ and $R^{3'}$ are OH, an L-amino acid ester, a D-amino acid ester or an optionally substituted -O-C(O)-C_{1-12} alkyl.

136. The method of any of Claims 118-135, wherein the compounds can be present in the β-D or β-L configuration.

137. The method of any of Claims 118-135, wherein the virus is a Coronavirus.

138. The method of Claim 137, wherein the Coronavirus is human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2.

139. The method of Claim 137, wherein the Coronavirus is SARS-CoV-2.

140. The method of any of Claims 118-135, wherein the compound is co-administered with one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

141. The method of Claim 140, wherein the compound is administered with remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814, or a pharmaceutically-acceptable salt or prodrug thereof.

142. The method of Claim 140, wherein the additional active compound is a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

143. The method of Claim 140, wherein the one or more additional active agents comprise an anticoagulant or a platelet aggregation inhibitor.

144. The method of Claim 140, wherein the one or more additional active agents comprise an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

145. The use of a compound of any of Claims 118-135 in the preparation of a medicament for use in treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection.

146. The use of Claim 145, wherein the infection is a Coronaviridae infection.

147. The use of Claim 146, wherein the Coronavirus is human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2.

148. The use of Claim 146, wherein the Coronavirus is SARS-CoV2.

149. The use of Claim 145, wherein the medicament further comprises one or more additional active compounds selected from the group consisting of fusion inhibitors, entry inhibitors, protease inhibitors, polymerase inhibitors, antiviral nucleosides, viral entry inhibitors, viral maturation inhibitors, JAK inhibitors, angiotensin-converting enzyme 2 (ACE2) inhibitors, SARS-CoV-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

150. The use of Claim 145, wherein the medicament further comprises remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814 or a pharmaceutically-acceptable salt or prodrug thereof.

151. The use of Claim 145, wherein the medicament further comprises a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof.

152. The use of Claim 145, wherein the medicament further comprises an anticoagulant or a platelet aggregation inhibitor.

153. The use of Claim 145, wherein the medicament further comprises an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

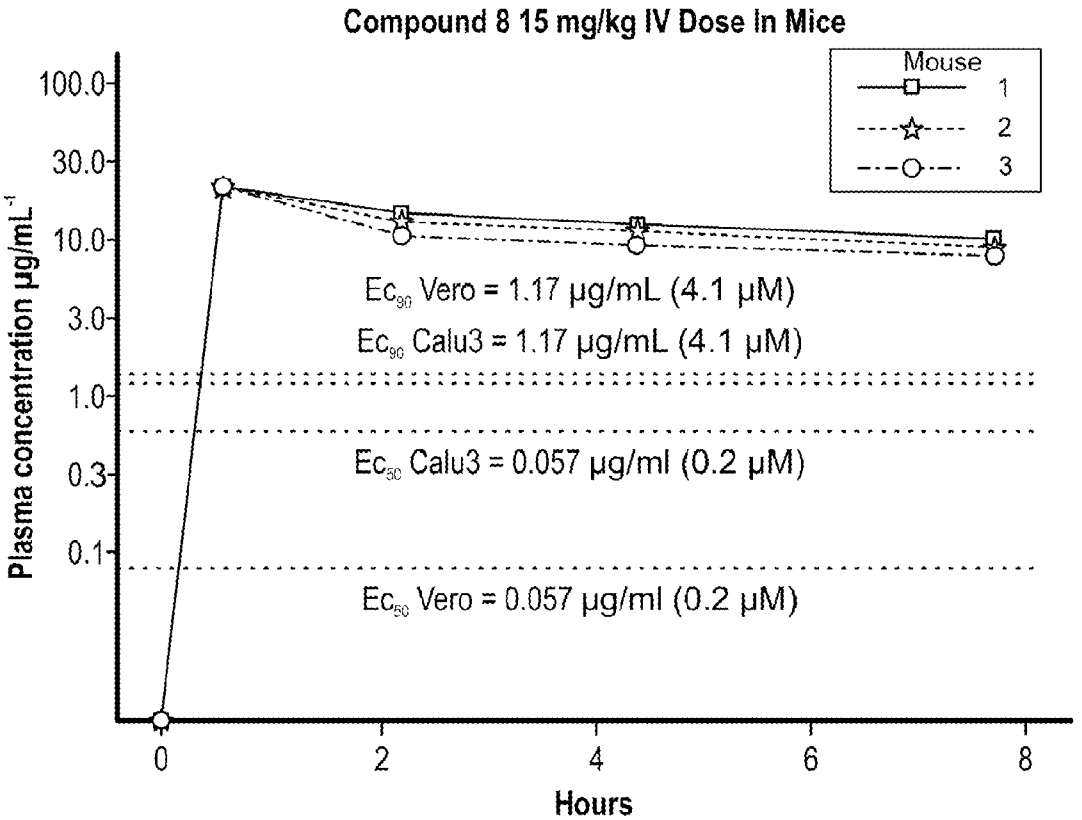
154. The use of Claim 145, wherein the medicament is a transdermal composition or a nanoparticulate composition.

155. The method of any of Claims 1-65, 76-107, or 118-144, wherein the compound is administered in combination with an NS5A inhibitor.

156. The method of Claim 155, wherein the NS5A inhibitor is daclastavir.

157. The use of any of Claims 66-75, 108-117, or 145-154, wherein the medicament also comprises an NS5A inhibitor.

158. The use of Claim 157, wherein the NS5A inhibitor is daclastavir.

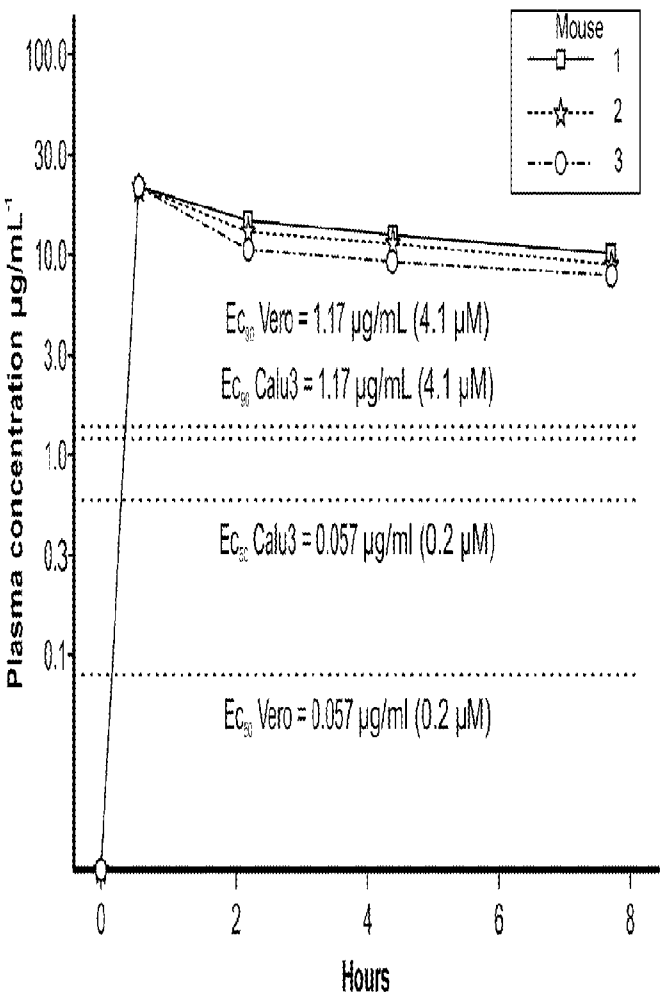


Mean C_{max} = 20 µg/mL

Mean $t_{1/2}$ = 8.5 hr

IV	15	mg/kg				
ID	1	2	3	mean	SD	%CV
Cmax, (µg/ml)	18.6	20.5	20.9	20	1.23	6.14
Tmax, (hr)	0.5	0.5	0.5	0.5	0	0
AUCinf, (µg/mL.hr)	175.2	160.3	205.6	180.4	23.1	12.8
$t_{1/2}$, (hr)	9.77	7.03	8.80	8.53	1.39	16.29
MRT, (hr)	13.39	10.09	12.66	12.05	1.73	14.37
CL/F, (L/hr)/kg	0.086	0.094	0.073	0.084	0.010	12.35

Compound 8 concentrations were > *in vitro* EC_{90} for > 7hr after IV administration.



Mean C_{max} = 20 µg/mL

Mean $t_{1/2}$ = 8.5 hr

IV	15	mg/kg				
ID	1	2	3	mean	SD	%CV
C_{max}, (µg/ml)	18.6	20.5	20.9	20	1.23	6.14
Tmax, (hr)	0.5	0.5	0.5	0.5	0	0
AUCinf, (µg/mL.hr)	175.2	160.3	205.6	180.4	23.1	12.8
$t_{1/2}$, (hr)	9.77	7.03	8.80	8.53	1.39	16.29
MRT, (hr)	13.39	10.09	12.66	12.05	1.73	14.37
CL/F, (L/hr)/kg	0.086	0.094	0.073	0.084	0.010	12.35

Compound 8 concentrations were > *in vitro* EC_{90} for > 7hr after IV administration.