SARS, and OC-43. In other examples, the compounds described herein can be used for treating or preventing infections by Flaviviruses, Picornaviridae, Togavirodae, Bunyaviridae and other RNA viruses.

In one example, 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 are disclosed.

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

In another example, pharmaceutical compositions including one or more of the compounds described herein are disclosed, which in one example 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-specific human monoclonal antibodies, including CR3022, and agents of distinct or unknown mechanism.

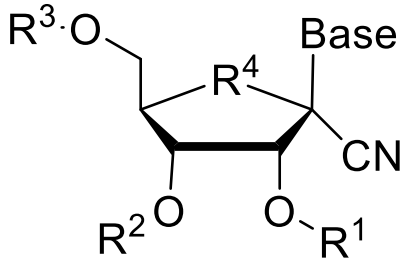
In yet another example, processes for preparing the specific nucleoside compounds described herein are disclosed.

In some examples, 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 examples, 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.

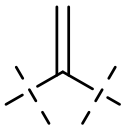
In another example, ester prodrugs were prepared to improve the oral bioavailability of drugs.

In an aspect, there is provided a use of a compound of Formula (**A**):



Formula **A**

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

R^4 is O, CH_2, S, Se, or  ,

R^1 and R^2 are independently selected from the group consisting of 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)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')$_2$, 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', a lipid ester, a lipid carbonate, (in which the lipid is an optionally substituted C_{12-22} alkyl, an

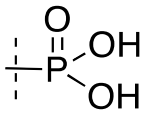
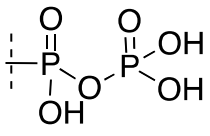
optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

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;

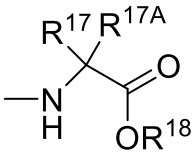
R^3 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, 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^6R^7, 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^6 and R^7 are independently selected from the group consisting of:

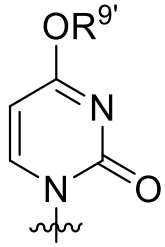
(*a*) OR^{15} where R^{15} selected from the group consisting of H,  ,  , Li, Na, K, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, optionally substituted -C(NR')OR', optionally substituted -C(NR')SR', optionally substituted -C(NR')$N(R')_2$, optionally substituted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

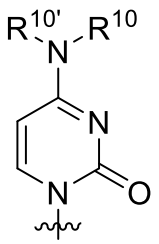
benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20}alkyl, C_{2-3}(alkyl)OC_{1-20}alkene, C_{2-3}(alkyl)OC_{1-20}alkyne, aryl, and heteroaryl, such as phenyl and pyridinyl, wherein aryl and heteroaryl are optionally substituted with zero to three substituents independently selected from the group consisting 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, 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 

or 

;

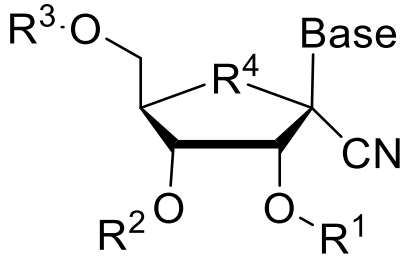
$R^{9'}$ is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, an (acyloxybenzyl)ester, an (acyloxybenzyl)ether, an

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),

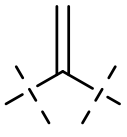
R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, (acyloxybenzyl)amide, (acyloxybenzyl)amine, optionally substituted (acyloxybenzyl)esters, an optionally substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)S-R', an optionally 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 aspect, there is provided a use of a compound of Formula (**A**):



Formula **A**

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

R^4 is O, CH_2, S, Se, or  ,

R^1 and R^2 are independently selected from the group consisting of 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)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)$N(R')_2$, 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', a lipid ester, a lipid carbonate, (in which 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),

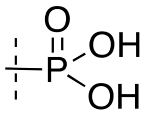
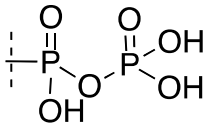
R' is C_{1-16} alkyl, C_{2-16} alkenyl, C_{2-16} alkynyl, or C_{3-7} cycloalkyl,

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;

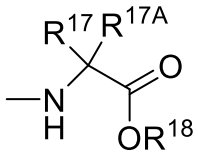
R^3 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, optionally substituted (acyloxybenzyl)ester, an optionally

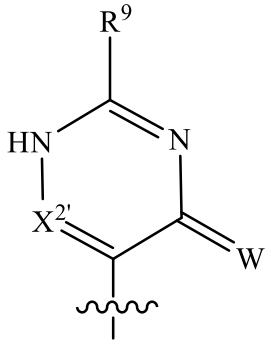
substituted -C(O)-R', an optionally substituted -C(O)O-R', an optionally substituted -C(O)SR', an optionally substituted -C(S)SR', PEG ester, PEG carbonate, an optionally substituted -CH_2-O-C(O)-R', an optionally substituted -CH_2-O-C(O)O-R', an optionally substituted -CH_2-CH_2-S-C(O)-R', an optionally 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^6R^7, 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^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, 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, 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, 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;

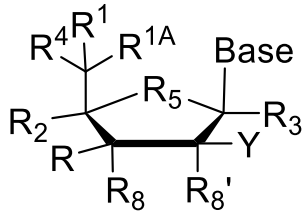
Base is  ,

$R^{9'}$ 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,

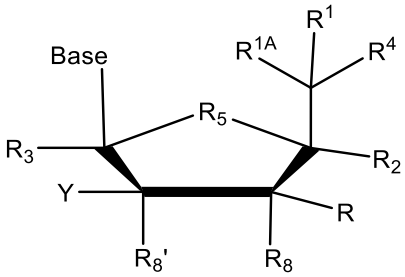
wherein a lipid is an optionally substituted C_{12-22} alkyl, an optionally substituted C_{12-22} alkenyl, an optionally substituted C_{12-22} alkynyl or an optionally substituted C_{12-22} alkoxy),

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 aspect, there is provided a use of a compound of Formula (**A**) or Formula **(A1)**:



Formula A



Formula A1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, 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;

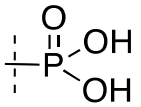
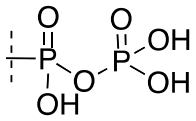
R^3 is CN,

R^5 is O, S, Se, CH_2, CHF, CF_2, -C(CH_3)-, -C(cyclopropyl)-, C=CF_2 or C=CH_2,

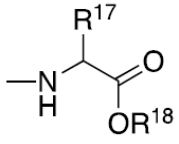
R^8 and $R^{8'}$ are independently selected from the group consisting of H, OH, halo, an optionally substituted O-linked amino acid, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, 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,

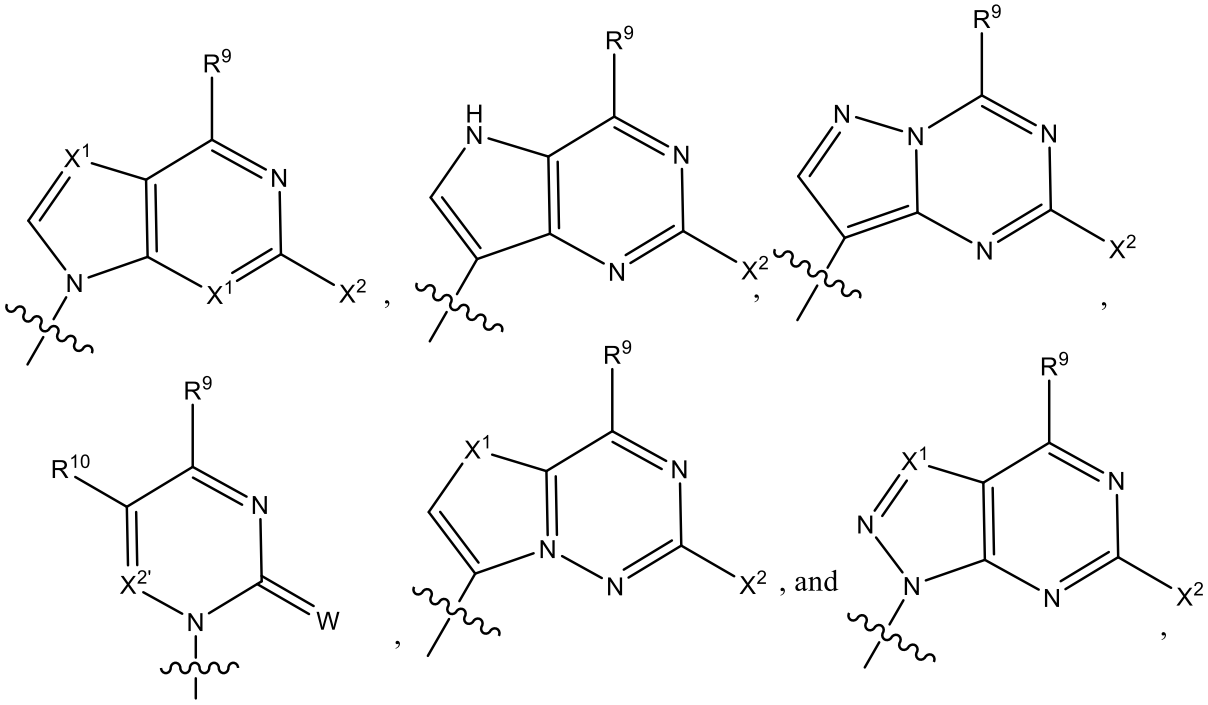
R^6 and R^7 are independently selected from the group consisting of:

(*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,

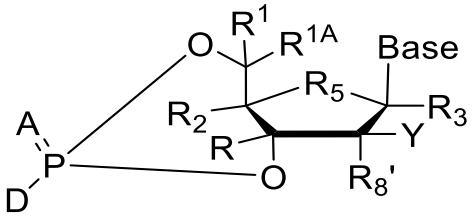
$R^{9'}$ is OH, NH_2, SH, NHOH, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, or -O-C(O)O-C_{3-6} cycloalkyl,

R^{10} is H or F,

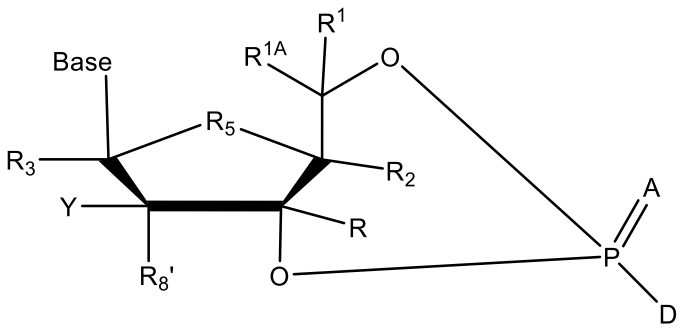
$X^{2'}$ is N or CH, and

W is O or S.

In another aspect, there is provided a use of a compound of Formula (**B**) or **(B1)**:



Formula B



Formula B1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

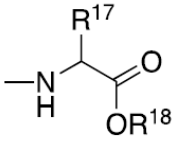
Base, Y, R, R^1, R^{1A}, R^2, R^3, R^5, and $R^{8'}$ are as defined in Formula A,

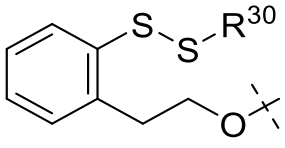
A is O or S, and

D is selected from the group consisting of:

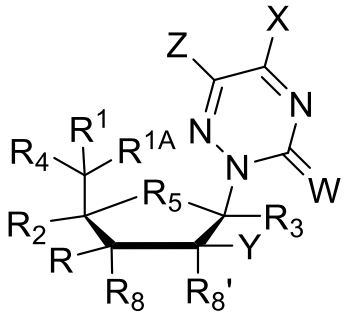
(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, and heteroaryl, such as phenyl and pyridinyl,

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 $(CH_2)_{0-6}$ $CON(R^{16})_2$;

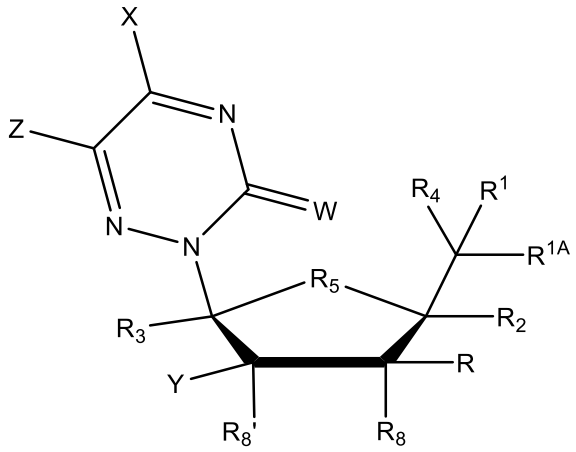
(b) the ester of a D- or L-amino acid  , R^{17} and R^{18} are independently H, C_{1-20} alkyl, the carbon chain derived from a fatty alcohol or C_{1-20} alkyl optionally substituted with a C_{1-6} alkyl, alkoxy, di(C_{1-6}alkyl)- amino, fluoro, C_{3-10} cycloalkyl, cycloalkyl-C_{1-6} alkyl, cycloheteroalkyl,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

In another aspect, there is provided a use of a compound of Formula **(C)** or **(C1):**



Formula C



Formula C1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

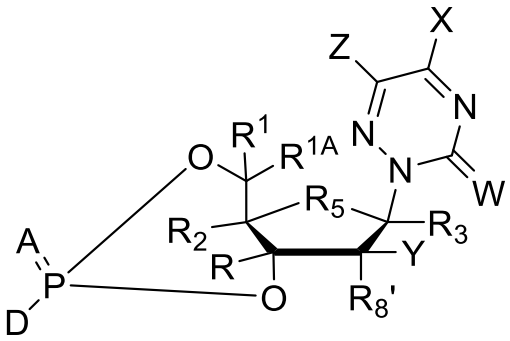
R, R^1, R^{1A}, R^2, R^3, R^5, R^8, $R^{8'}$ and Y are as defined in Formula A,

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,

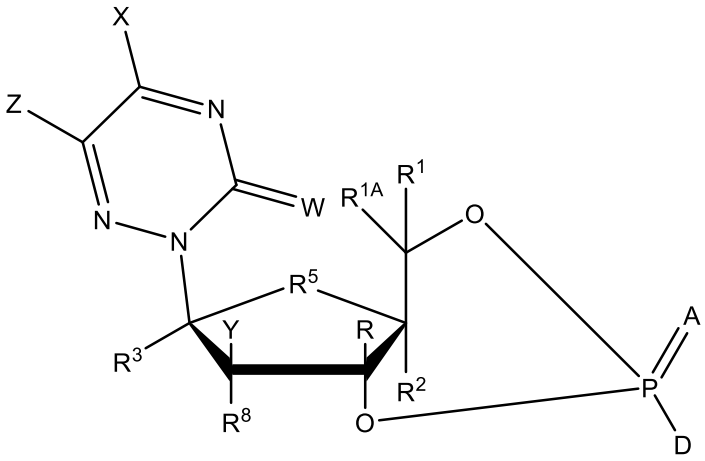
Z is H or F, and

W is O or S.

In another aspect, there is provided a use of a compound of Formula (**D**) or **(D1)**:



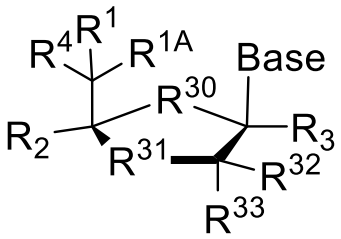
Formula D



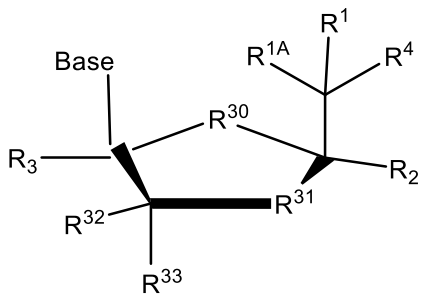
Formula D1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, 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.

In another aspect, there is provided a use of a compound of Formula (**E**) or **(E1)**:



Formula E



Formula E1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

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

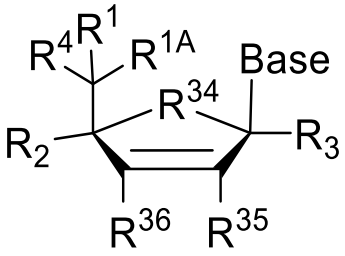
R^{30} is O, S, or CH_2,

R^{31} is O or S,

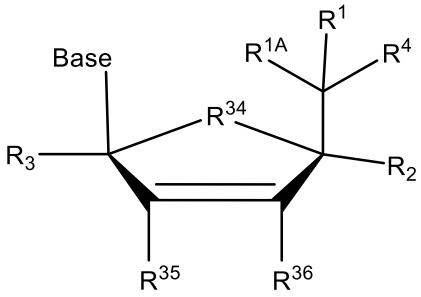
R^{31} is O when R^{30} is S, and

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.

In another aspect, there is provided a use of a compound of Formula (**F**) or **(F1)**:



Formula F



Formula F1

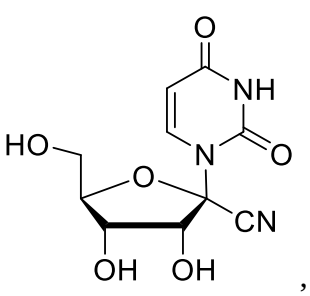
or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

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

R^{34} is O, S, or CH_2, and

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

In another aspect, there is provided a use of a compound of one of the following formulas: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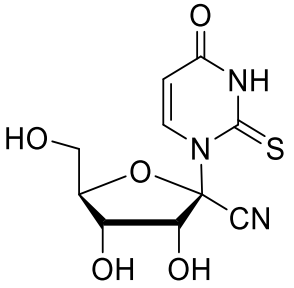
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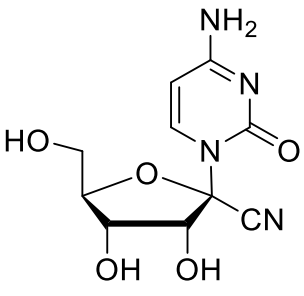
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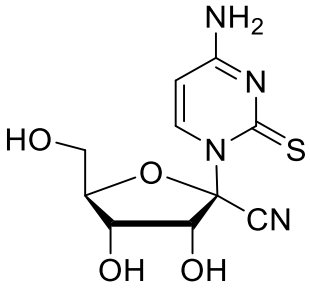
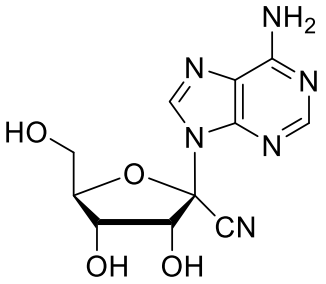
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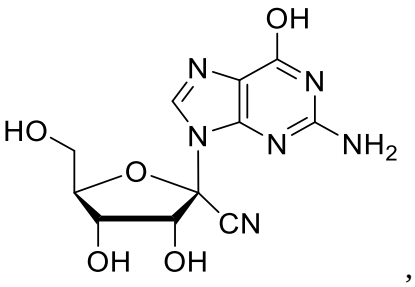
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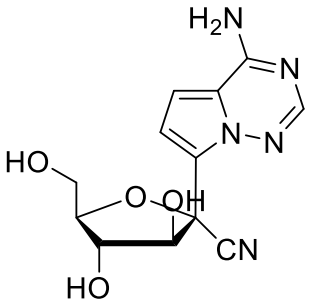
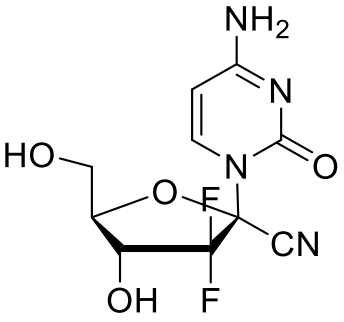
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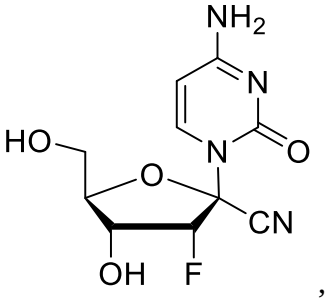
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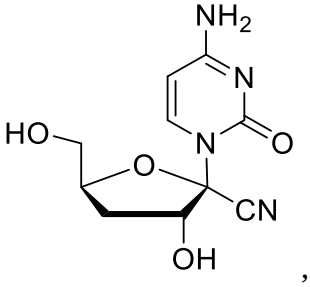
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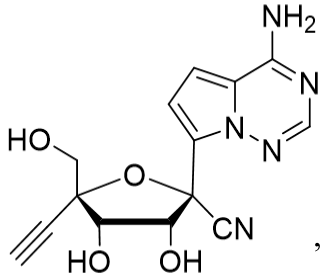

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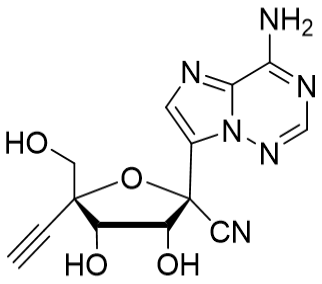

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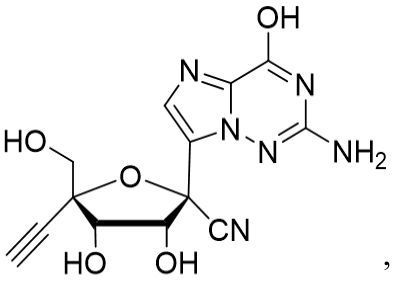

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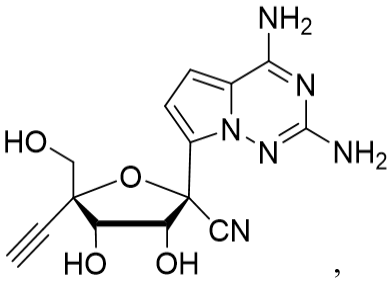

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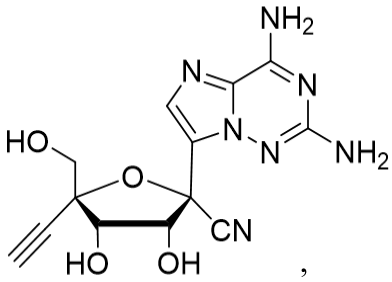

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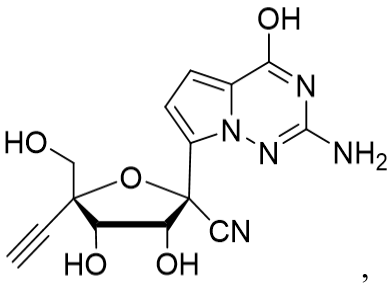
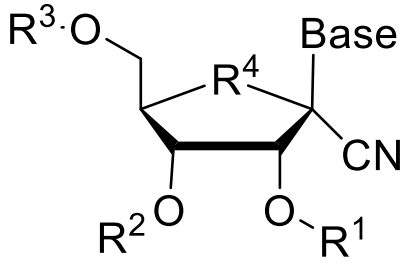


,

or a pharmaceutically-acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection.

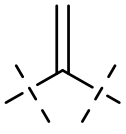
We claim:

1. Use of a compound of Formula (**A**):



Formula **A**

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

R^4 is O, CH_2, S, Se, or  ,

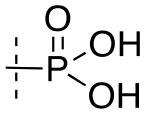
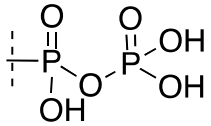
R^1 and R^2 are independently selected from the group consisting of H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)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)$N(R')_2$, 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', a lipid ester, a lipid carbonate, (in which 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;

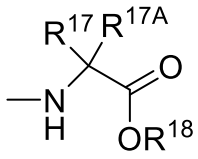
R^3 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, 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^6R^7, 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,

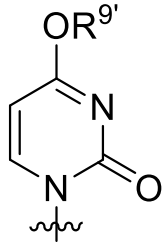
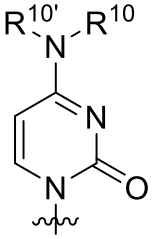
R^6 and R^7 are independently selected from the group consisting of:

(*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, 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, 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, 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  or  ;

$R^{9'}$ 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

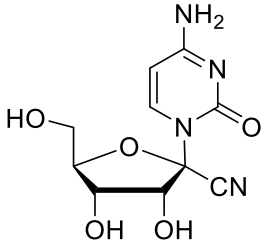
substituted -C(O)S-R', an optionally substituted -C(S)S-R', an optionally substituted C_{1-12}-alkyl, an optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted -C(NR')OR', an optionally substituted -C(NR')SR', 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.

2. The use of Claim 1, wherein R^4 is O, CH_2 or S; R^4 is O and R^1, R^2, R^3, R^9, R^{10} and $R^{10'}$ are not all H; R^1 and R^2 are H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl; R^3 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl; R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, an optionally substituted -C(O)-C_{1-12} alkyl, with the proviso that R^{10} and $R^{10'}$ cannot both be OH; R^9 is H, an L-amino acid ester with the oxygen to which it is attached, a D-amino acid ester with the oxygen to which it is attached, or an optionally substituted -C(O)-C_{1-12} alkyl; or R^{10} and $R^{10'}$ are both H.

3. The use of Claim 1, wherein the compound is one of the following compounds: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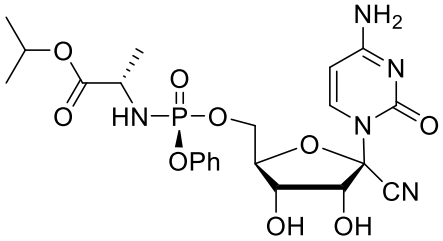
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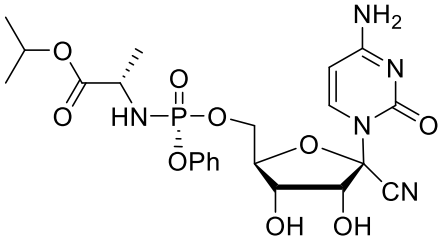
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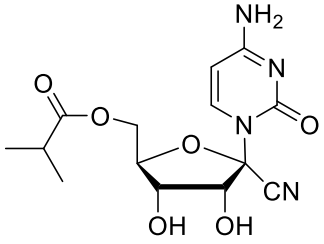
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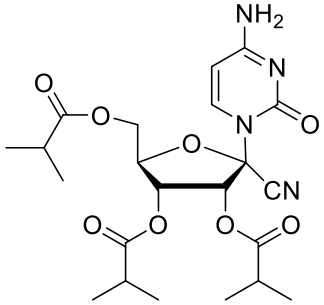
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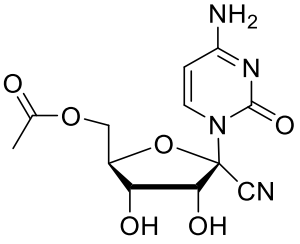
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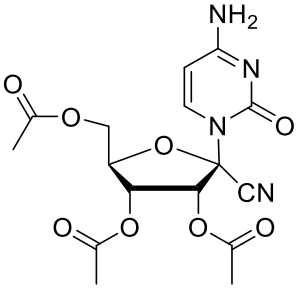
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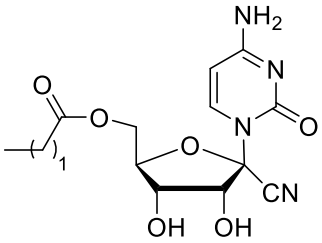
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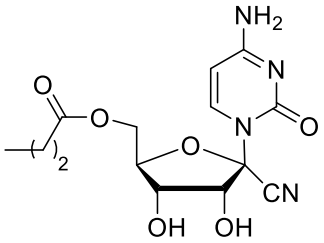
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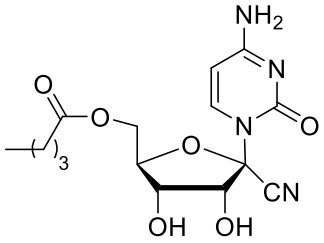
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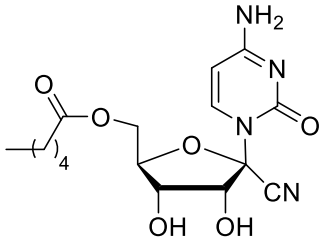
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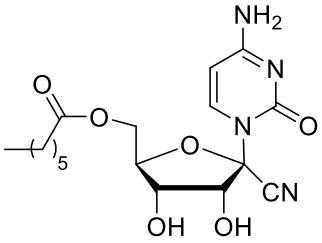
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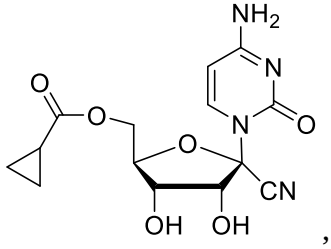
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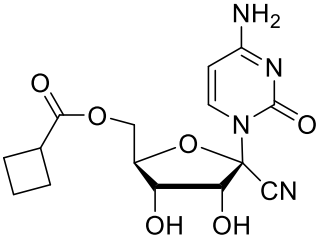
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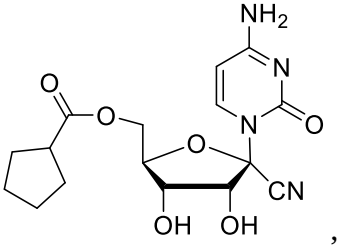
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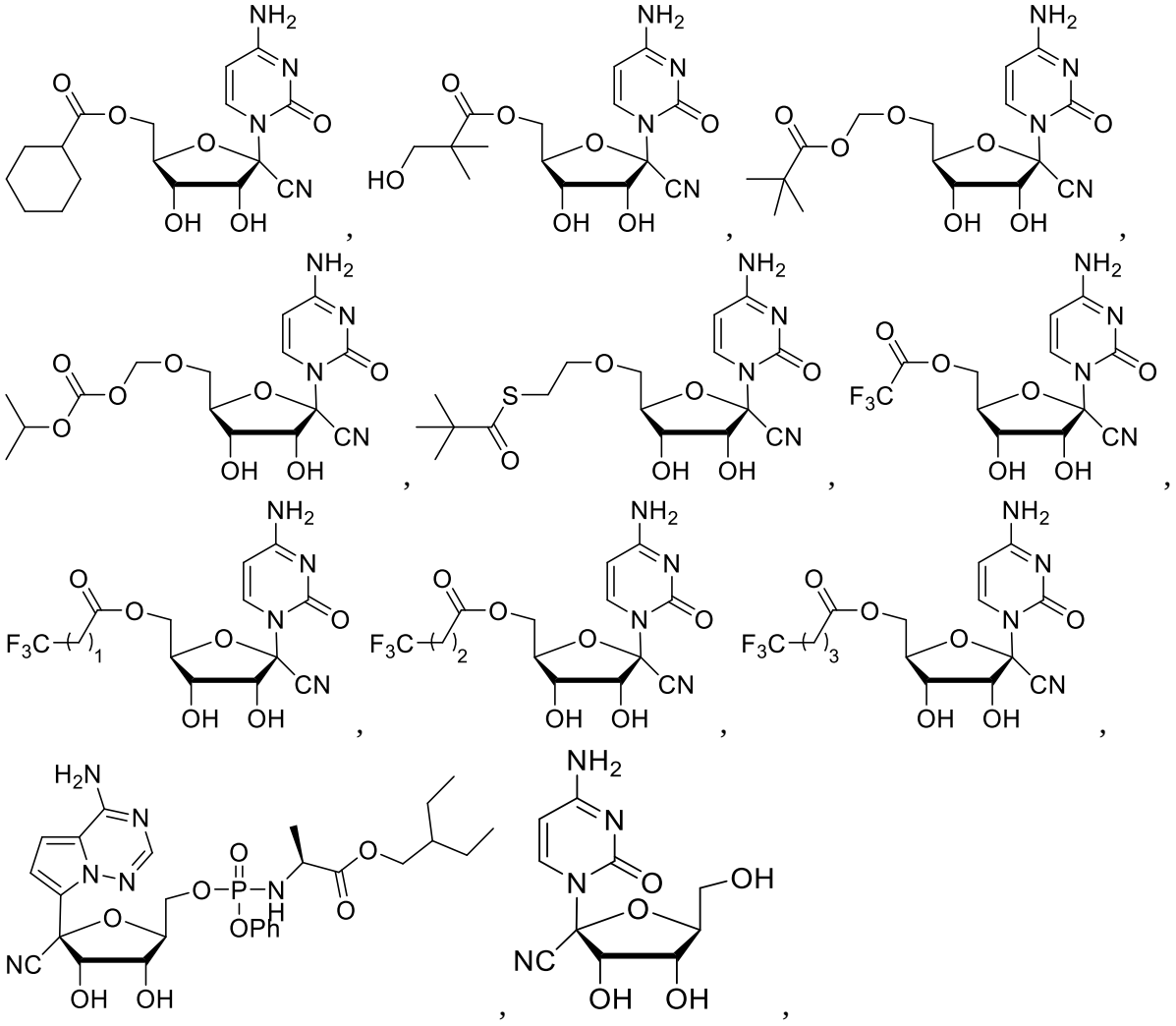

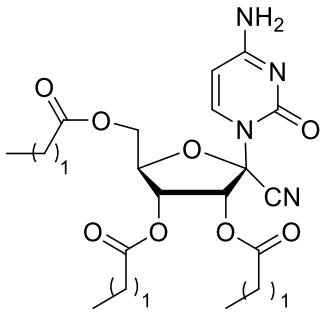
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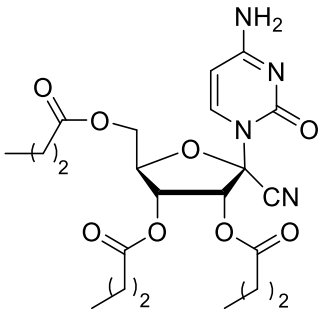
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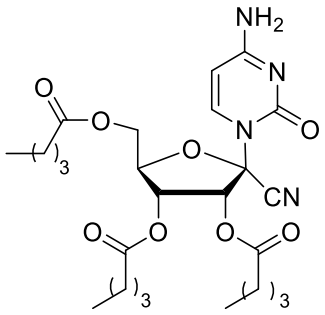
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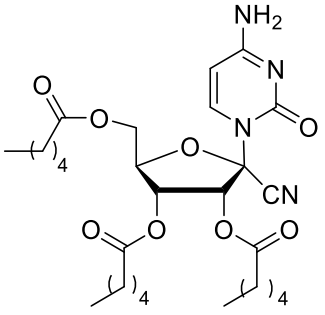
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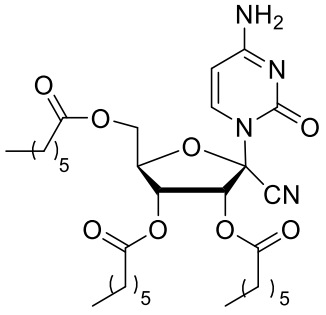
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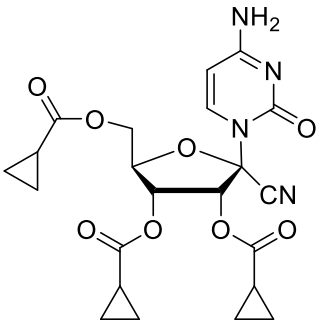
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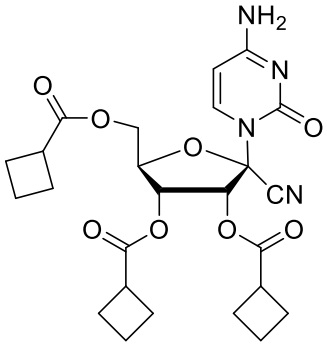
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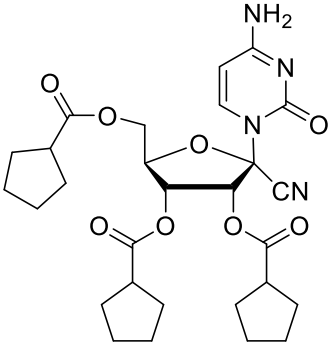
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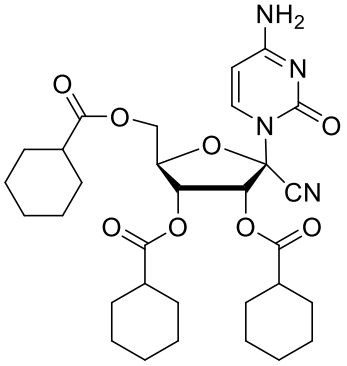
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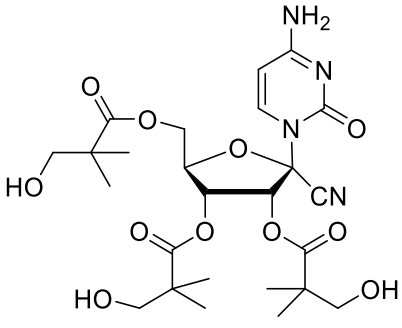
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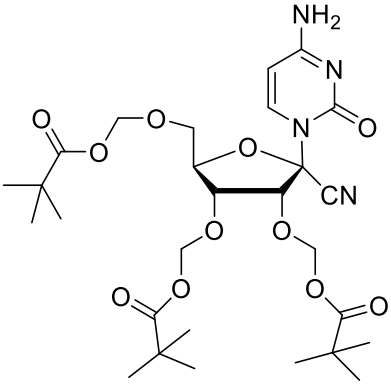
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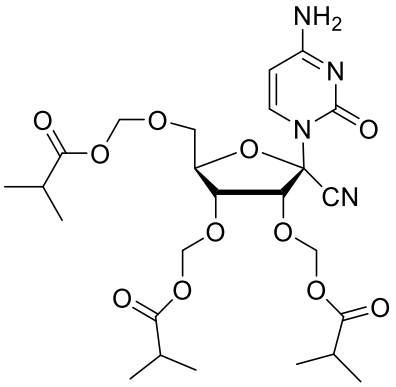
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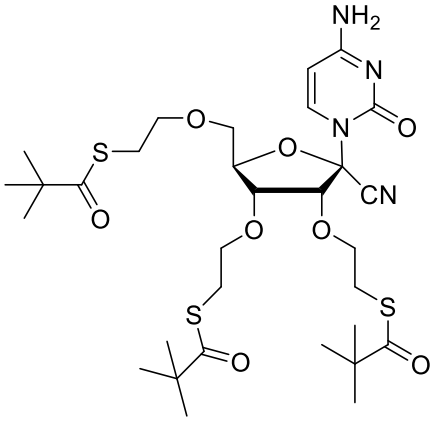
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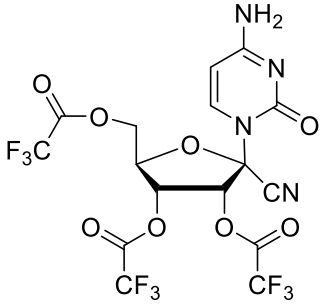
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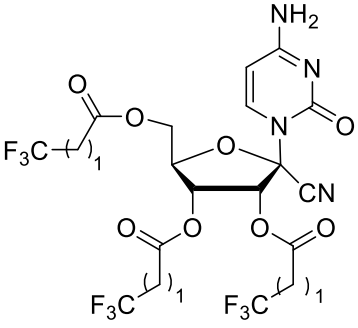
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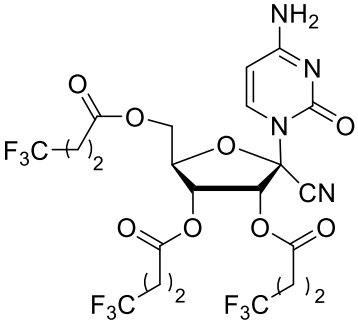
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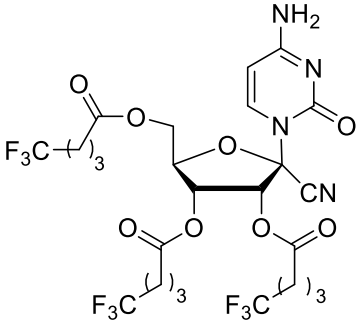
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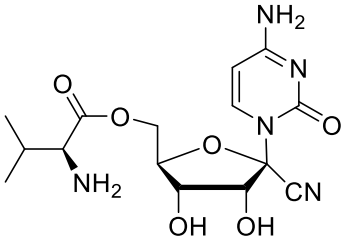
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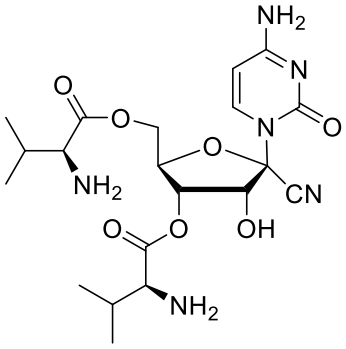
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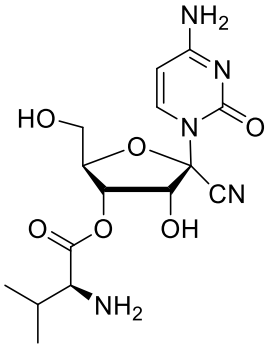
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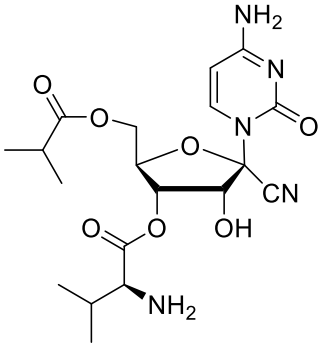
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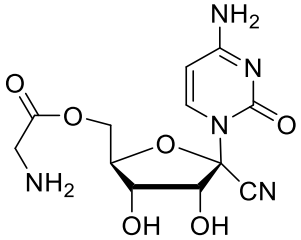
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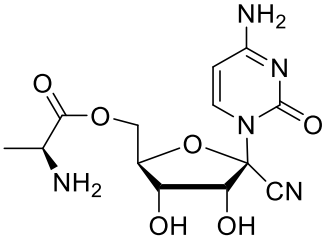
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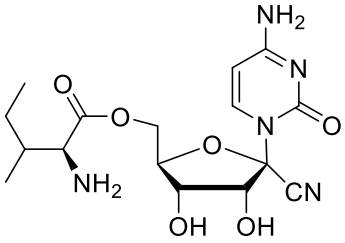
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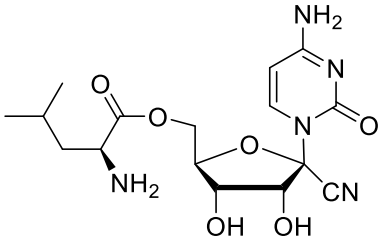
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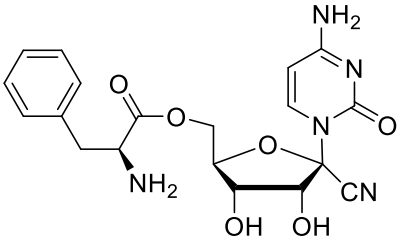
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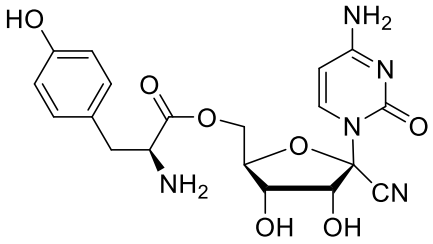
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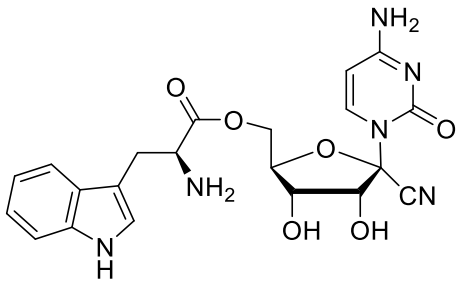
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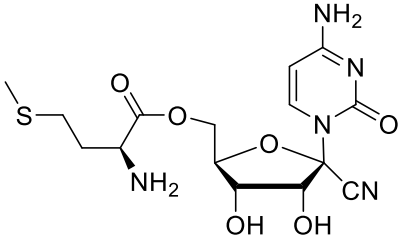
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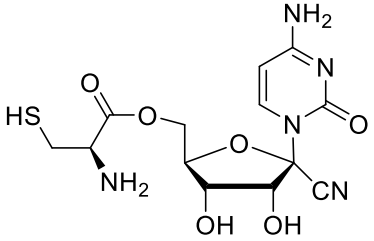
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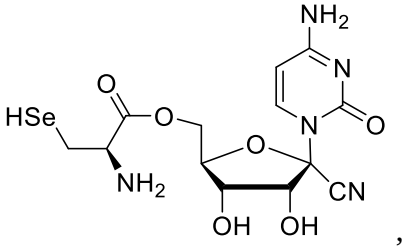
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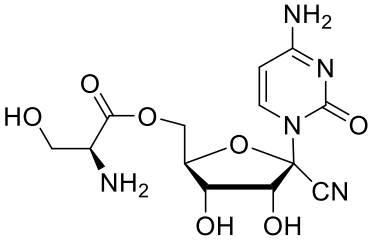
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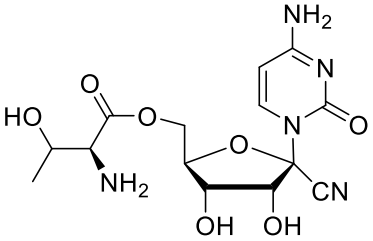
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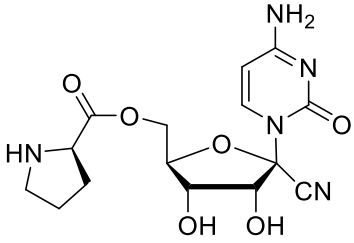
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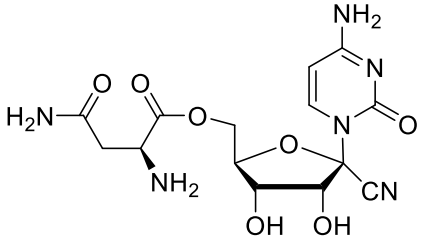
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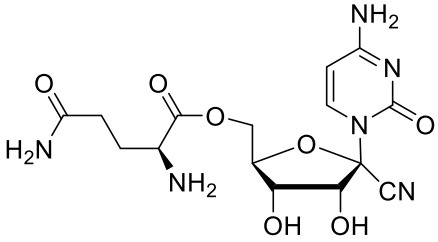
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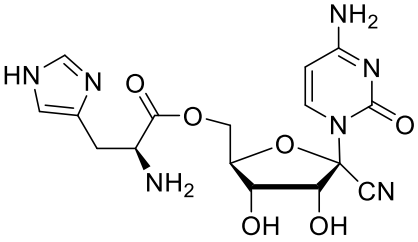
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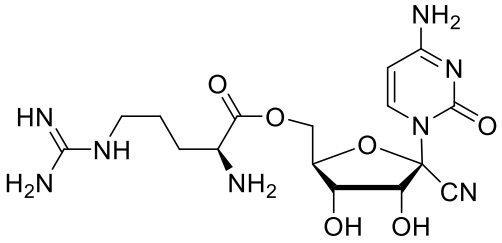
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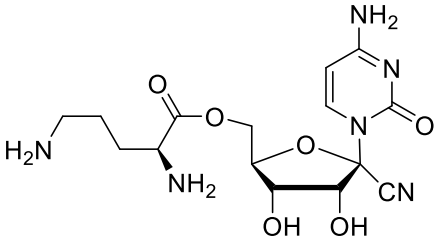
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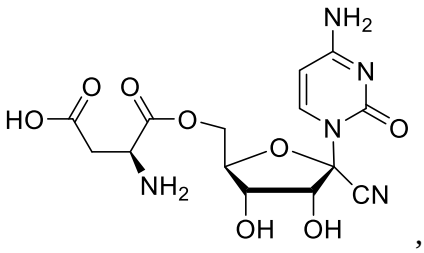
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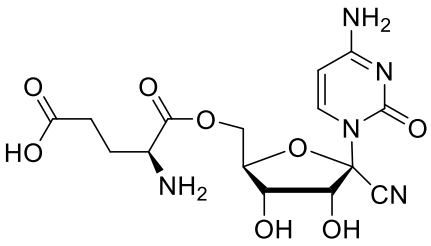
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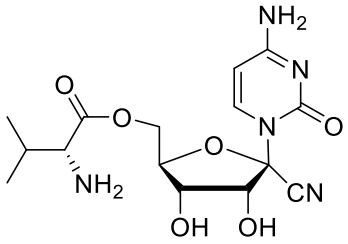
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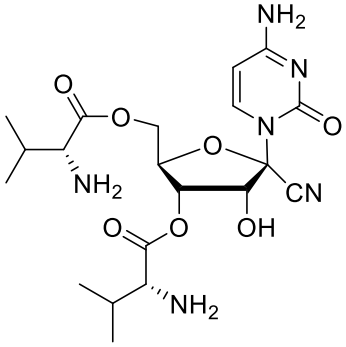
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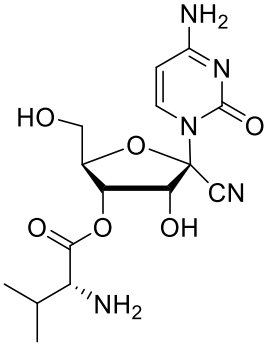
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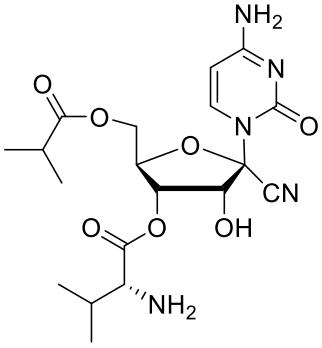
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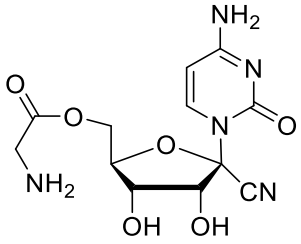
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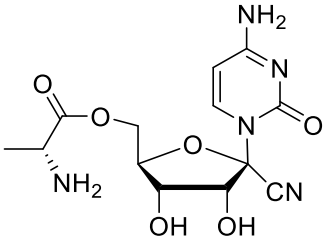
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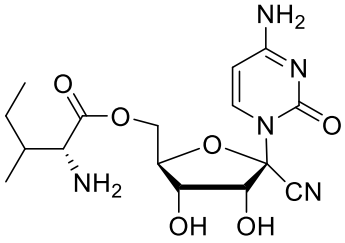
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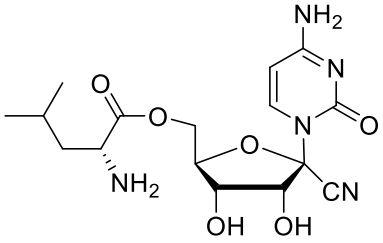
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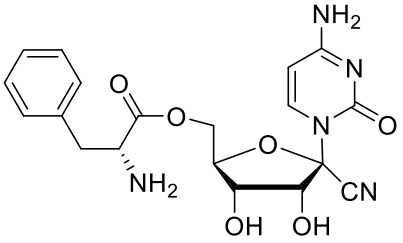
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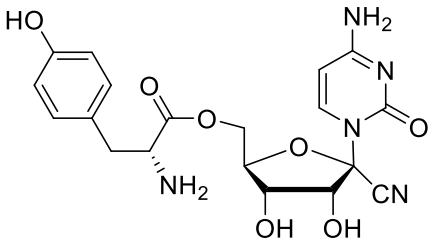
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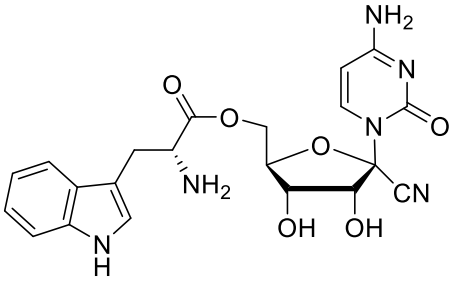
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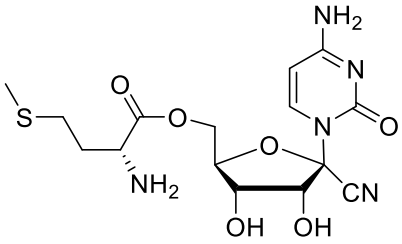
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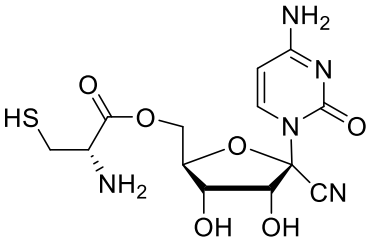
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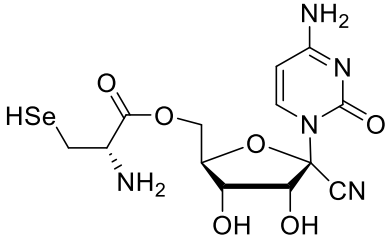
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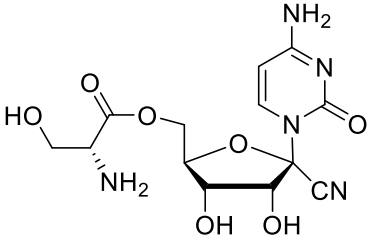
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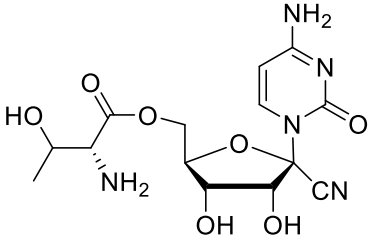
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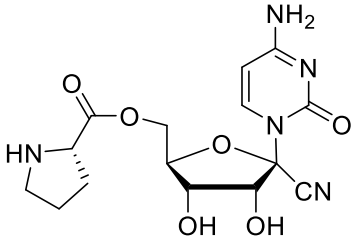
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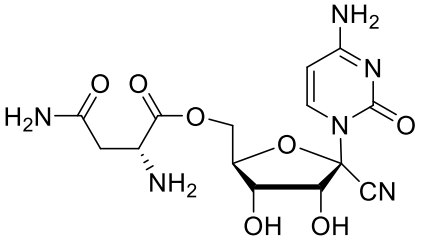
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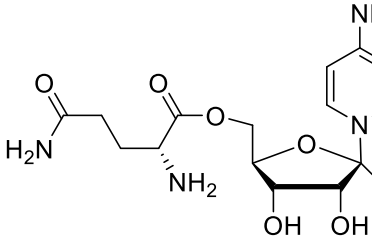
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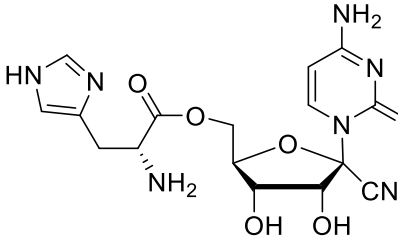
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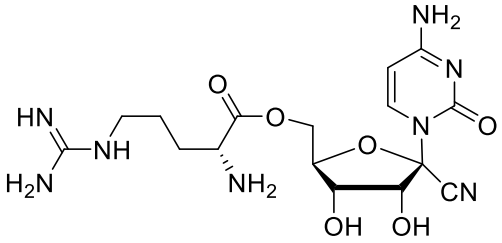
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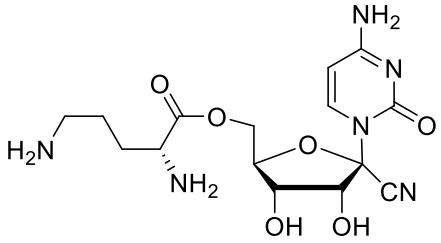
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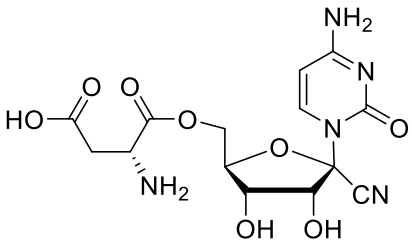
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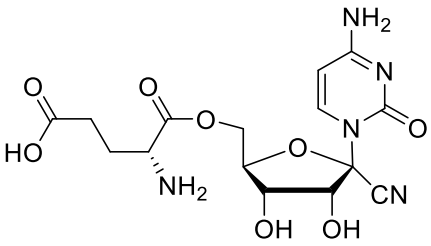
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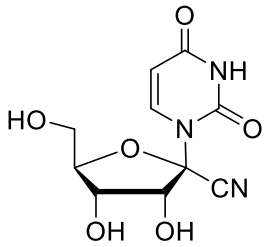
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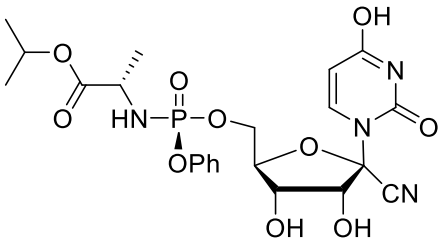
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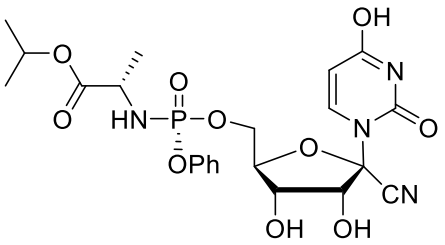
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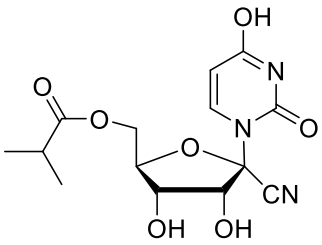
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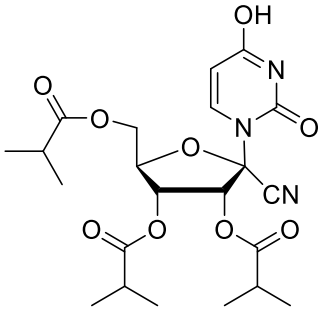
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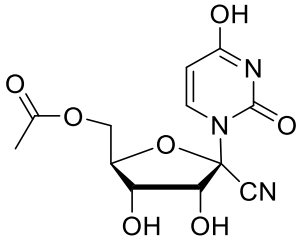
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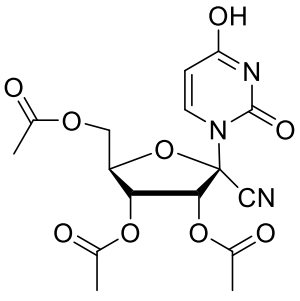
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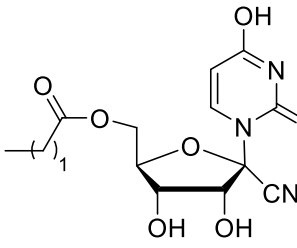
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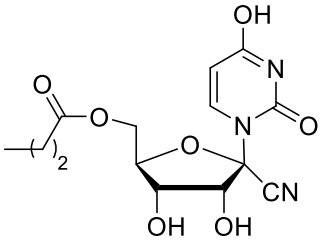
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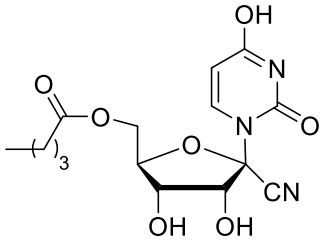
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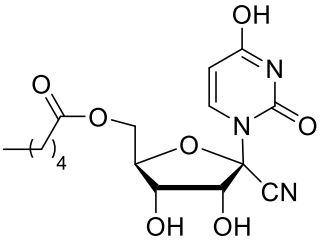
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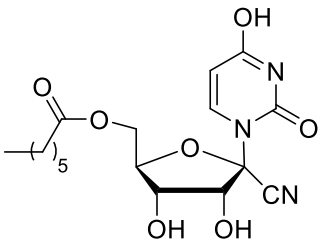
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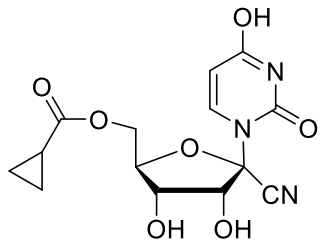
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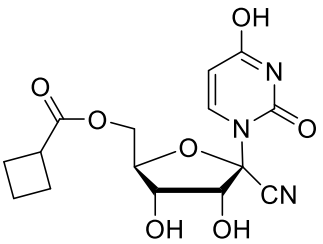
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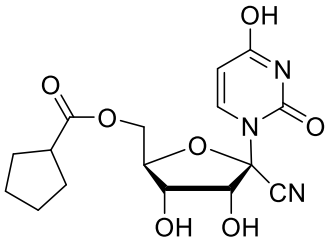
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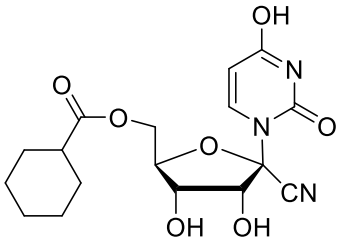
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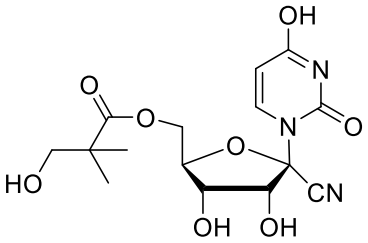
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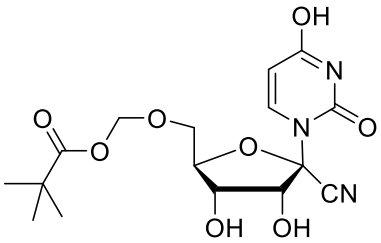
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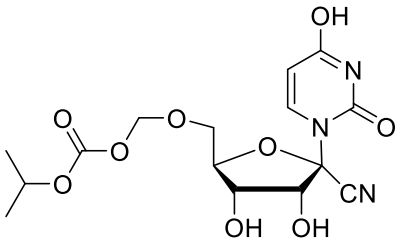
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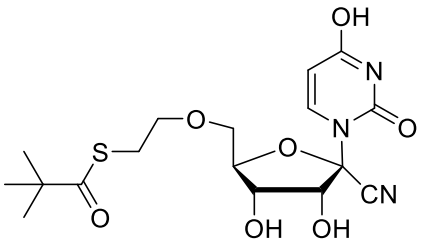
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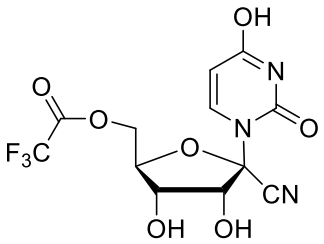
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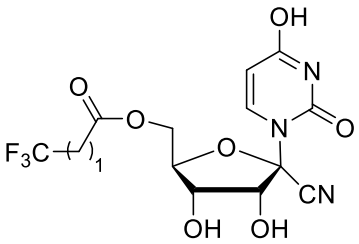
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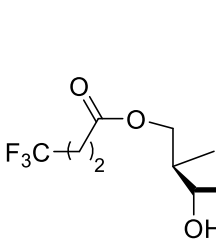
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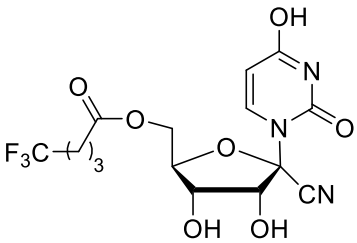
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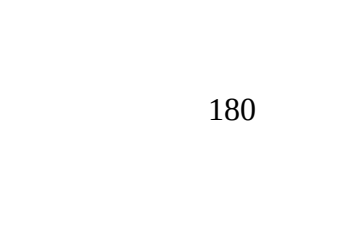
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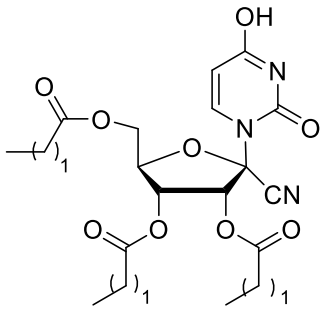
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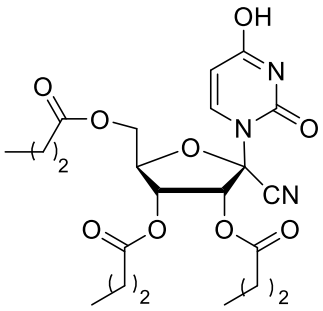
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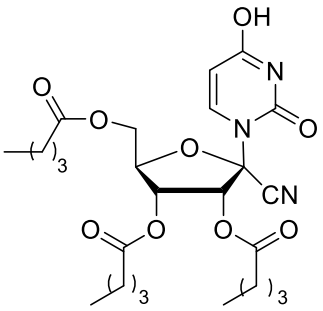
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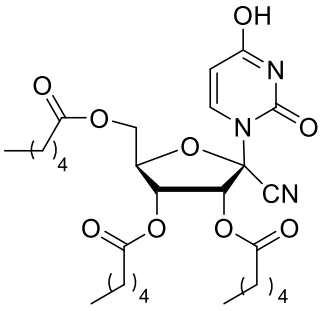
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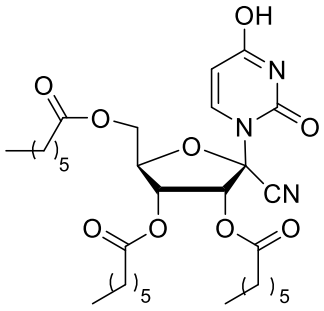
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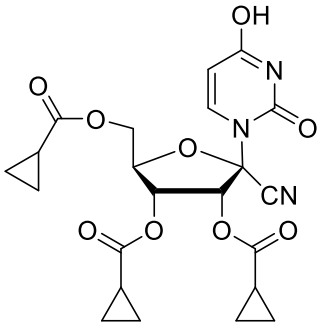
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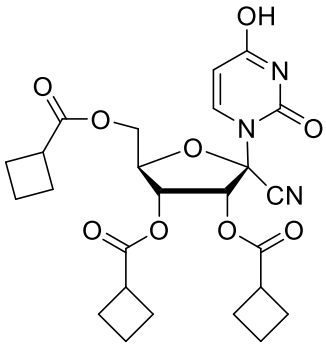
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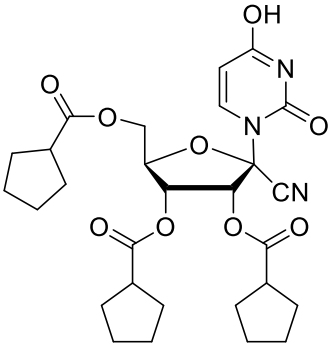
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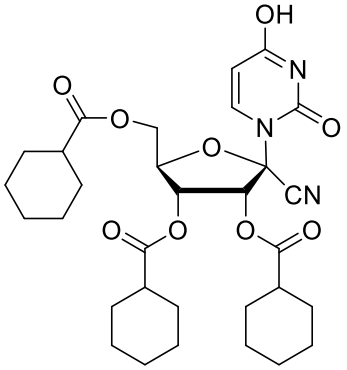
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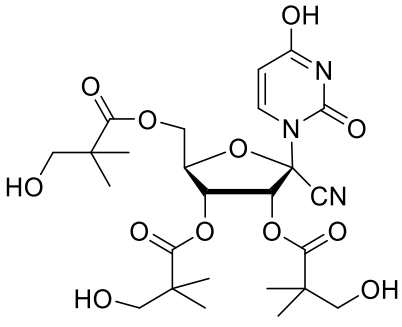
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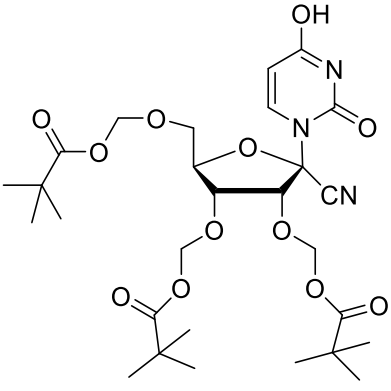
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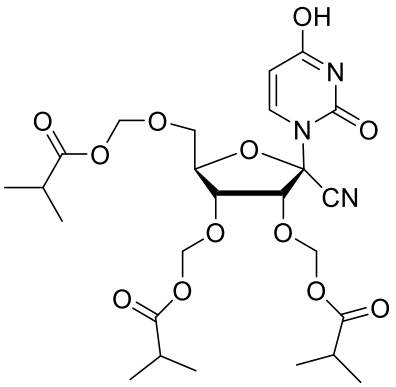
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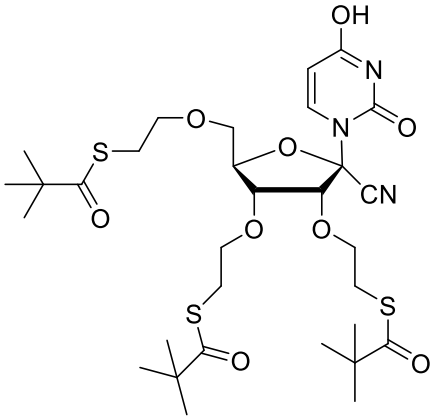
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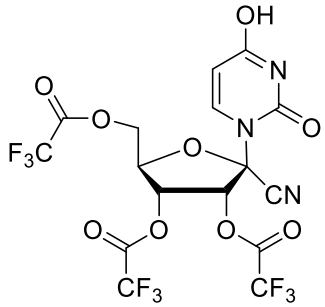
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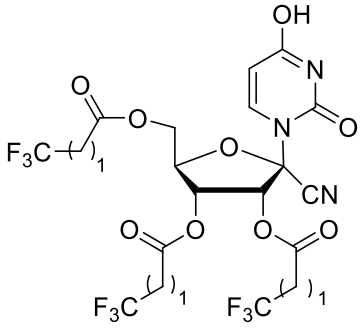
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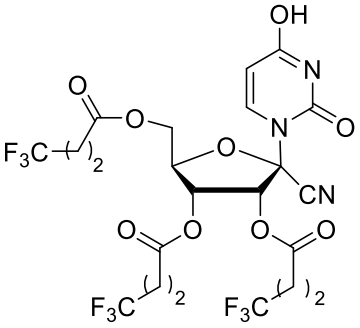
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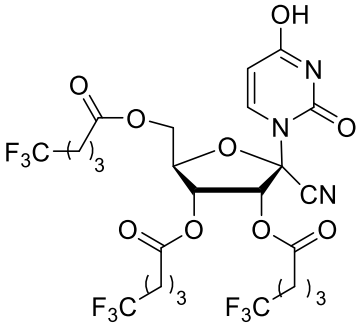
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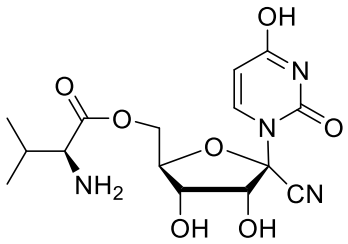
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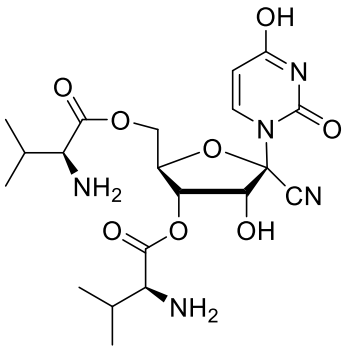
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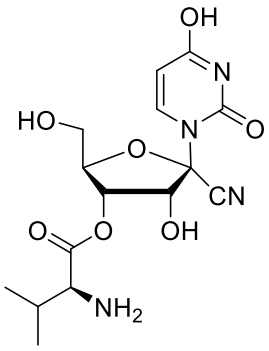
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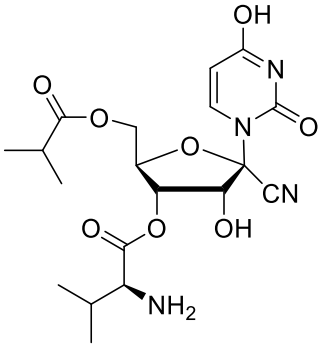
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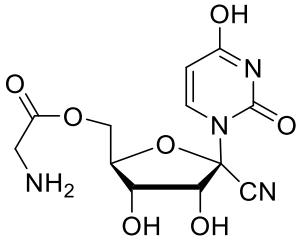
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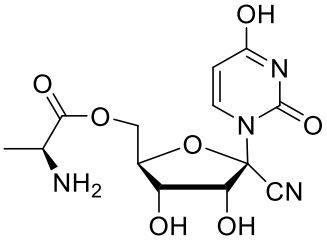
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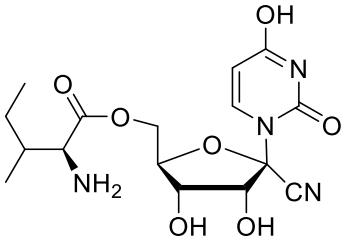
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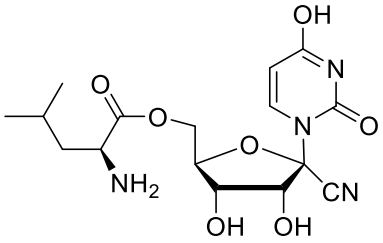
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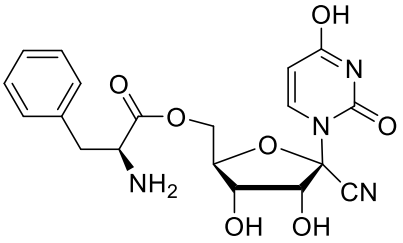
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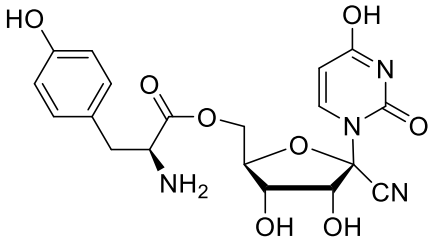
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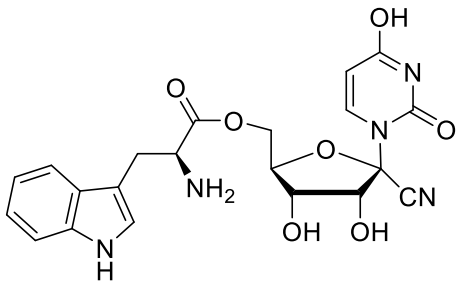
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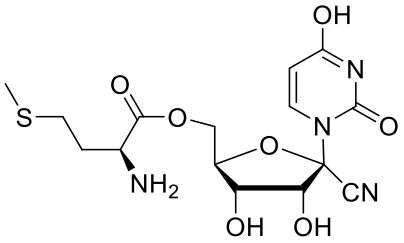
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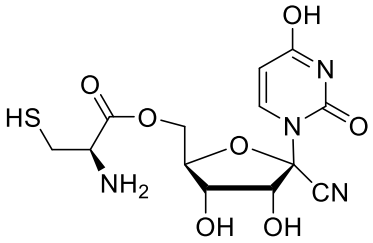
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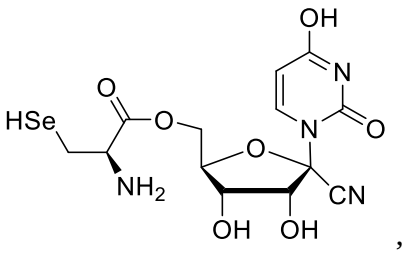
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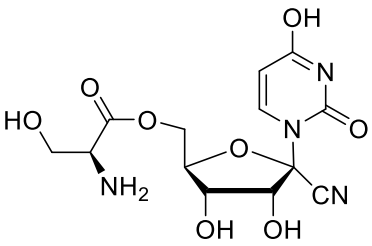
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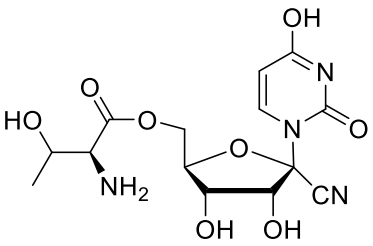
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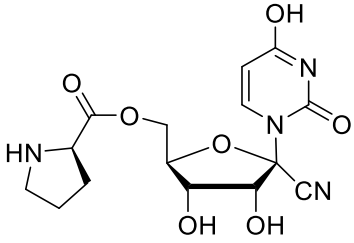
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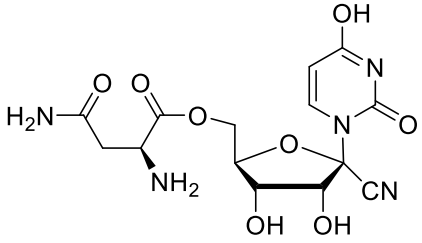
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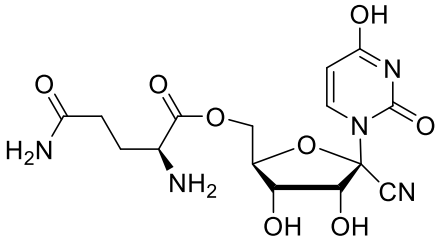
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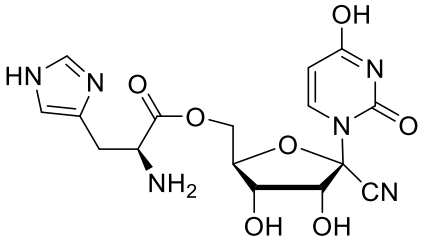
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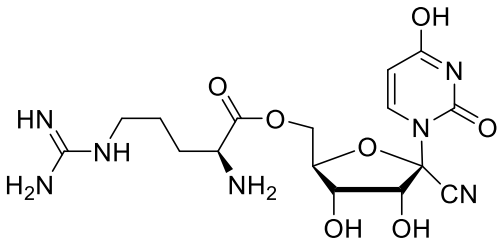
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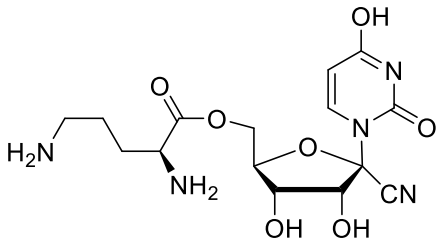
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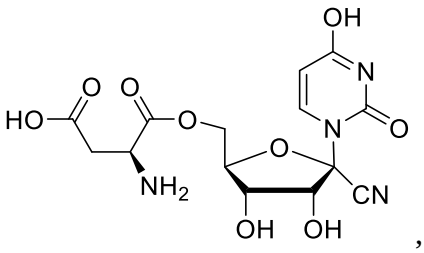
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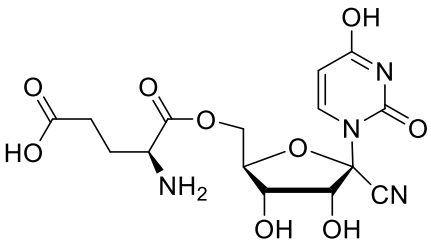
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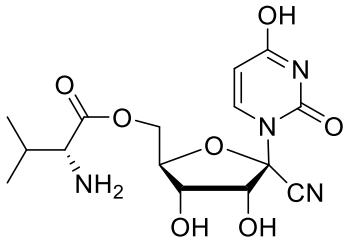
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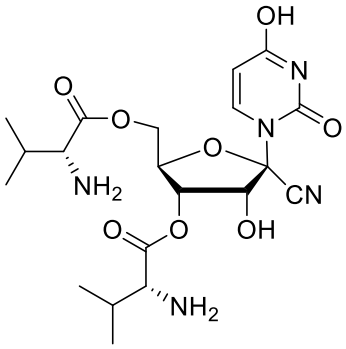
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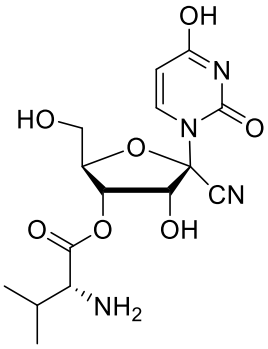
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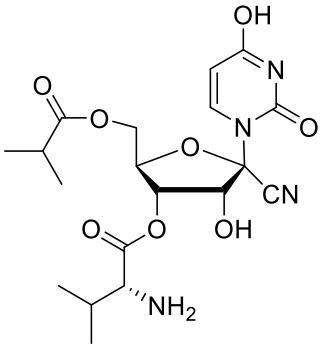
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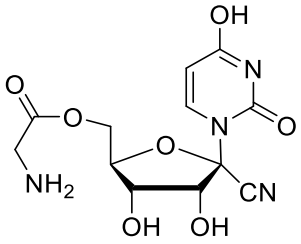
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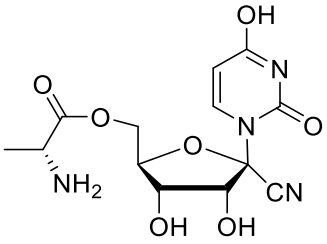
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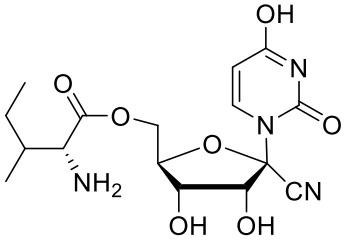
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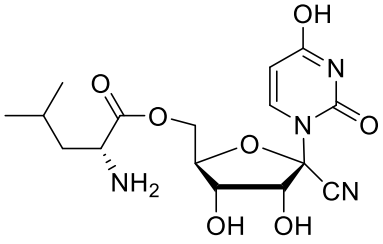
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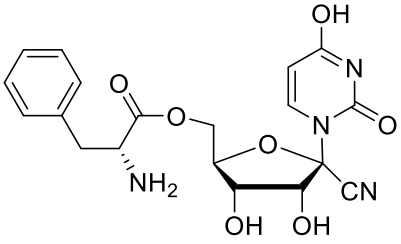
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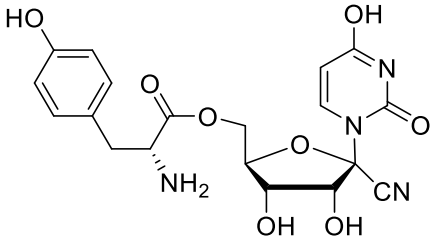
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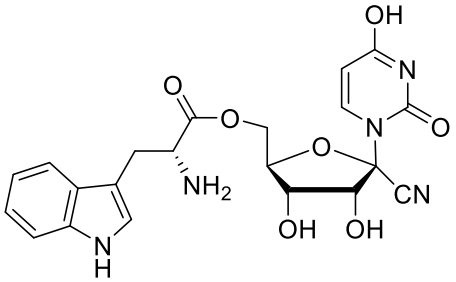
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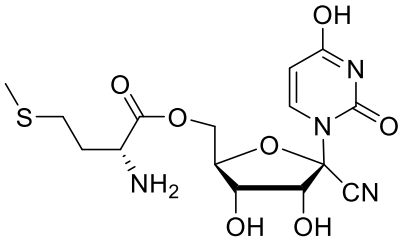
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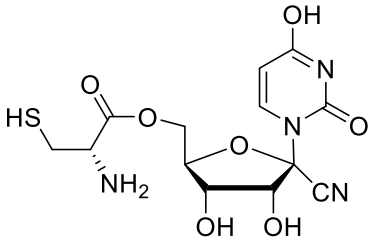
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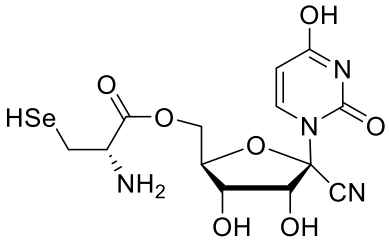
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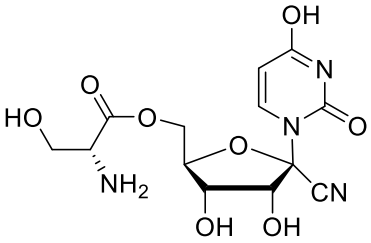
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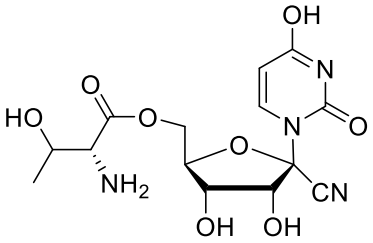
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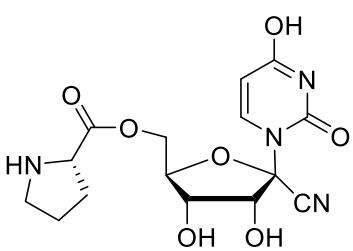
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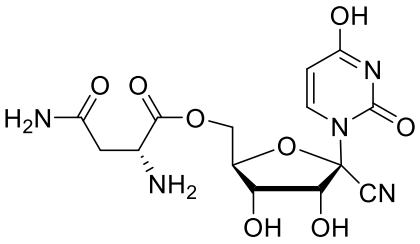
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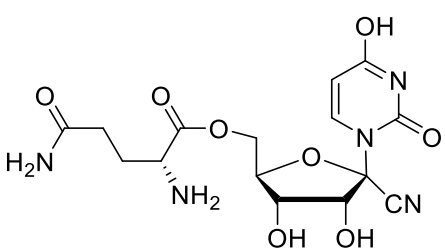
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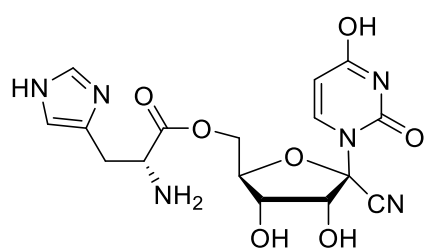
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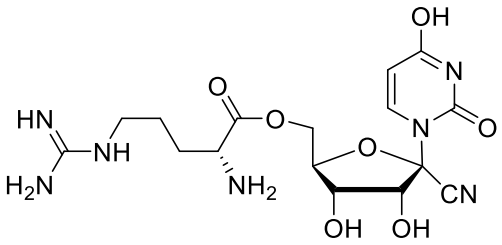
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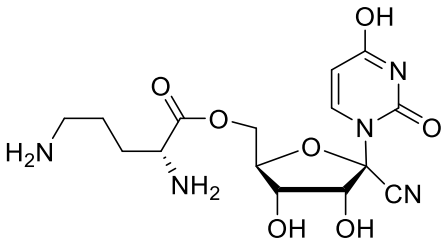
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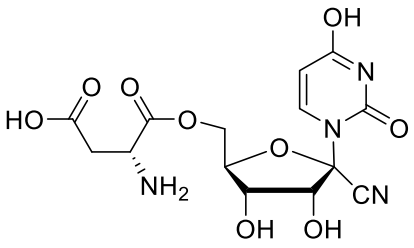
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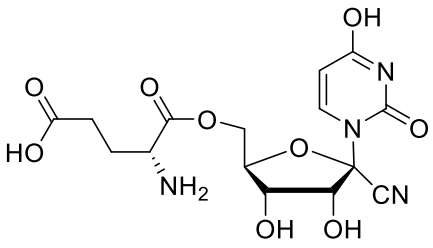
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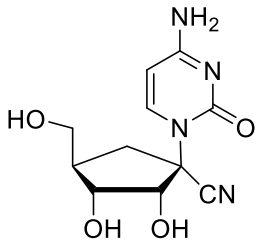
or a pharmaceutically acceptable salt or prodrug thereof;

or wherein the compound has one of the following formulas: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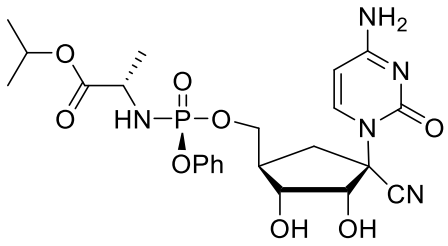
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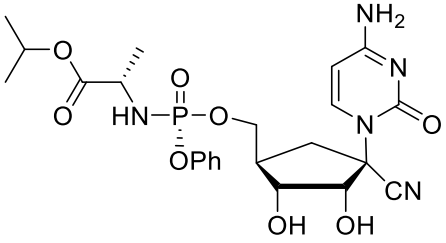
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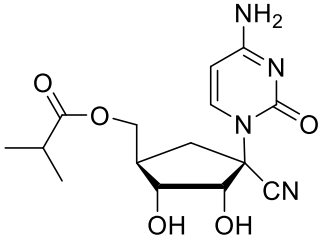
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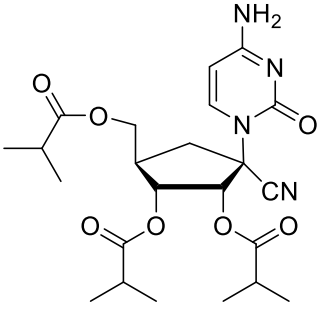
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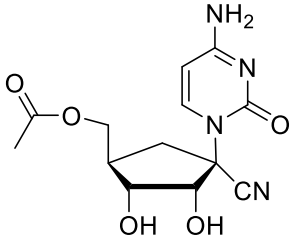
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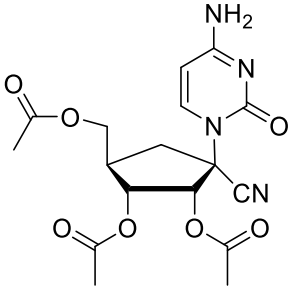
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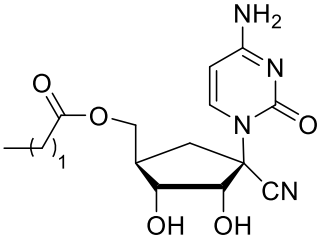
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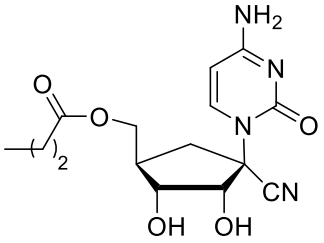
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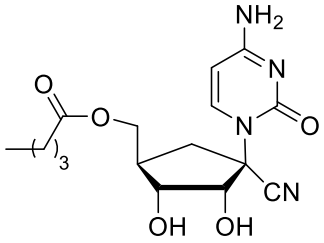
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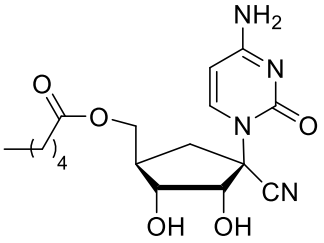
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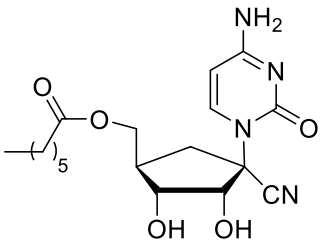
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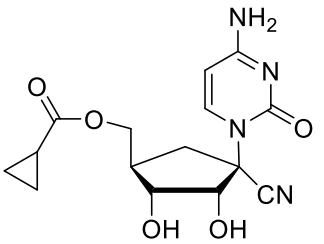
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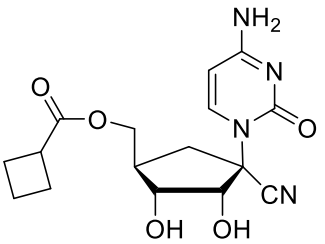
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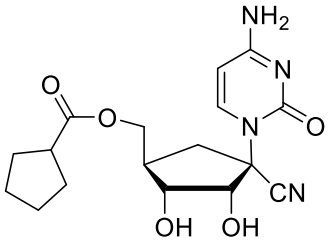
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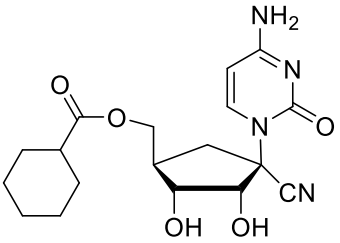
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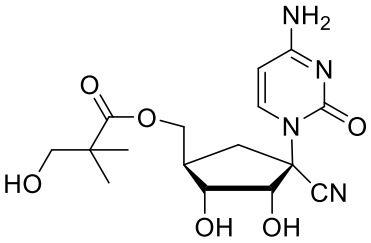
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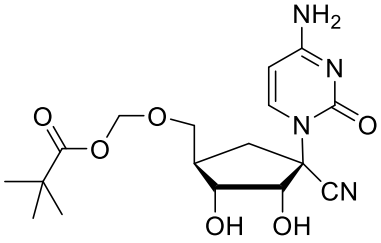
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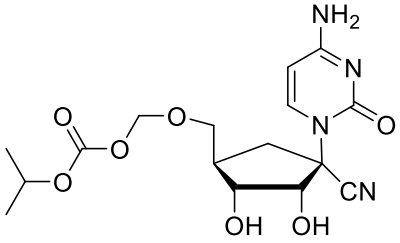
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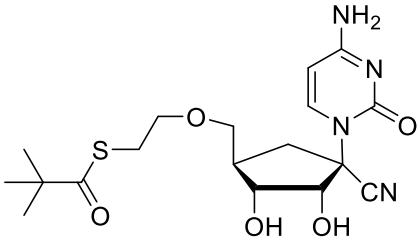
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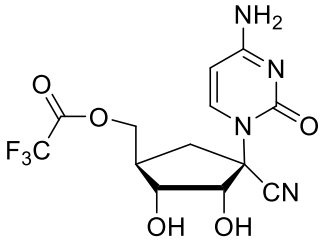
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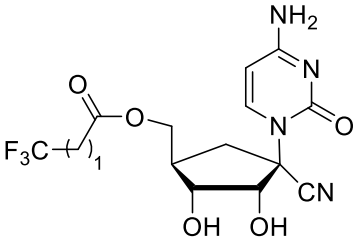
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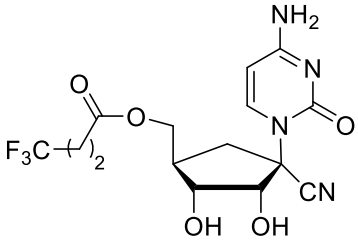
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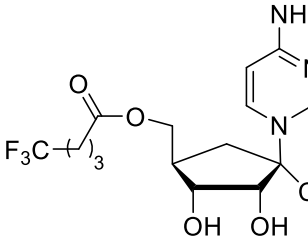
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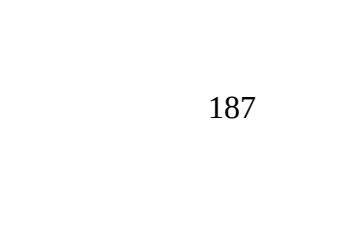
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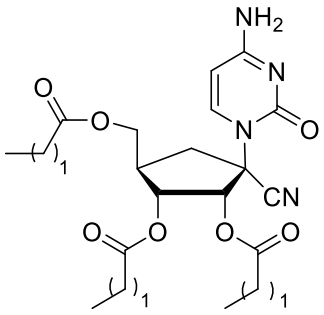
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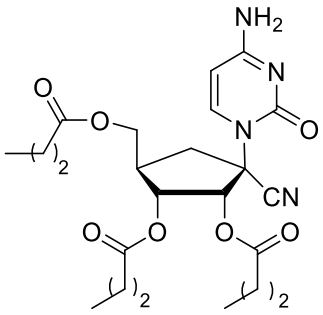
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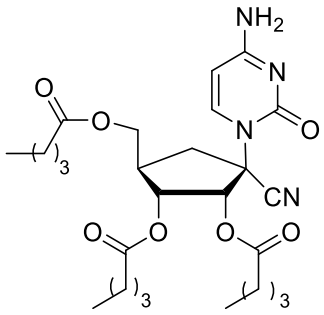
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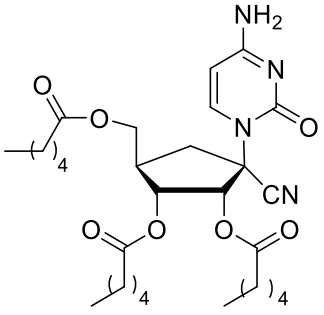
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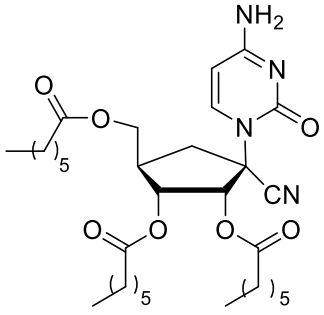
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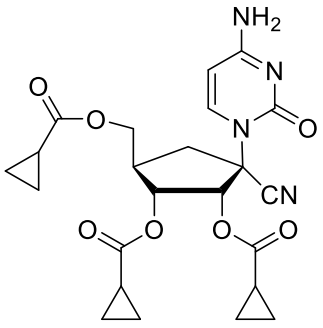
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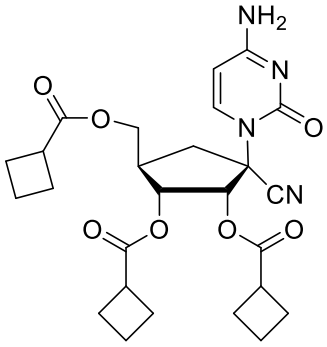
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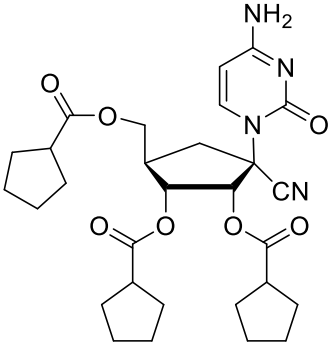
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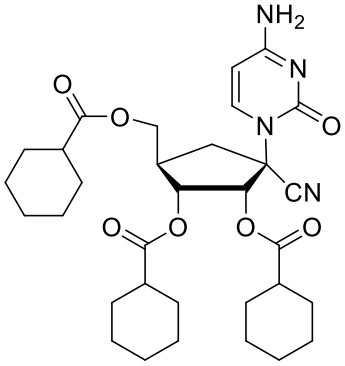
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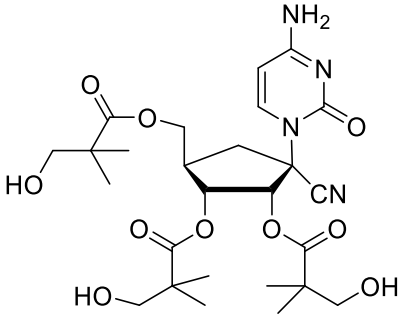
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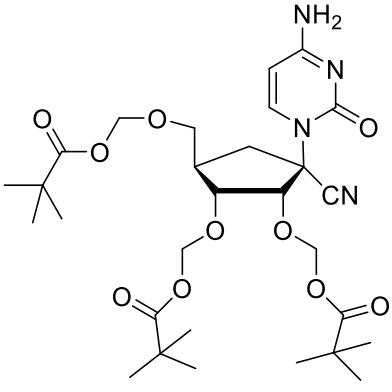
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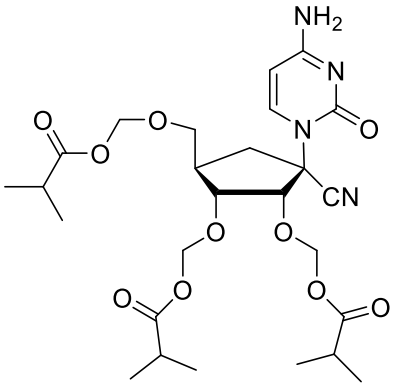
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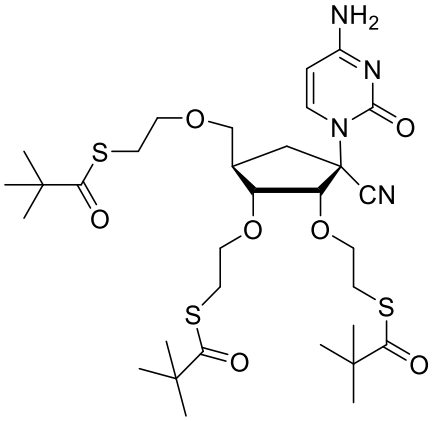
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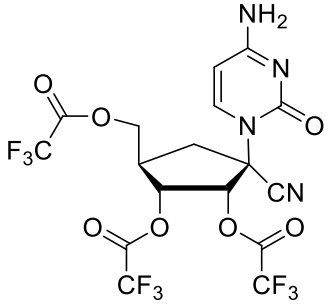
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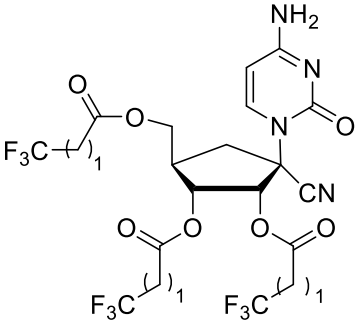
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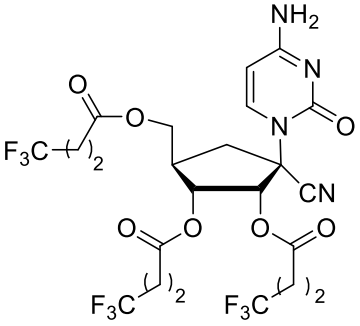
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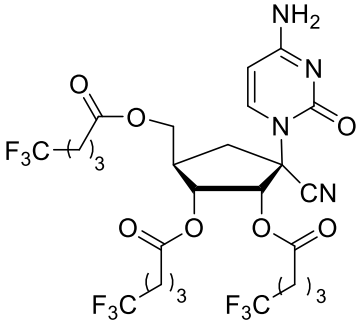
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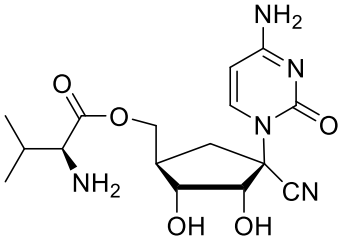
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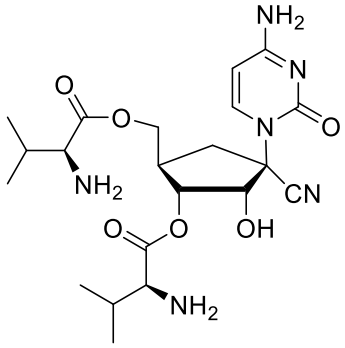
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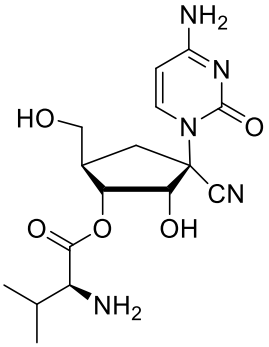
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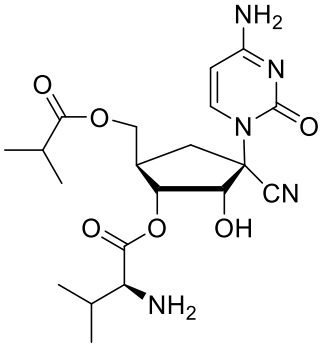
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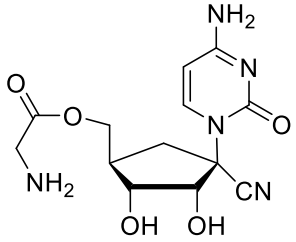
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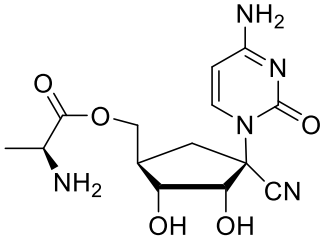
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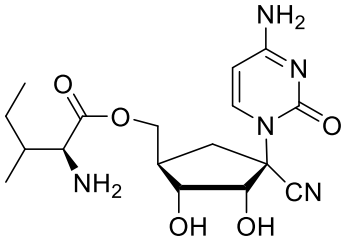
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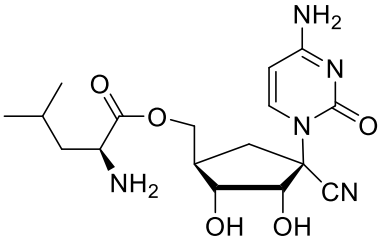
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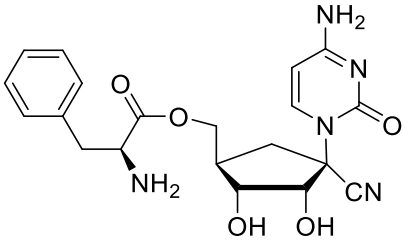
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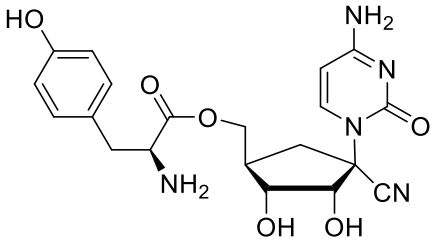
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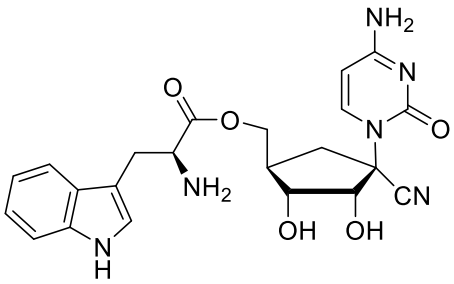
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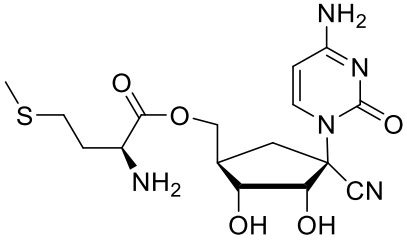
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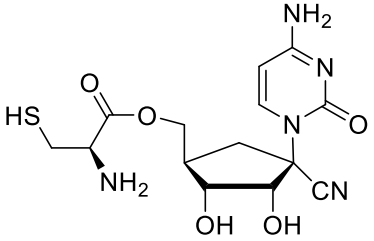
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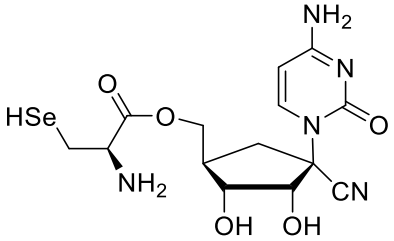
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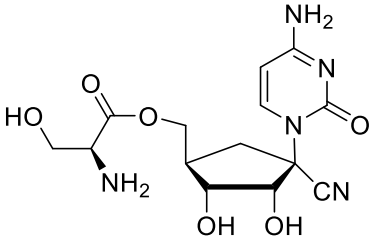
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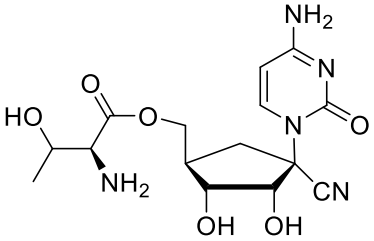
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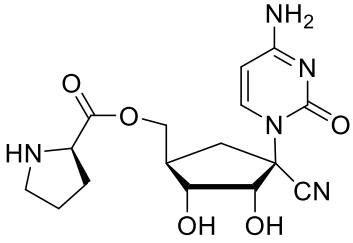
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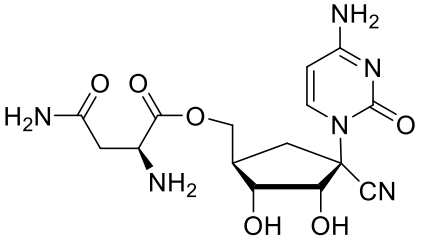
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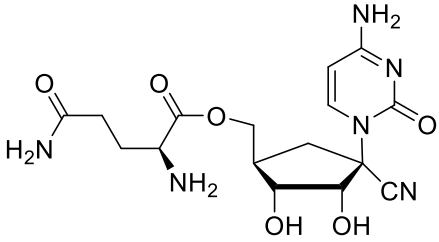
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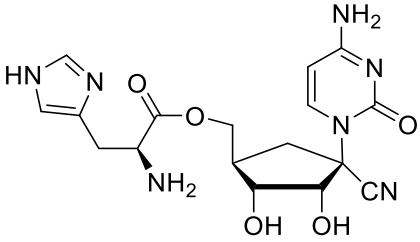
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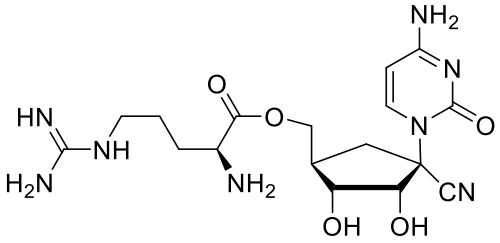
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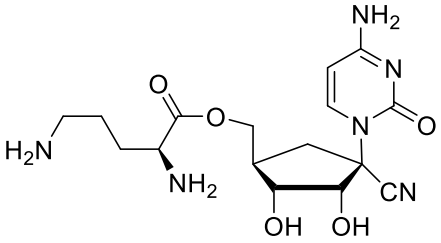
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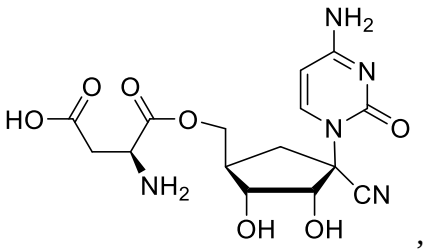
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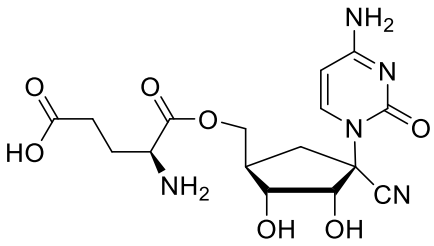
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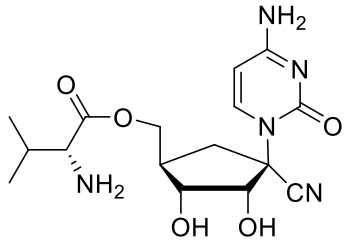
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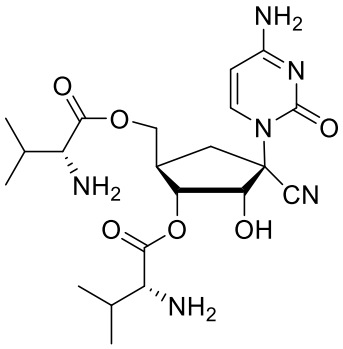
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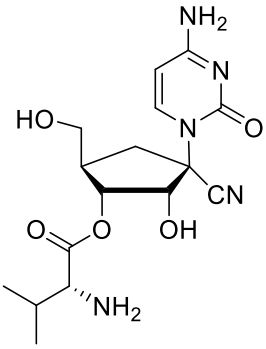
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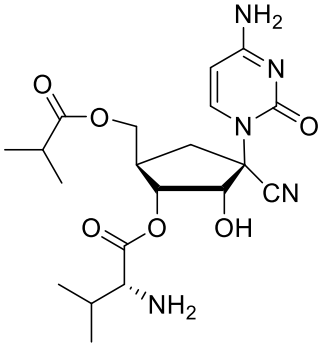
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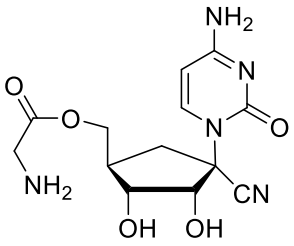
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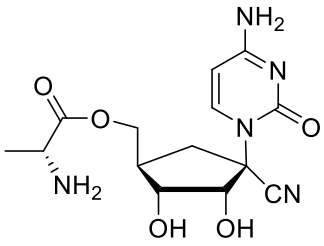
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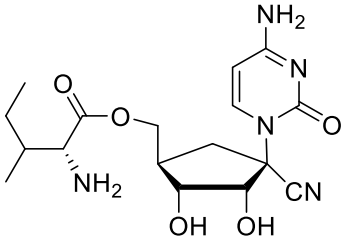
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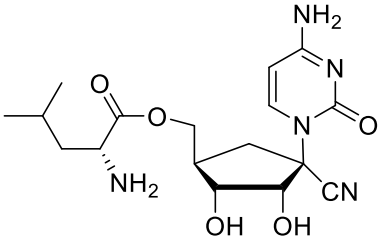
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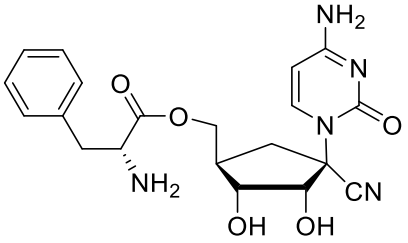
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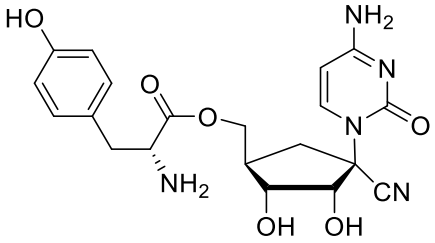
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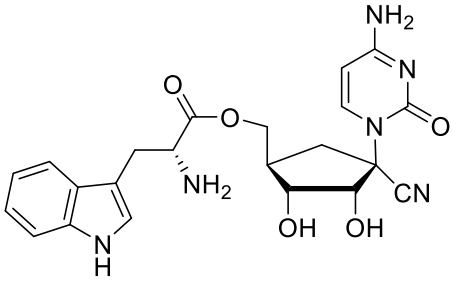
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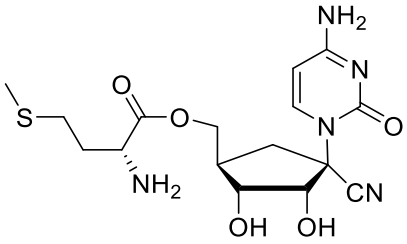
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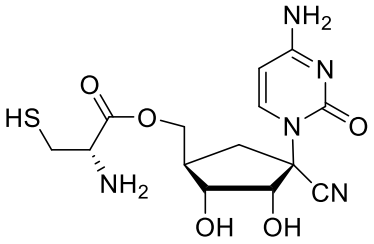
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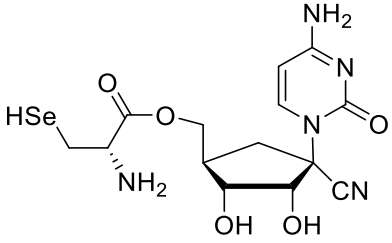
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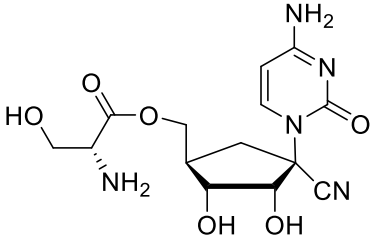
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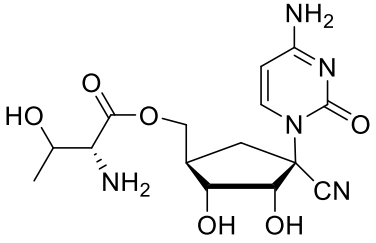
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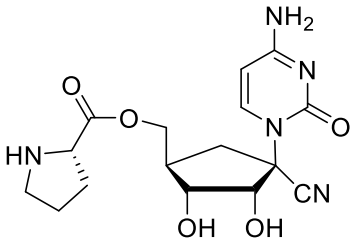
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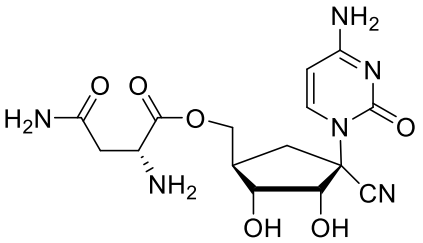
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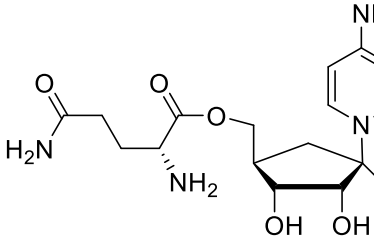
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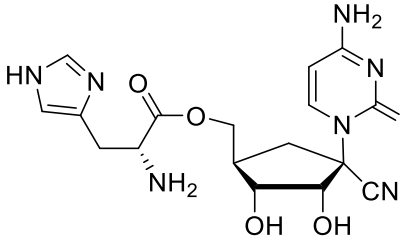
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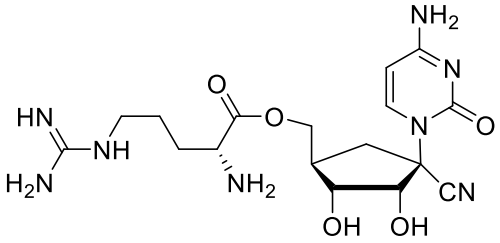
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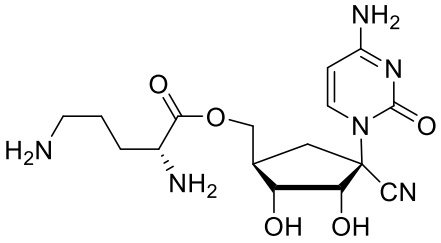
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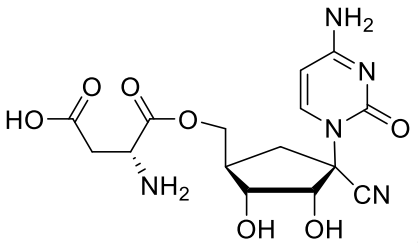
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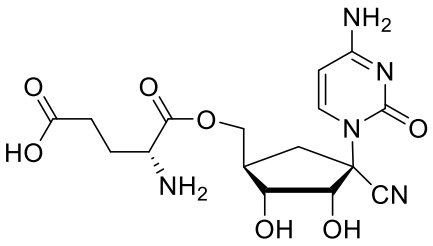
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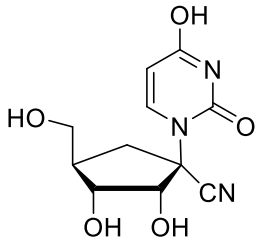
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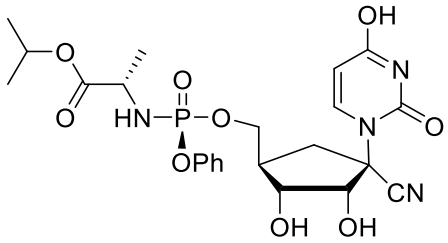
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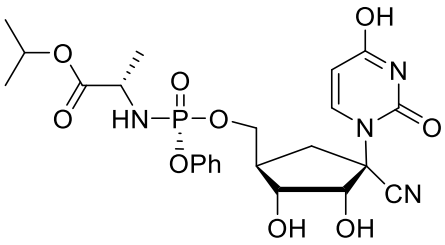
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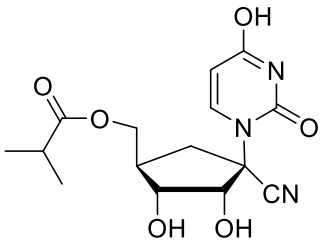
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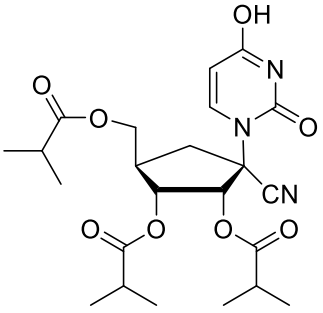
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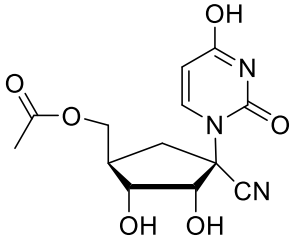
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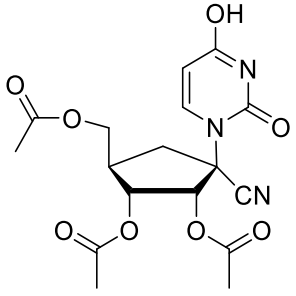
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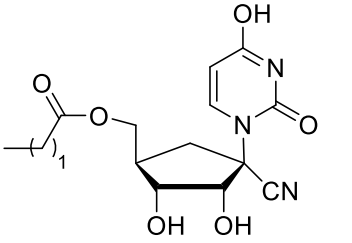
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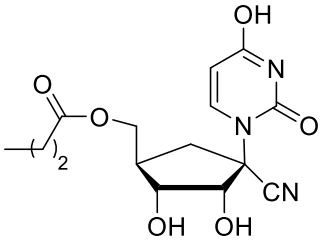
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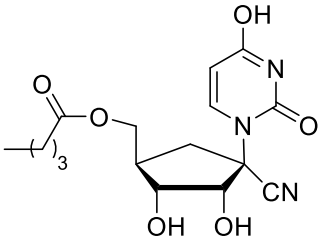
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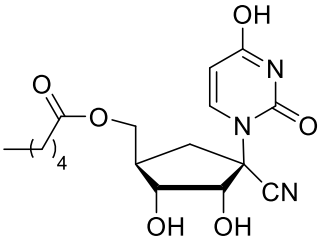
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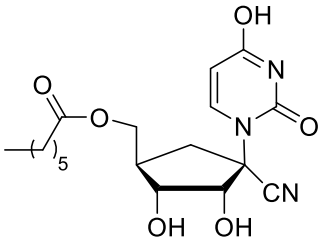
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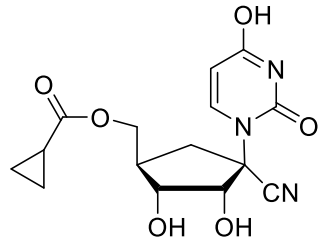
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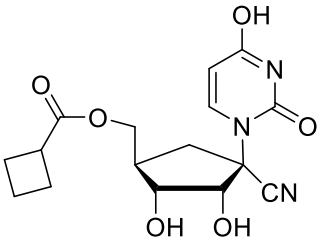
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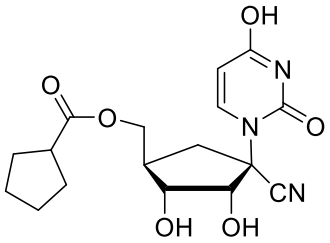
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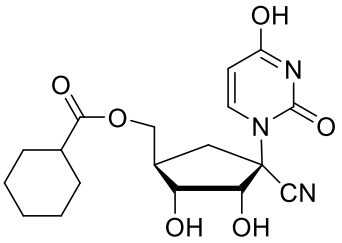
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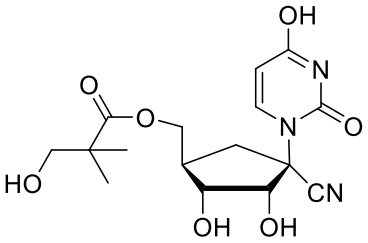
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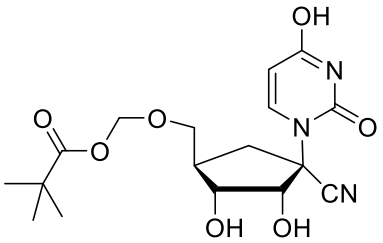
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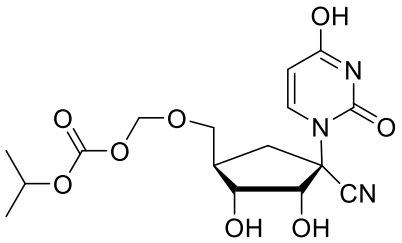
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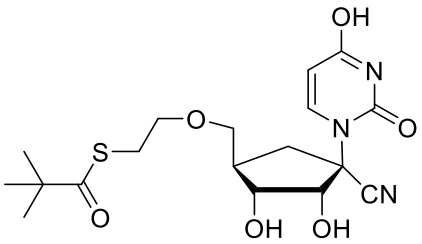
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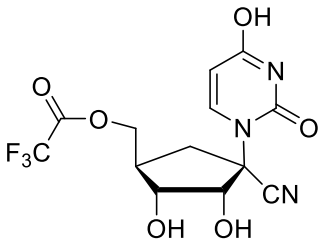
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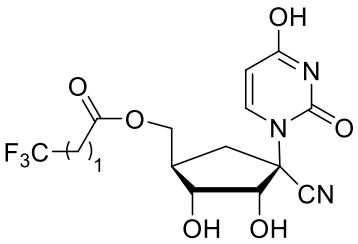
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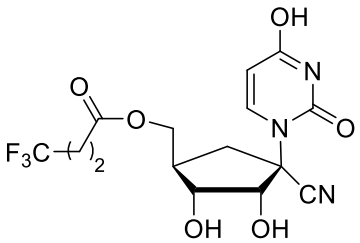
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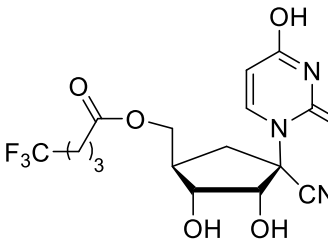
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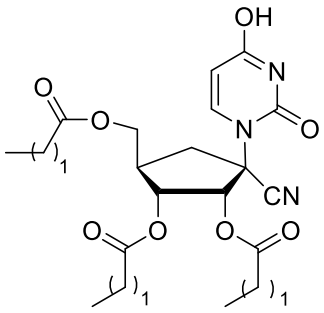
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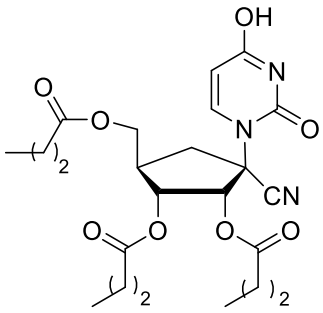
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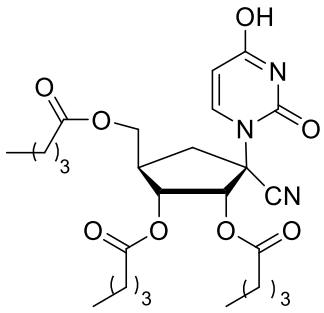
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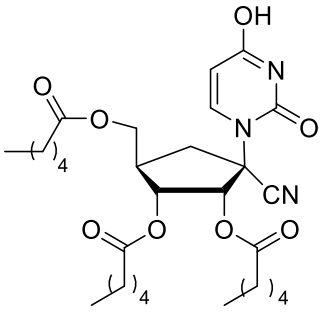
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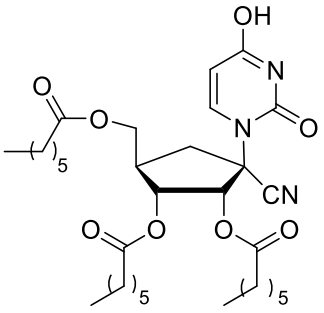
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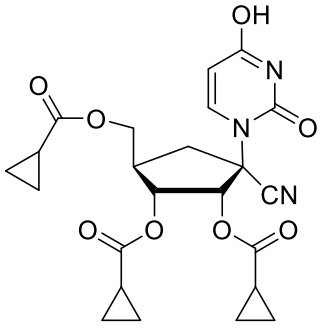
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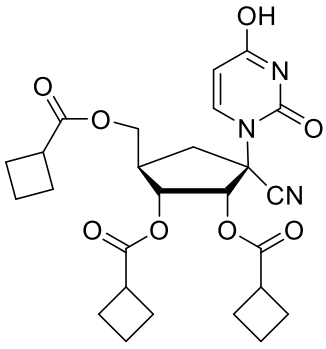
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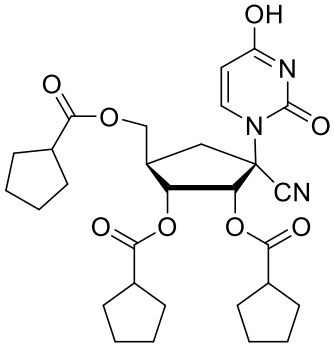
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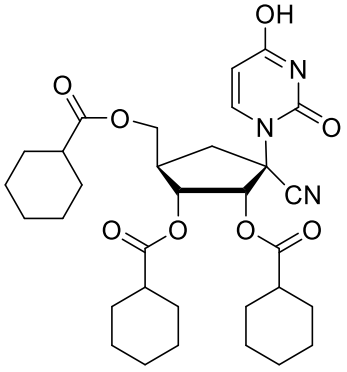
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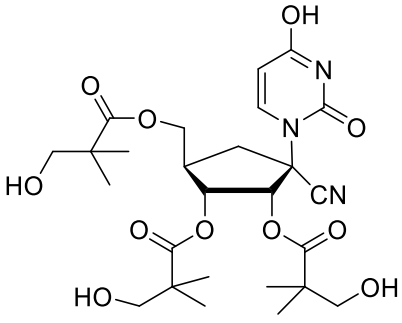
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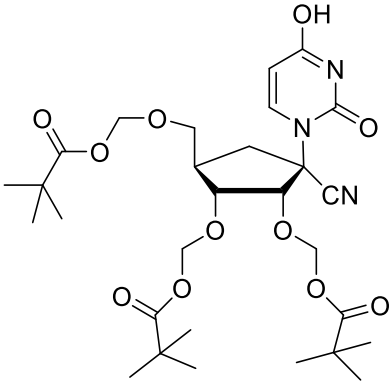
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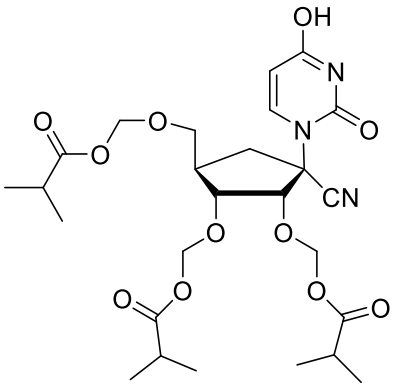
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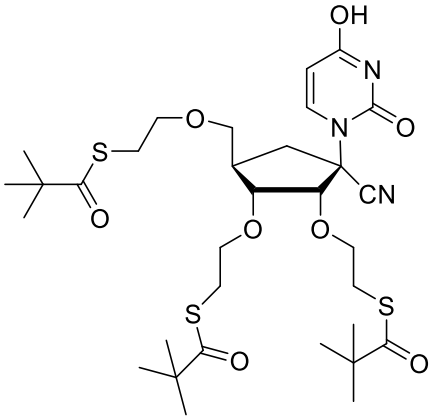
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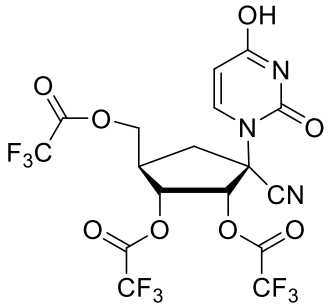
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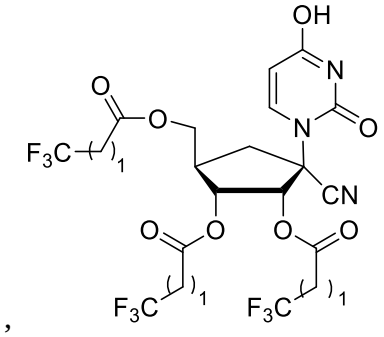
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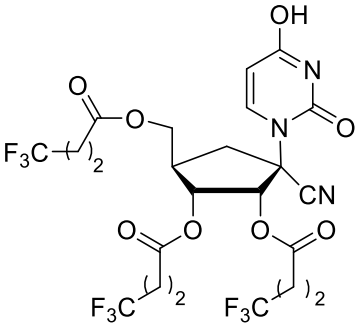
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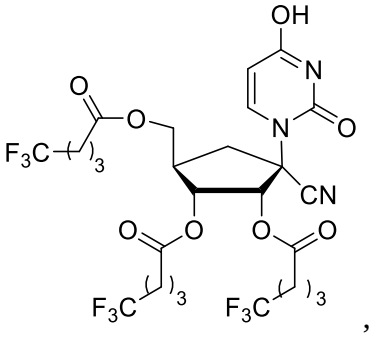
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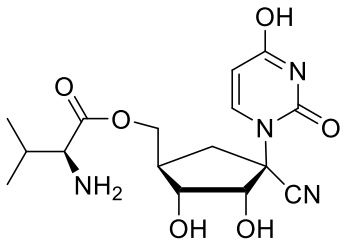
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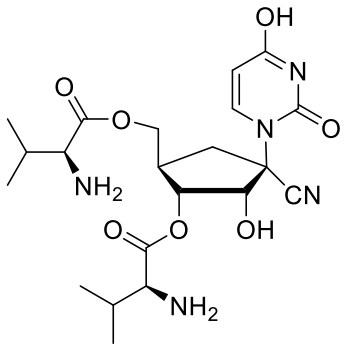
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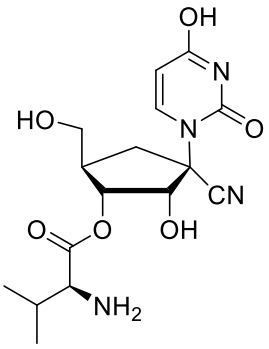
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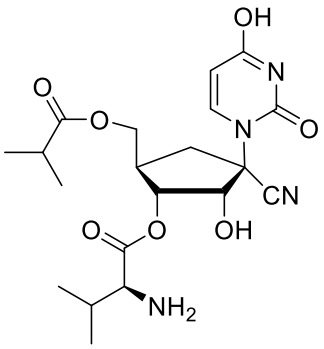
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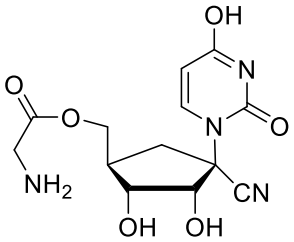
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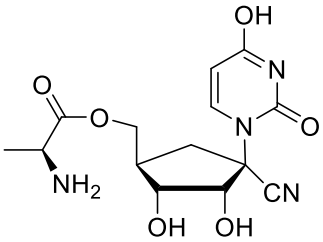
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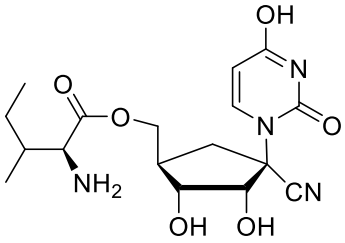
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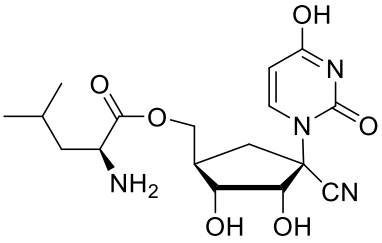
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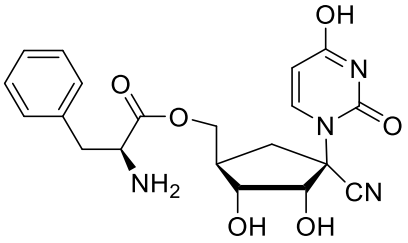
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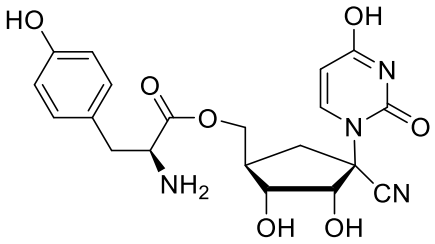
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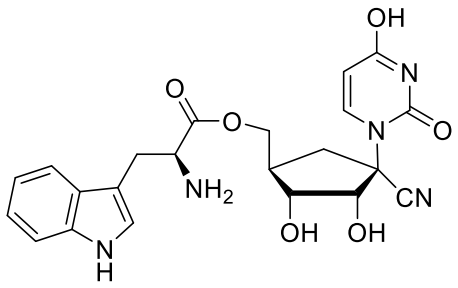
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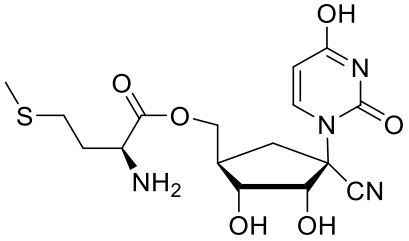
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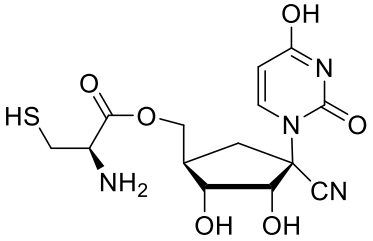
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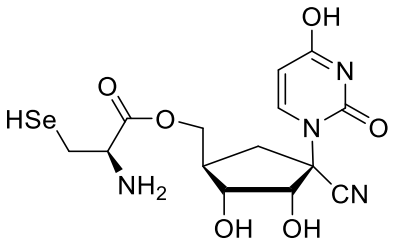
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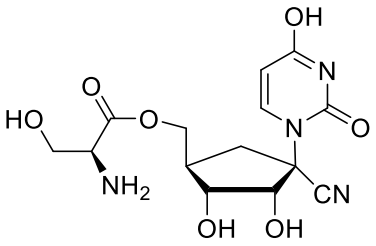
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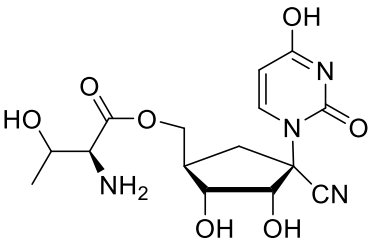
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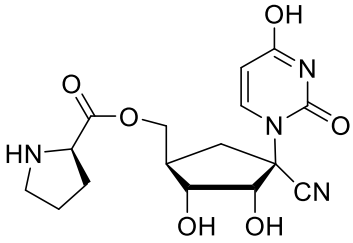
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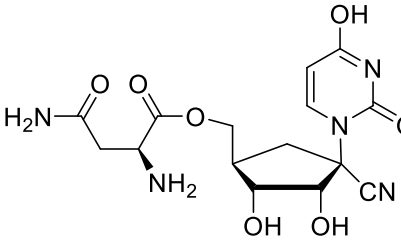
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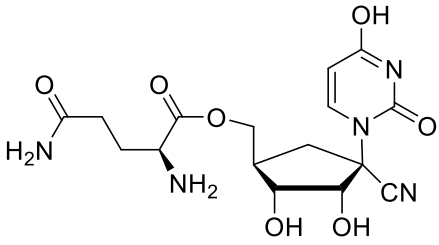
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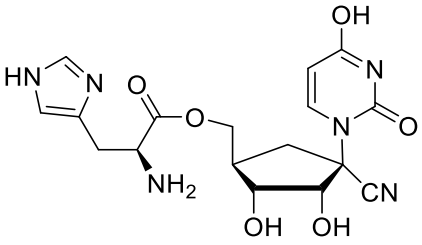
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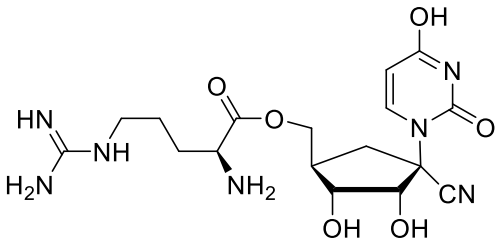
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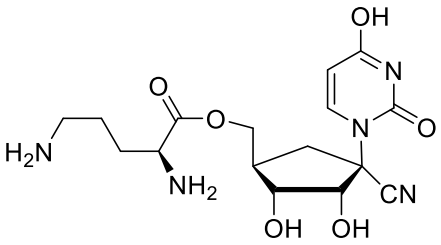
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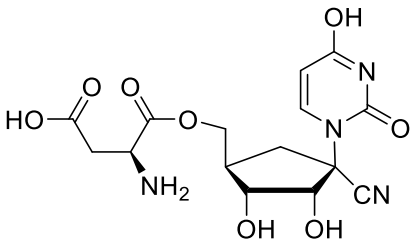
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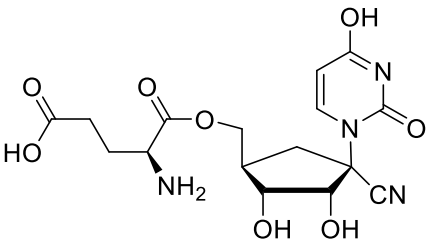
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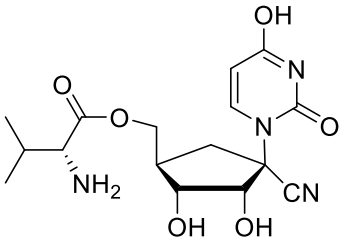
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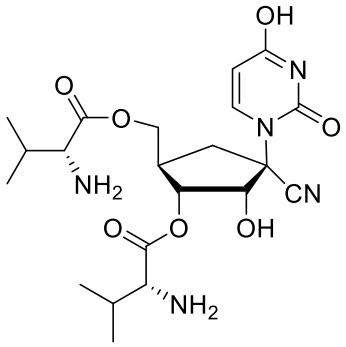
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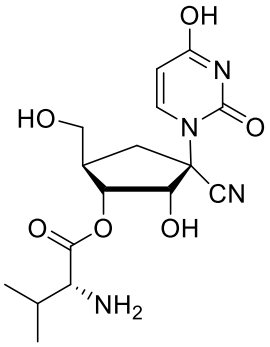
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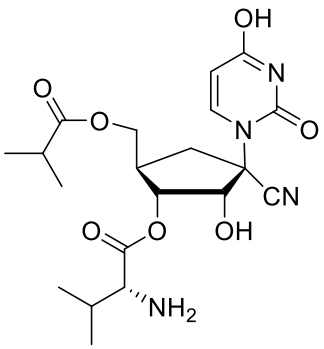
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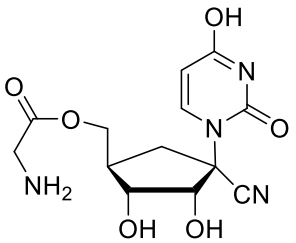
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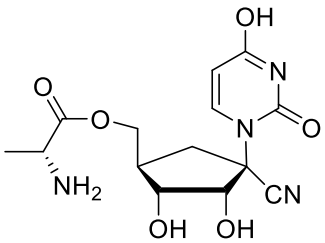
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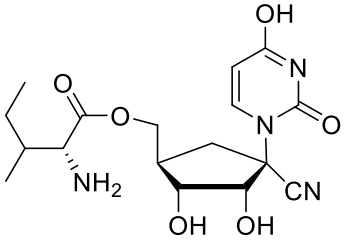
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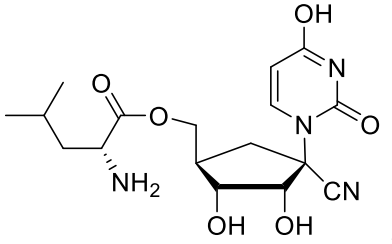
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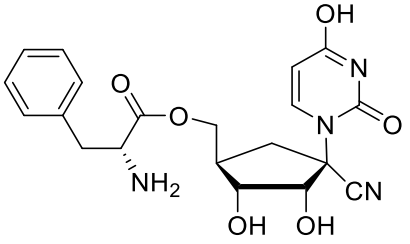
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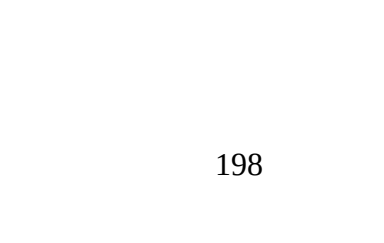
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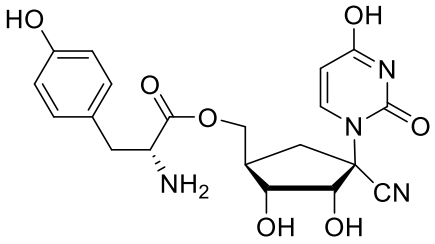
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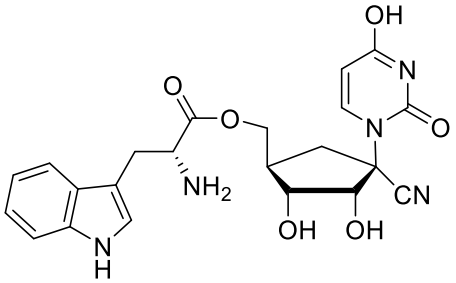
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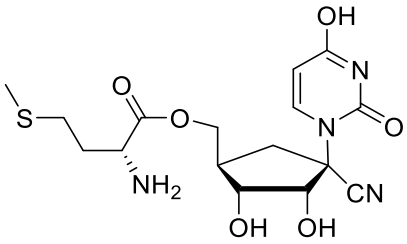
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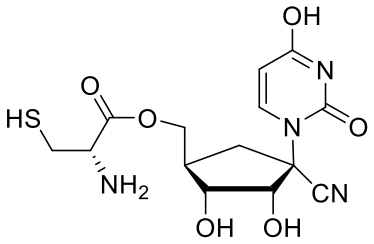
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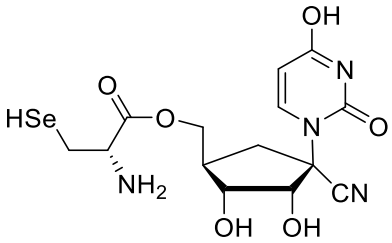
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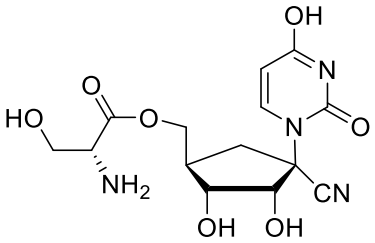
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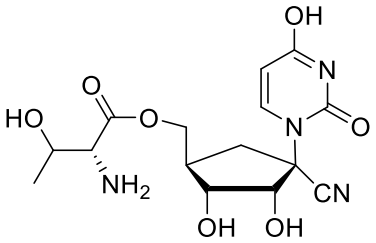
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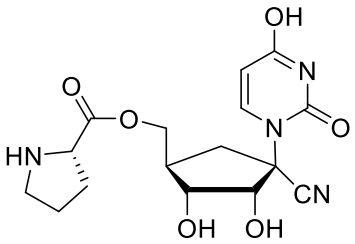
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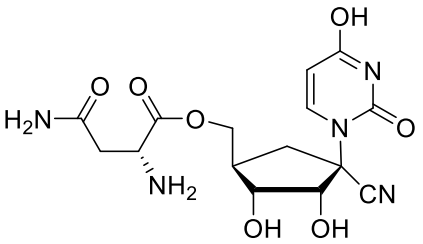
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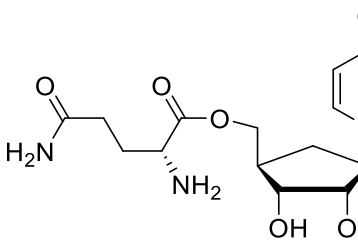
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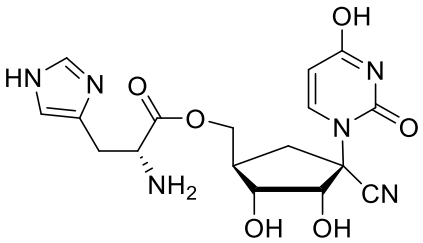
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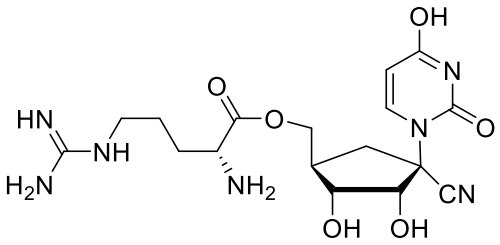
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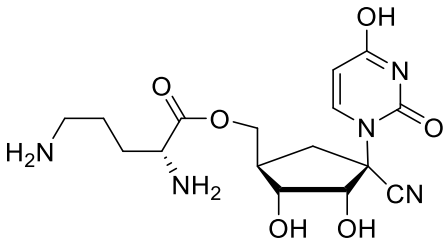
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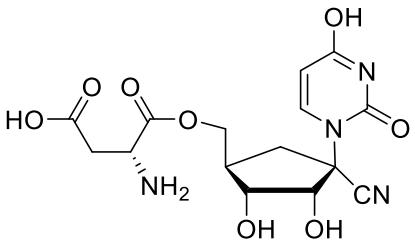
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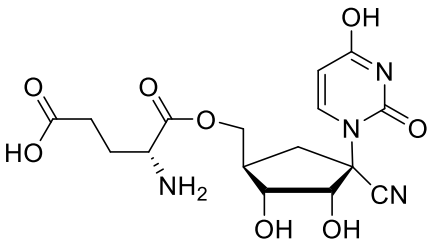
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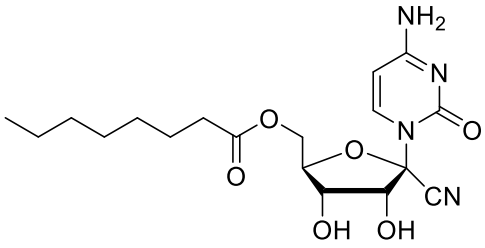
or a pharmaceutically acceptable salt or prodrug thereof; or wherein the compound is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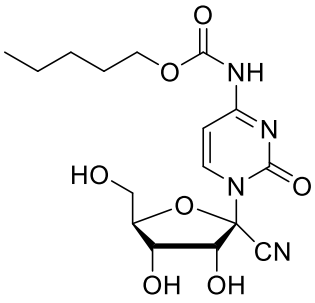
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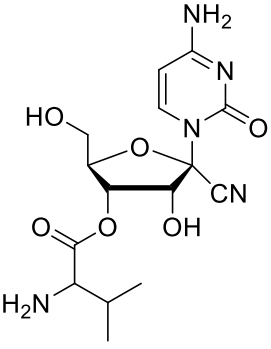
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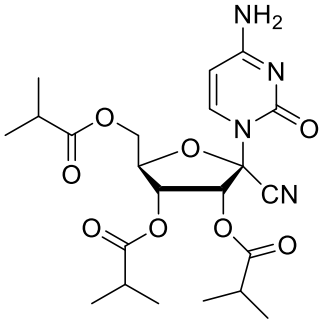
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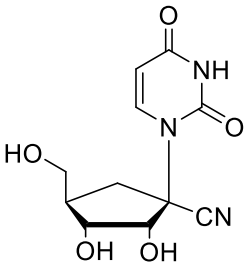
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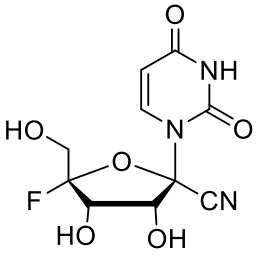
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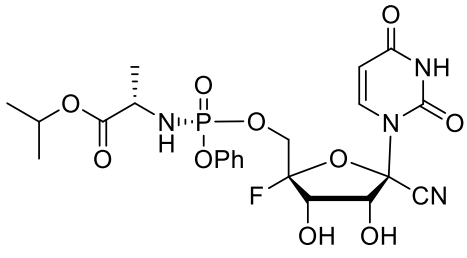
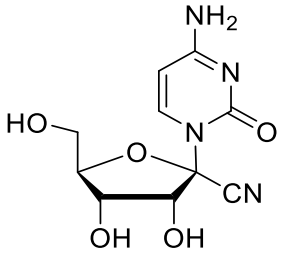
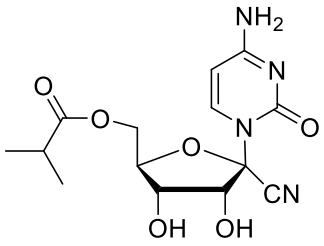
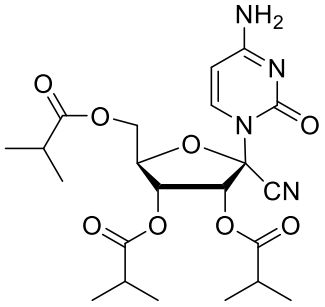
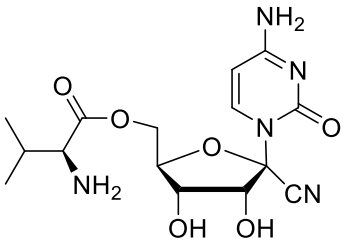
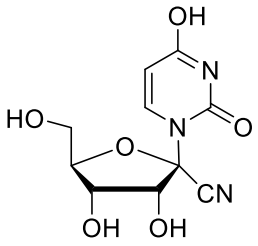
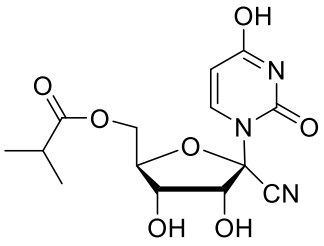
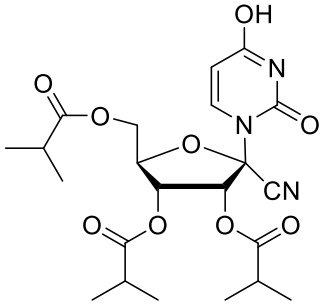
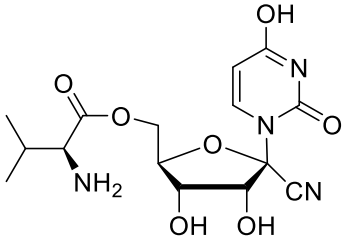

, or a pharmaceutically-acceptable salt or prodrug thereof.

4. The use of Claim 3, wherein the compound is  ,

 ,  ,  ,

 ,  ,  , or

 , or a pharmaceutically-acceptable salt or prodrug thereof.

5. The use of any of Claims 1-4, wherein the compounds can be present in the β-D or β-L configuration.

6. The use of any of Claims 1-5, wherein the infection is a Coronaviridae infection,

wherein the Coronavirus is preferably human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2, more preferably SARS-CoV-2.

7. The use of any of Claims 1-5, wherein the medicament further comprises:

i) 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;

ii) remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814 or a pharmaceutically-acceptable salt or prodrug thereof;

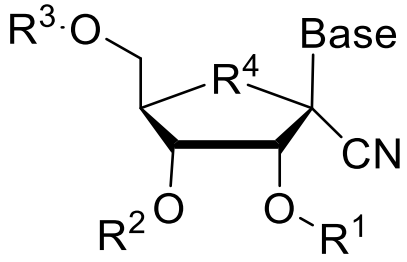
iii) a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof;

iv) an anticoagulant or a platelet aggregation inhibitor; or

v) an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

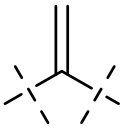
8. The use of any of Claims 1-5, wherein the medicament is a transdermal composition or a nanoparticulate composition.

9. Use of a compound of Formula (**A**):



Formula **A**

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

R^4 is O, CH_2, S, Se, or  ,

R^1 and R^2 are independently selected from the group consisting of 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)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 -

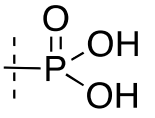
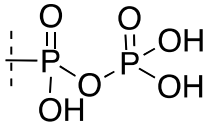
C(NR')SR', an optionally substituted -C(NR')N(R')$_2$, and an optionally substituted –O-C(O)N(R')$_2$, PEG ester, PEG carbonate, an optionally substituted -CH$_2$-O-C(O)-R', an optionally substituted -CH$_2$-O-C(O)O-R', an optionally substituted -CH$_2$-CH$_2$-S-C(O)-R', a lipid ester, a lipid carbonate, (in which 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,

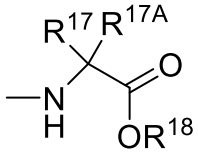
wherein optional substituents are selected from the group consisting of halo, C$_{1-12}$ haloalkyl, C$_{1-16}$ alkyl, C$_{2-16}$ alkenyl, C$_{2-16}$ alkynyl, C$_{3-7}$ cycloalkyl, hydroxyl, carboxyl, C$_{1-12}$ acyl, aryl, heteroaryl, C$_{1-6}$ acyloxy, amino, amido, carboxyl derivatives, alkylamino, 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;

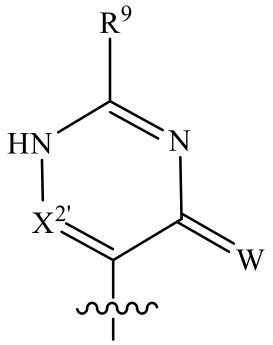
R^3 is H, an L-amino acid ester, a D-amino acid ester, an N-substituted L-amino acid ester, an N-substituted D-amino acid ester, an N,N-disubstituted L-amino acid ester, an N,N-disubstituted D-amino acid ester, (acyloxybenzyl)ester, (acyloxybenzyl)ether, optionally substituted bis-acyloxybenzyl)ester, 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^{6}R^7, 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^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, 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, 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, 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  ,

$R^{9'}$ 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.

10. The use of Claim 9, wherein R^4 is O, CH_2 or S; R^4 is O and R^1, R^2, R^3, R^9, R^{10} and $R^{10'}$ are not all H; R^1 and R^2 are H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl; R^3 is H, an L-amino acid ester, a D-amino acid ester or an optionally substituted -C(O)-C_{1-12} alkyl; R^{10} and $R^{10'}$ are independently H, OH, an L-amino acid amide, a D-amino acid amide, an optionally substituted -C(O)-C_{1-12} alkyl, with the proviso that R^{10} and $R^{10'}$ cannot both be OH; R^9 is H, an L-amino acid ester with the oxygen to which it is attached, a D-amino acid ester with the oxygen to which it is attached, or an optionally substituted -C(O)-C_{1-12} alkyl; or R^{10} and $R^{10'}$ are both H.

11. The use of any of Claims 9-10, wherein the compounds can be present in the β-D or β-L configuration.

12. The use of any of Claims 9-11, wherein the infection is a Coronaviridae infection, wherein the Coronavirus is preferably human coronavirus 229E, SARS, MERS, SARS-CoV-1, OC43, or SARS-CoV-2, more preferably SARS-CoV-2.

13. The use of any of Claims 9-11, wherein the medicament further comprises:

i) 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;

ii) remdesivir, N-hydroxy cytidine, molnupiravir, PF-07321332, PF-07304814 or a pharmaceutically-acceptable salt or prodrug thereof;

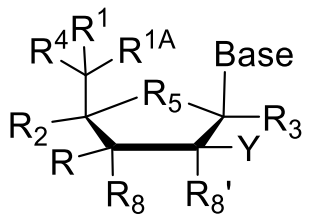
iii) a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof;

iv) an anticoagulant or a platelet aggregation inhibitor; or

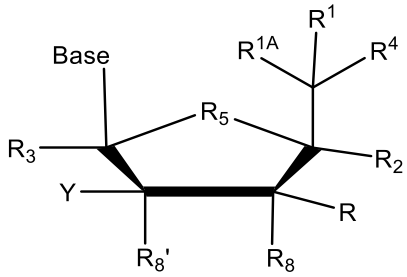
v) an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

14. The use of any of Claims 9-11, wherein the medicament is a transdermal composition or a nanoparticulate composition.

15. Use of a compound of Formula (**A**) or Formula **(A1)**:



Formula A



Formula A1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, 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;

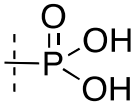
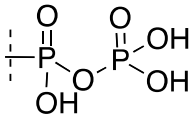
R^3 is CN,

R^5 is O, S, Se, CH_2, CHF, CF_2, -C(CH_3)-, -C(cyclopropyl)-, C=CF_2 or C=CH_2,

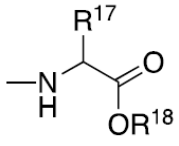
R^8 and $R^{8'}$ are independently selected from the group consisting of H, OH, halo, an optionally substituted O-linked amino acid, substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, 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,

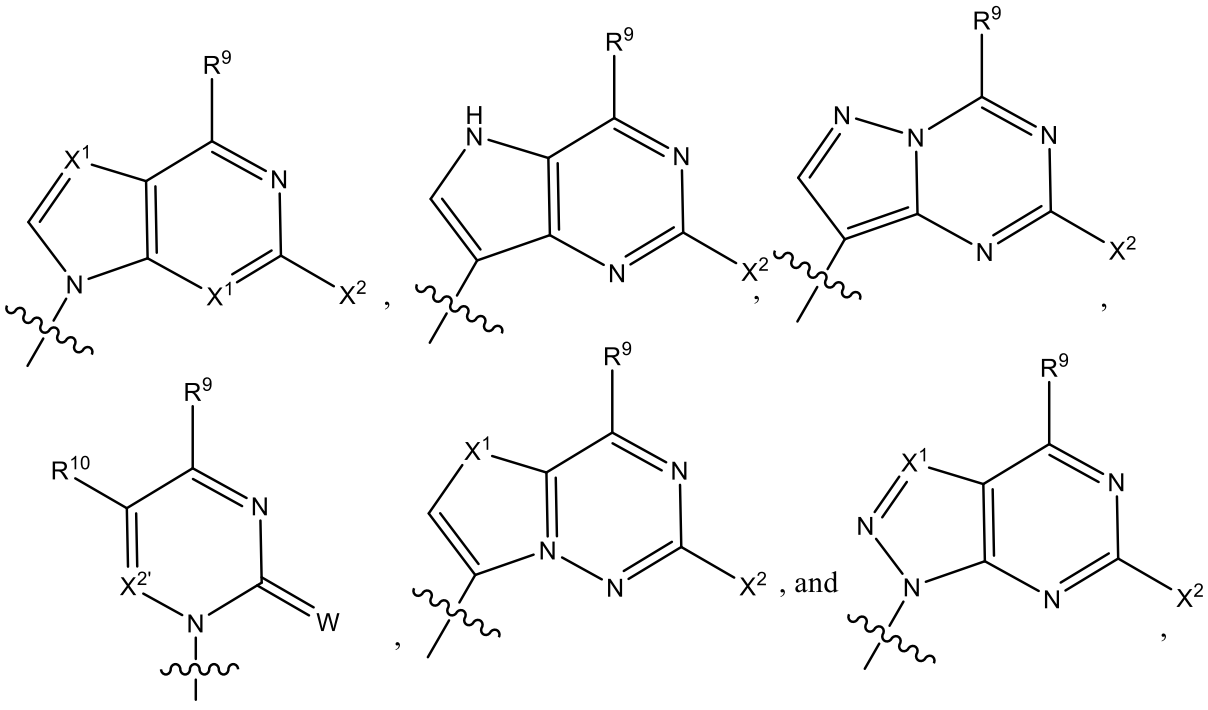
R^6 and R^7 are independently selected from the group consisting of:

(*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,

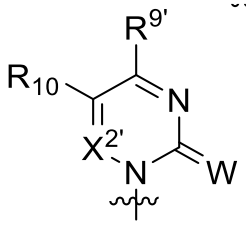
$R^{9'}$ is OH, NH_2, SH, NHOH, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, or -O-C(O)O-C_{3-6} cycloalkyl,

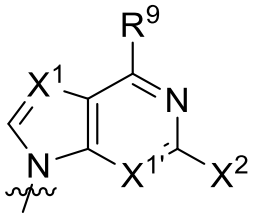
R^{10} is H or F,

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

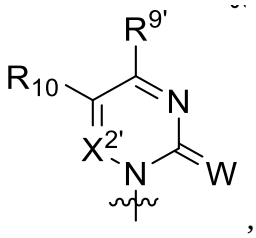
W is O or S.

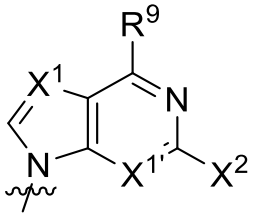
16. The use of Claim 15, wherein R^5 is O; R^2 is H or substituted or unsubstituted C_{2-8} alkynyl; R^1 is and R^{1A} are H; R^8 and $R^{8'}$ are OH; R^4 is OH or O-P(O)R^6R^7; Base is



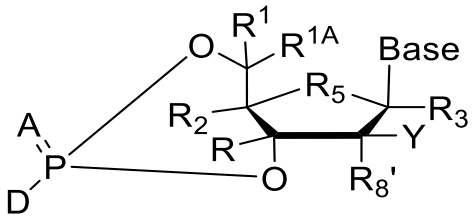
or


; $R^{9'}$ is OH, NH_2, or NHOH; or X^2 is NH_2, OH or

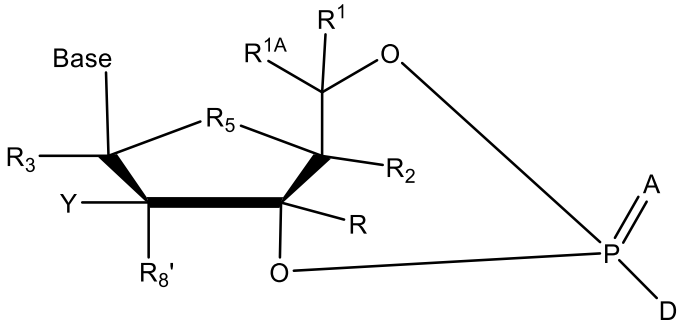
SH, wherein optionally, when Base is  , $R^{9'}$ is OH, NH_2, or NHOH; or when

Base is  , X^2 is NH_2, OH or SH.

17. Use of a compound of Formula (**B**) or **(B1)**:



Formula B



Formula B1

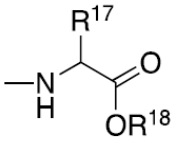
or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

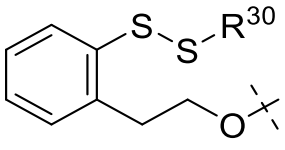
Base, Y, R, R^1, R^{1A}, R^2, R^3, R^5, and $R^{8'}$ are as defined in Formula A,

A is O or S, and

D is selected from the group consisting of:

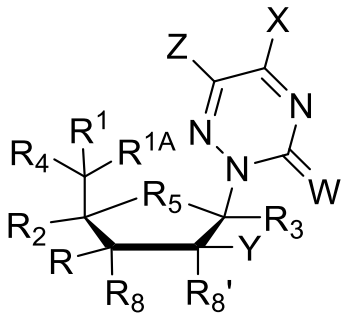
(a) OR^{15} where R^{15} is selected from the group consisting of H, substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6}cycloalkyl, C_{1-4}(alkyl)aryl, benzyl, C_{1-6} haloalkyl, C_{2-3}(alkyl)OC_{1-20} alkyl, aryl, and heteroaryl, such as phenyl and pyridinyl, wherein aryl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

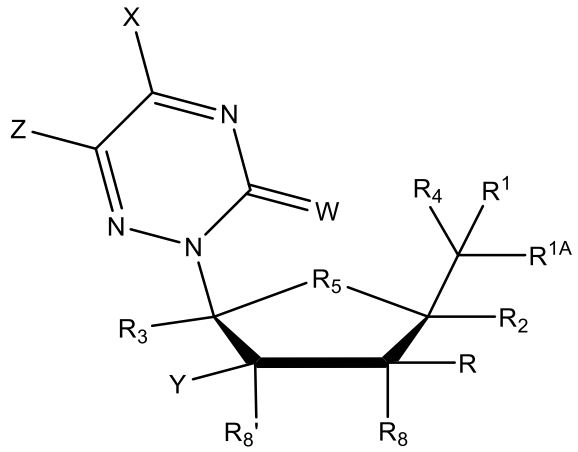
(c)  where R^{30} is selected from the group consisting of substituted or unsubstituted C_{1-20}alkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted (C_{2-10})alkene, substituted or unsubstituted (C_{2-10})alkyne, C_{1-4}(alkyl)aryl, aryl, heteroaryl, and C_{1-6} haloalkyl.

18. The use of Claim 17, wherein R^5 is O; R^2 is H or substituted or unsubstituted C_{2-8} alkynyl; $R^{8'}$ is OH; Y is H; R^1 and R^{1A} are H; or A is O.

19. Use of a compound of Formula **(C)** or **(C1):**



Formula C



Formula C1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

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

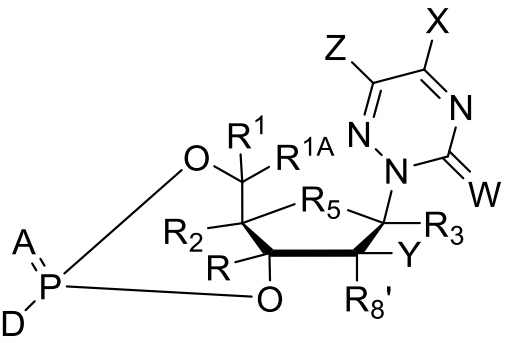
X is OH, NH_2, SH, NHOH, -O-C(O)-C_{1-12} alkyl, -O-C(O)-C_{2-12} alkenyl, -O-C(O)-C_{2-12} alkynyl, -O-C(O)-C_{3-6} cycloalkyl, -O-C(O)O-C_{1-12} alkyl, -O-C(O)O-C_{2-12} alkenyl, -O-C(O)O-C_{2-12} alkynyl, or -O-C(O)O-C_{3-6} cycloalkyl,

Z is H or F, and

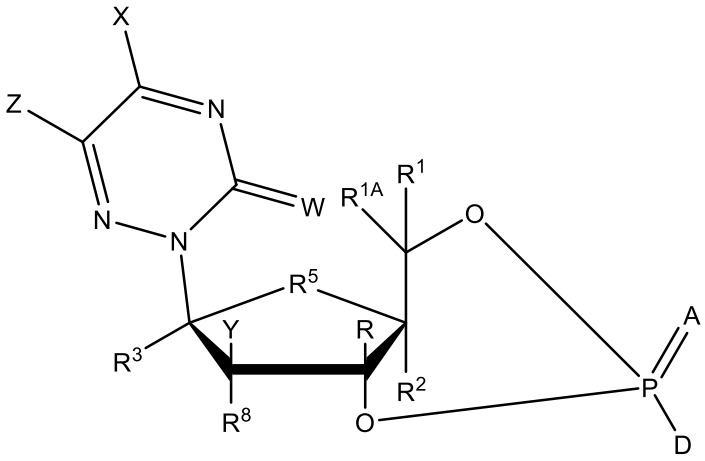
W is O or S.

20. The use of Claim 19, wherein R^5 is O; R^2 is H or substituted or unsubstituted C_{2-8} alkynyl; R^8 and $R^{8'}$ are OH; Y is H; R is H; Z is H; X is OH, NH_2 or NHOH; W is O; R^1 and R^{1A} are H; or R^4 is OH or O-P(O)R^6R^7.

21. Use of a compound of Formula (**D**) or **(D1)**:



Formula D

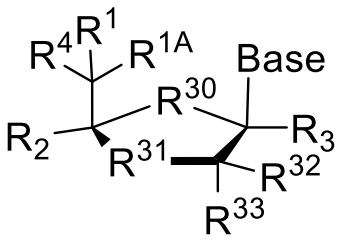


Formula D1

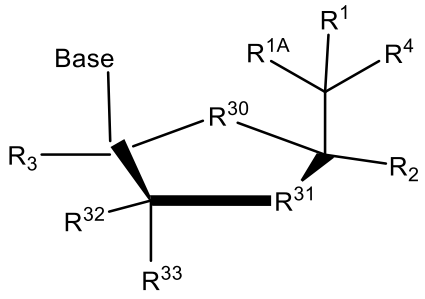
or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein R, R^1, R^{1A}, R^2, R^3, R^5, $R^{8'}$ and Y are as defined in Formula A, and A and D are as defined in Formula C.

22. The use of Claim 21, wherein R^5 is O; R^2 is H or substituted or unsubstituted C_{2-8} alkynyl; $R^{8'}$ is OH; Y is H; R is H; Z is H; X is OH, NH_2 or NHOH; W is O; R^1 and R^{1A} are H; or R^4 is OH or O-P(O)R^6R^7.

23. Use of a compound of Formula (**E**) or **(E1)**:



Formula E



Formula E1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

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

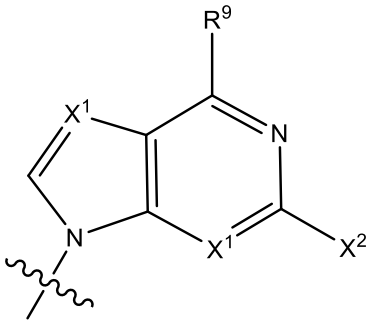
R^{30} is O, S, or CH_2,

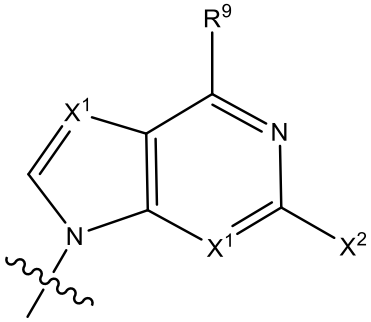
R^{31} is O or S,

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

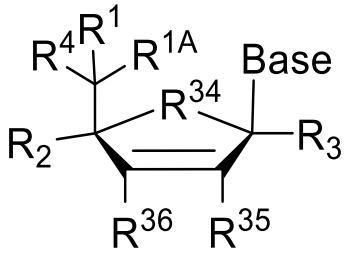
R^{32} and R^{33} are independently H, F, C_1-C_3 alkyl, C_2-C_3 alkene, or C_2-C_3 alkyne.

24. The use of Claim 23, wherein R^{30} is O; R^{31} is O; R^{32} and R^{33} are, independently, H or F; R^2 is N_3 or substituted or unsubstituted C_{2-8} alkynyl; R^1 and R^{1A} are H; R^4 is OH or O-

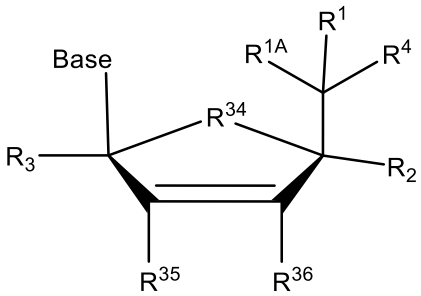
P(O)R^6R^7; Base is  ; or X^1 is N; wherein optionally when Base is

 , X^1 is N.

25. Use of a compound of Formula (**F**) or **(F1)**:



Formula F



Formula F1

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection, wherein:

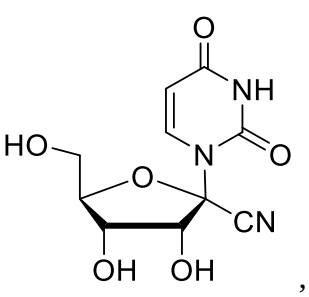
Base, R^1, R^{1A}, R^2, R^3, and R^4 are as defined in Formula A,

R^{34} is O, S, or CH_2, and

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

26. The use of Claim 25, wherein R^{35} and R^{36} are H; R^{34} is CH_2; R^4 is OH or O-P(O)R^6R^7; R^2 is H or substituted or unsubstituted $C_{2\text{-}8}$ alkynyl; or R^1 and R^{1A} are H.

27. Use of a compound of one of the following formulas:



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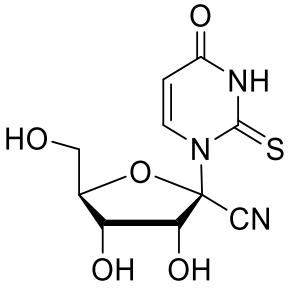

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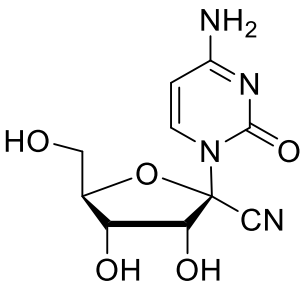

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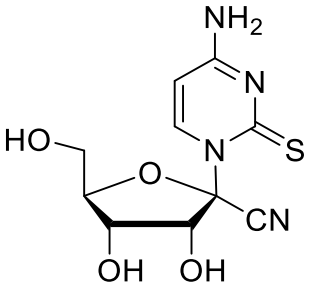

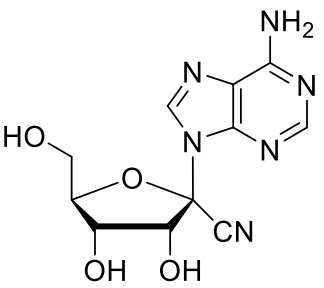

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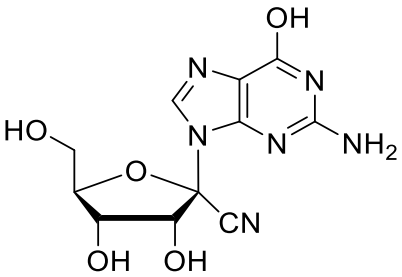

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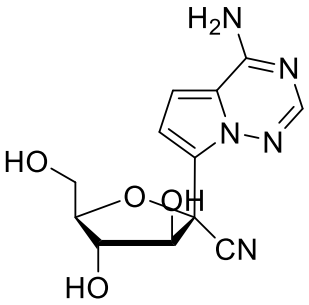
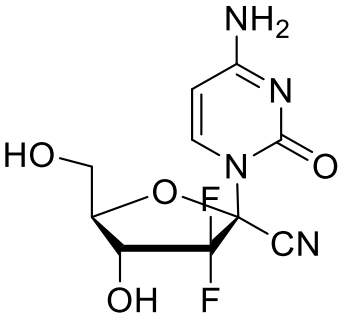
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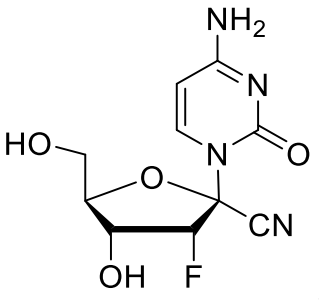
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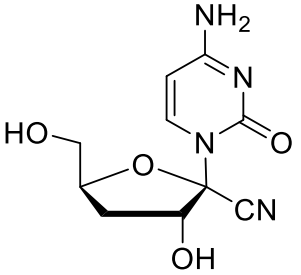
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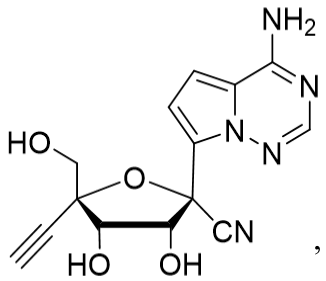
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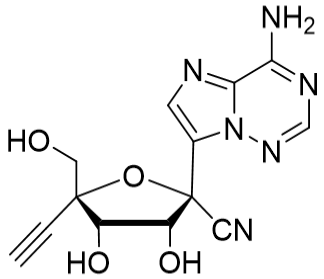
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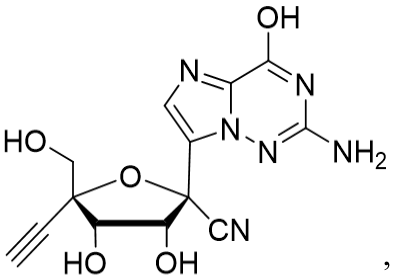
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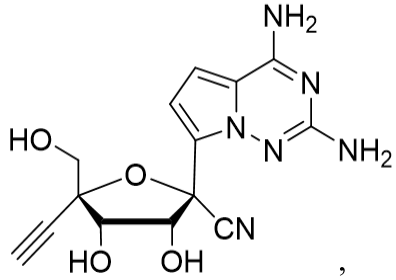
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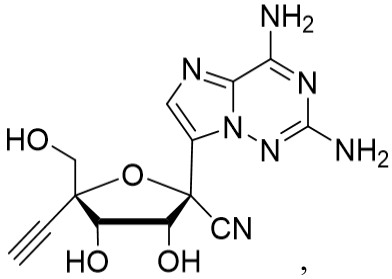
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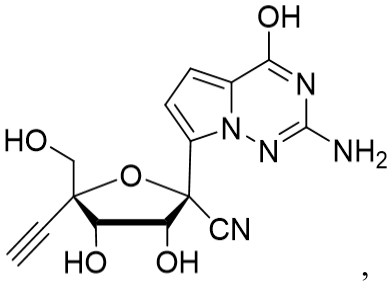
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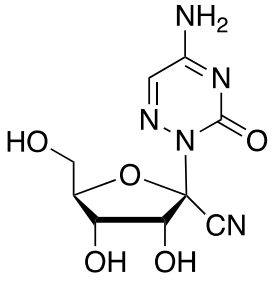
or a pharmaceutically-acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing Coronaviridae, Flaviviridae, Picornaviridae, Bunyaviridae, or Togaviridae infection.

28. The use of Claim 27, wherein the compound has the following formula:



, or a pharmaceutically-acceptable salt or prodrug thereof.

29. The use of any of Claims 15-28, wherein the compounds can be present in the β-D or β-L configuration.

30. The use of any of Claims 15-29, wherein the infection is a Coronaviridae infection, wherein the Coronavirus is preferably SARS-CoV2, MERS, SARS, or OC-43, more preferably SARS-CoV2.

31. The use of any of Claims 15-29, wherein the medicament further comprises:

i) 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;

ii) remdesivir, N-hydroxy cytidine, or a pharmaceutically-acceptable salt or prodrug thereof;

iii) a JAK inhibitor, and the JAK inhibitor is Jakafi, Tofacitinib, or Baricitinib, or a pharmaceutically-acceptable salt or prodrug thereof;

iv) an anticoagulant or a platelet aggregation inhibitor; or

v) an ACE-2 inhibitor, a CYP-450 inhibitor, or a NOX inhibitor.

32. The use of any of Claims 15-29, wherein the medicament is a transdermal composition or a nanoparticulate composition.

33. The use of any of Claims 1-5, 9-11, and 15-29, wherein the compound is to be administered in combination with an NS5A inhibitor.

34. The use of Claim 33, wherein the NS5A inhibitor is dataclastavir.