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

FIELD

This disclosure relates to N4-hydroxycytidine nucleoside derivatives, compositions, and methods related thereto. In certain embodiments, the disclosure relates to the treatment and prophylaxis of viral infections.

BACKGROUND

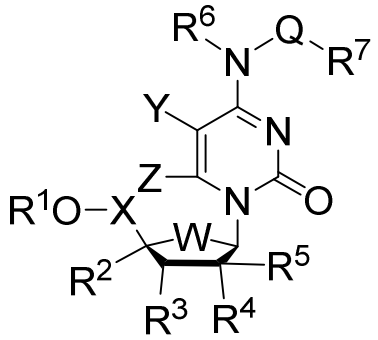
The causative agents for Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively) and Chikungunya fever (CHIK) are vector-borne viruses (family *Togaviridae*, genus *Alphavirus*) that can be transmitted to humans through mosquito bites. The equine encephalitis viruses are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

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

References cited herein are not an admission of prior art.

SUMMARY

This disclosure relates to N4-hydroxycytidine and derivatives, pharmaceutical compositions, and uses related thereto. In certain examples, the disclosure relates to a compound having formula I,



Formula I

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

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

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

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

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

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

In certain examples, the viral infection is an alphavirus or coronaviruses and flavivirus. In certain examples, the viral infection is an orthomyxoviridae or paramyxoviridae. In certain examples, the viral infection is selected from MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus,

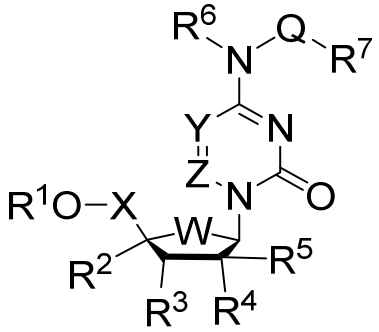
Venezuelan equine encephalitis virus, Ross River virus, Powassan virus, Barmah Forest virus and Chikungunya virus.

In certain examples, the compound or pharmaceutical composition is administered orally, intravenously, or through the lungs.

In certain examples, the disclosure relates to the use of a compound as described herein in the production of a medicament for the treatment of or prevention of a viral infection.

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

In one aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing human coronavirus, chikungunya, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, MERS coronavirus, Ross River infection, filoviridae virus, Ebola virus, or H5N1 influenza virus, the pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula I



Formula I,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

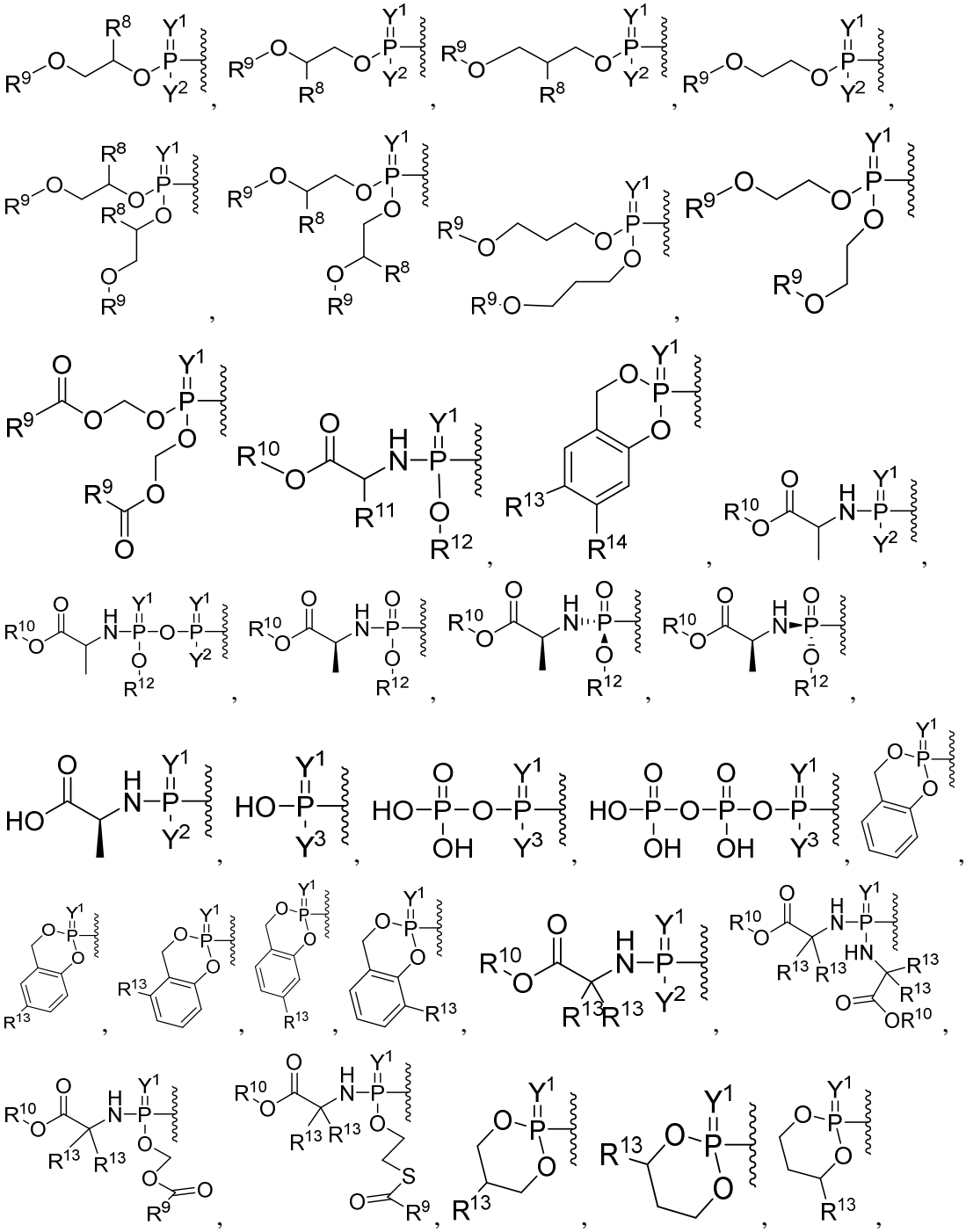
X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is



$C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, or R^1O- is selected from peptide or carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OOC_{1\text{-}2}$alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

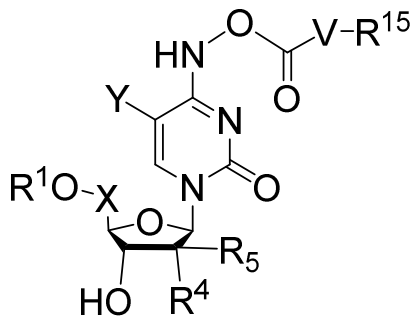
R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{6-12} arylsulfonyl, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

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

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula IB,



Formula IB,

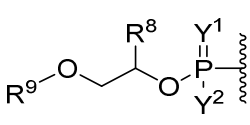
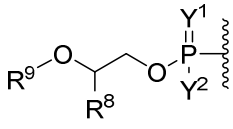
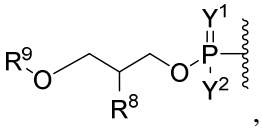
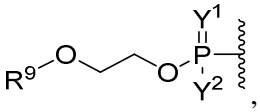
or salts thereof, wherein

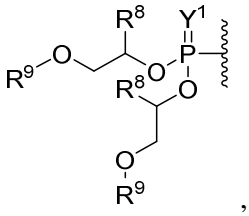
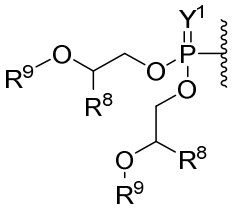
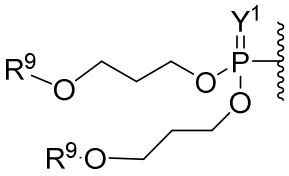
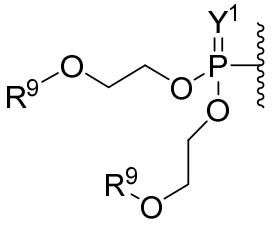
V is O, NH, or NR^{15};

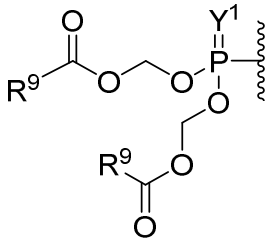
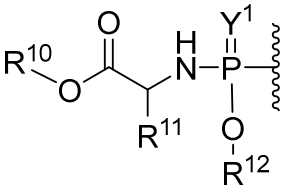
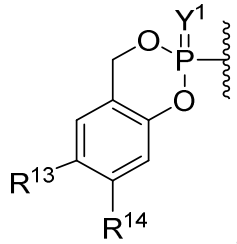
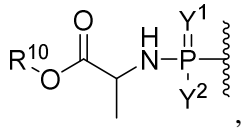
X is CH_2 or CD_2;

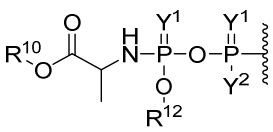
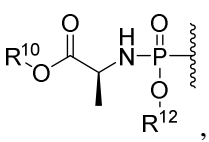
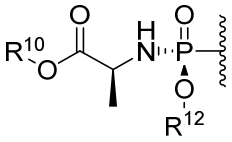
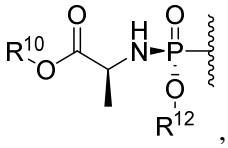
Y is H, D, F, CH_3, CD_3, or CF_3;

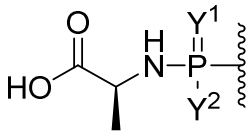
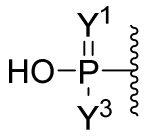
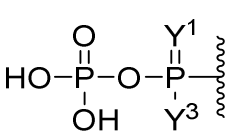
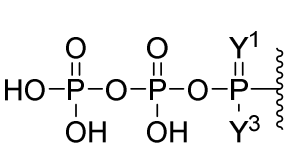
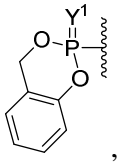
R^1 is hydrogen,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,
 ,

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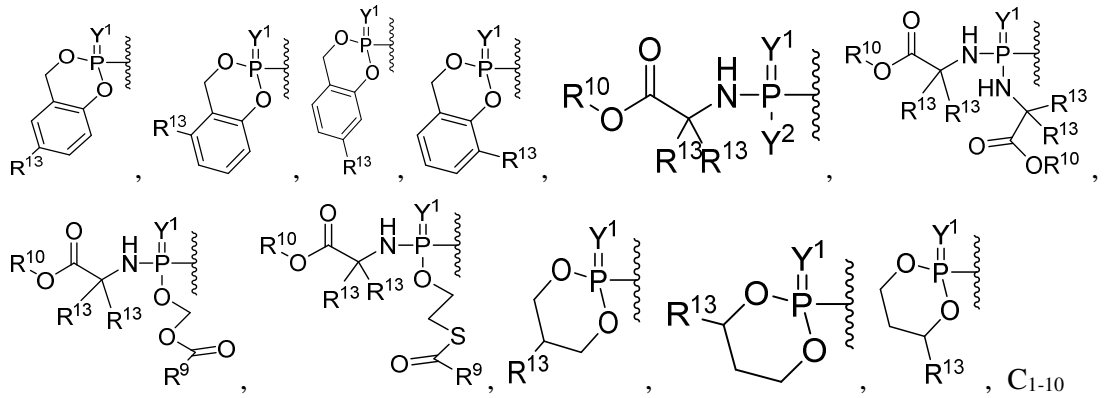


, $C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

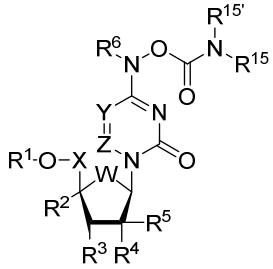
R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula ID,



Formula ID,

or salt thereof, wherein

W is O;

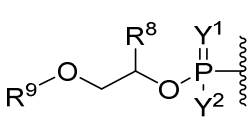
X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is hydrogen,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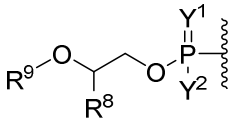
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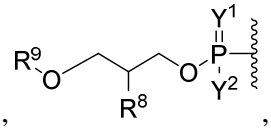
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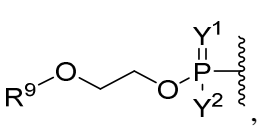
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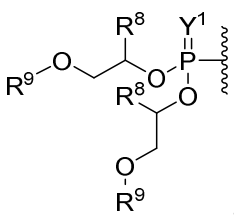
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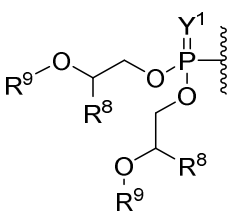
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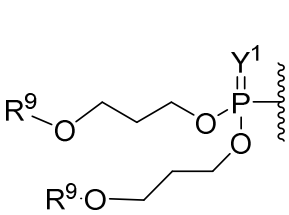
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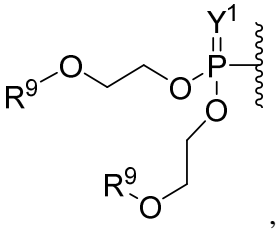
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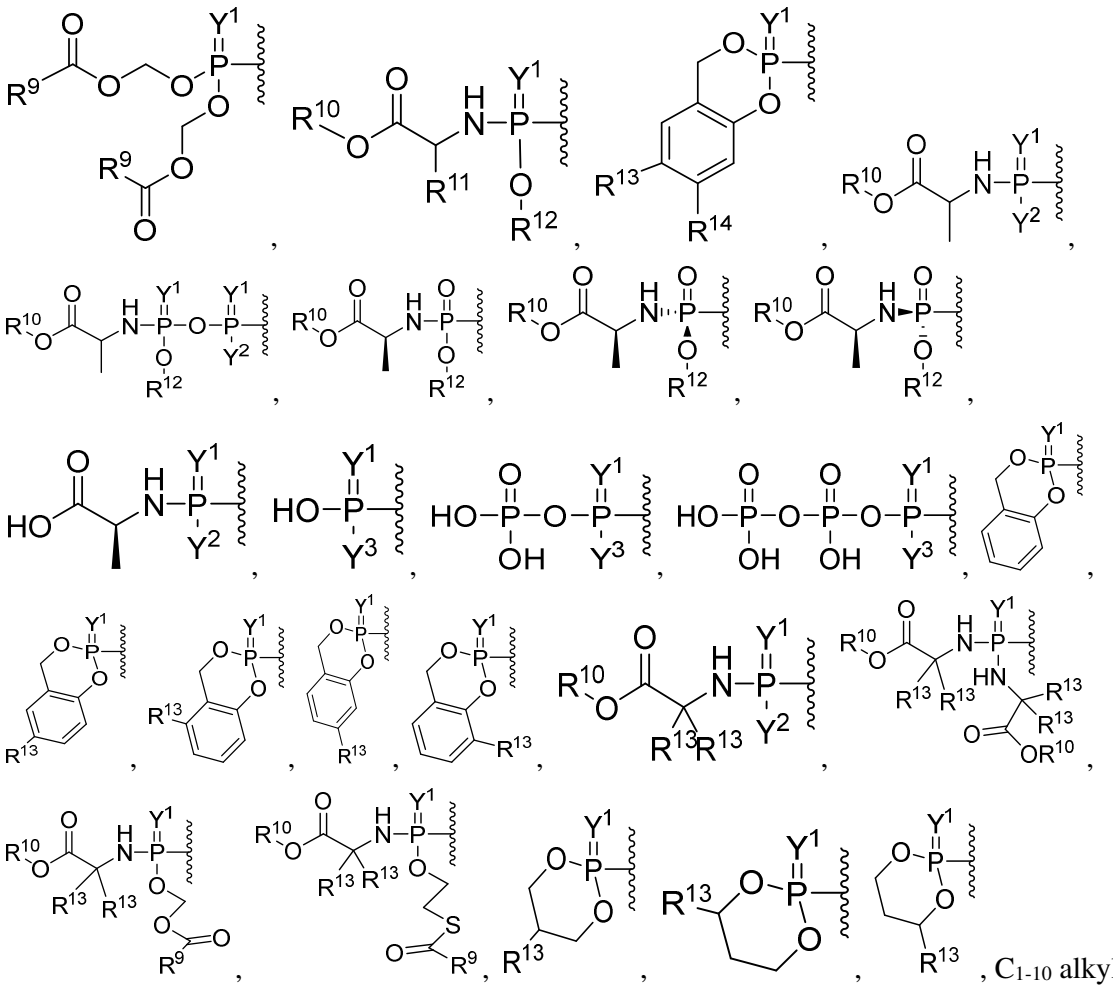


, $C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy,

alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

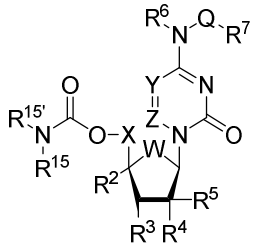
R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

$R^{15'}$ is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula IE,



Formula IE,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino;

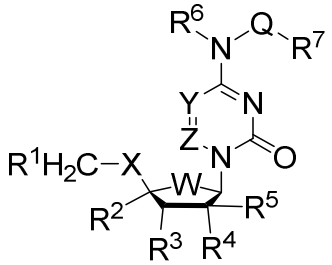
R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

$R^{15'}$ is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is an alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula II,



Formula II,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

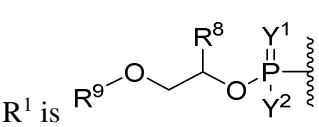
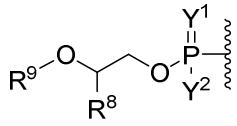
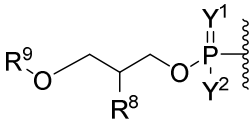
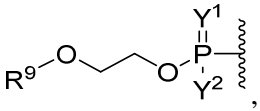
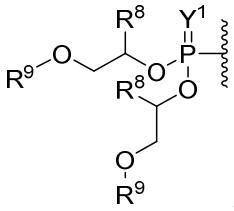
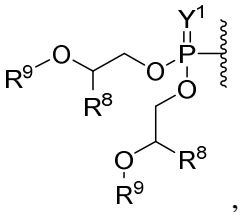
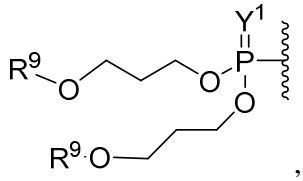
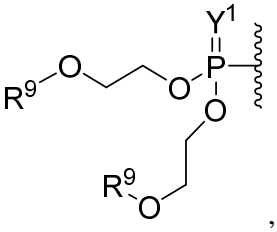
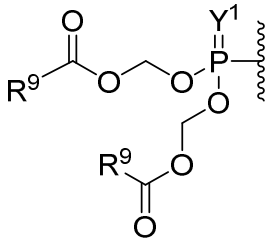
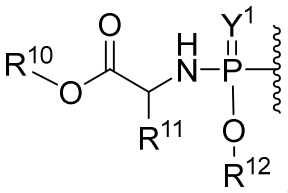
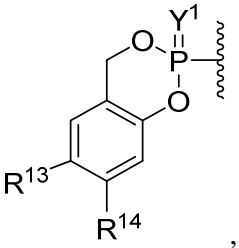
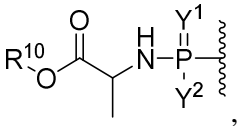
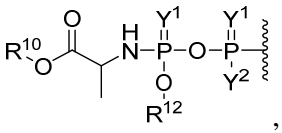
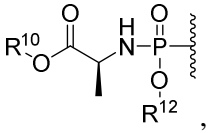
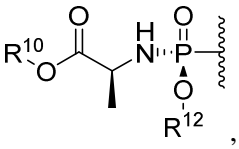
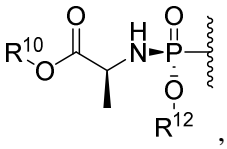
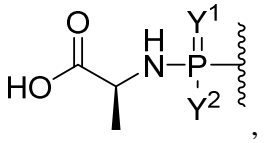
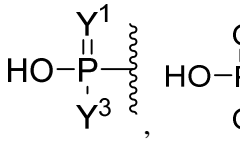
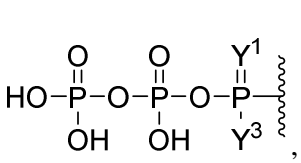
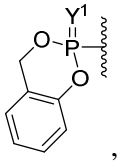
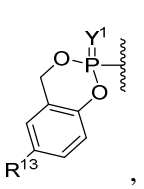
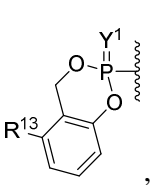
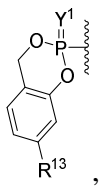
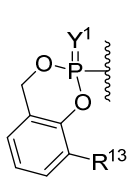
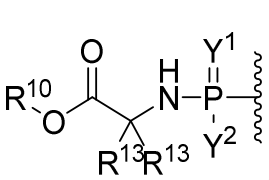
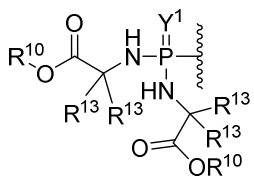
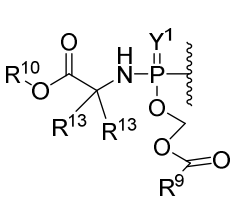
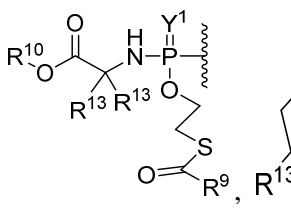
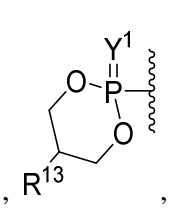
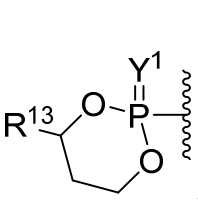
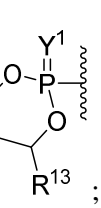
W is O;

X is CH_2 or O;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ;

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

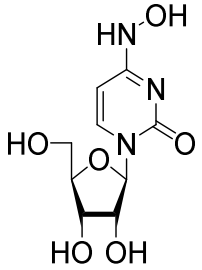
R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is an alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

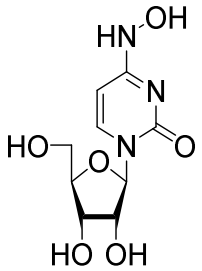
In one aspect, the present disclosure refers to use of a pharmaceutical composition as defined herein, in the manufacture of a medicament for treating or preventing a viral infection in a subject in need thereof.

In one aspect, the present disclosure refers to use of a compound with the structure:



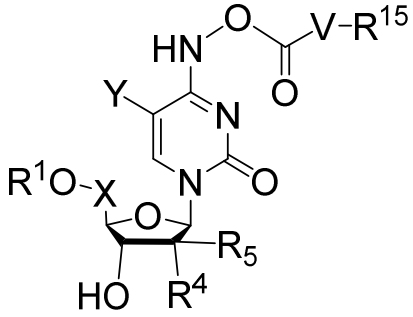
or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound, in the manufacture of a medicament for treating or preventing human coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, influenza virus, Ross River virus infection, filoviridae virus or Ebola virus infection in a patient in need thereof, wherein the medicament is to be administered to the lungs or contacted with infected cells.

In one aspect, the present disclosure refers to use of a compound with the structure:



in the manufacture of a medicament for the treatment or prevention of human coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, influenza virus, Ross River virus infection, filoviridae virus or Ebola virus infection in a patient in need thereof, wherein the compound is for administration through the lungs or by contacting with infected cells.

In one aspect, the present disclosure refers to use of a compound with the formula:



Formula IB,

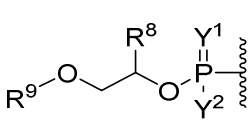
or a salt thereof, wherein

V is O, NH, or NR^{15};

X is CH_2 or CD_2;

Y is H, D, F, CH_3, CD_3, or CF_3;

R^1 is hydrogen,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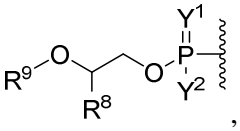
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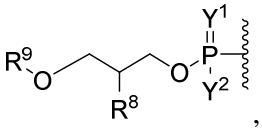
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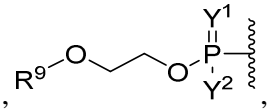
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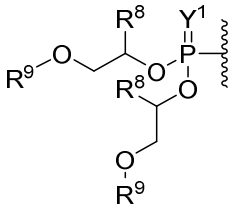
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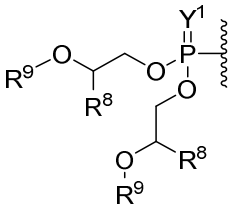
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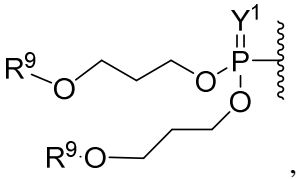
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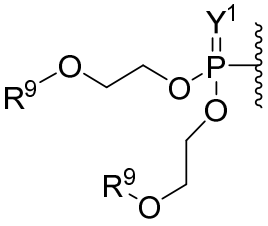
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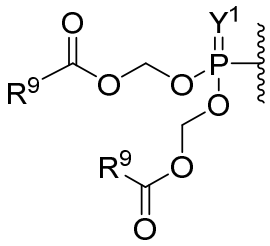
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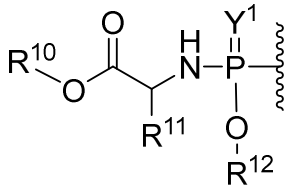
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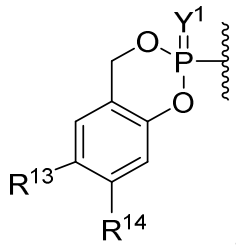
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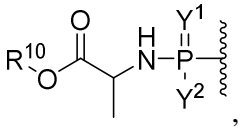
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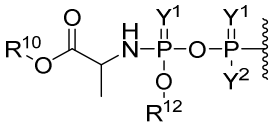
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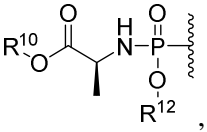
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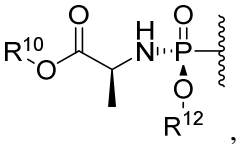
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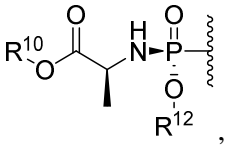
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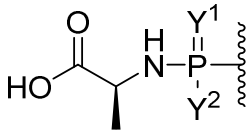
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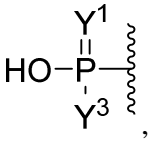
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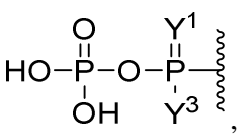
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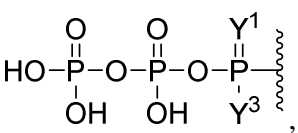
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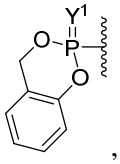
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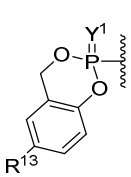
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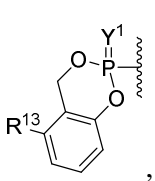
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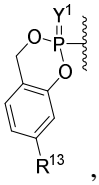
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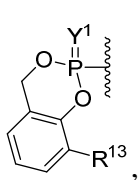
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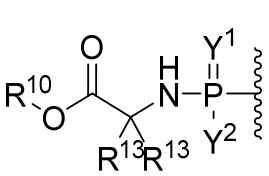
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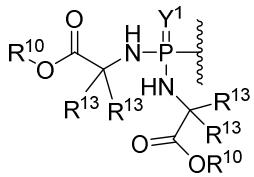
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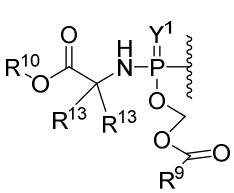
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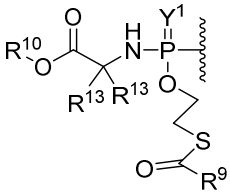
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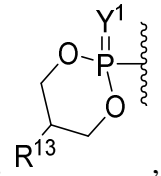
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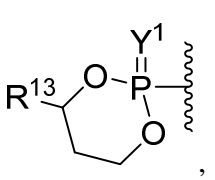
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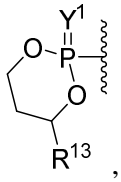

, $C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

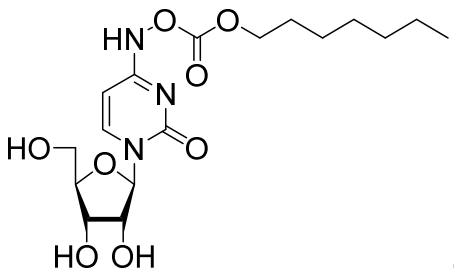
R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group,

in the manufacture of a medicament for treating or preventing a human coronavirus, SARS coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

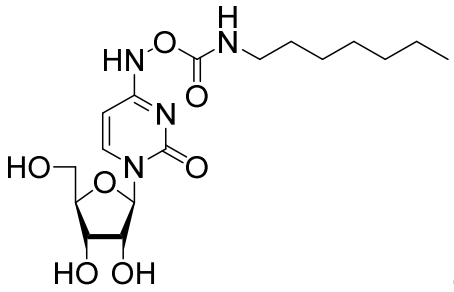
In one aspect, the present disclosure refers to use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

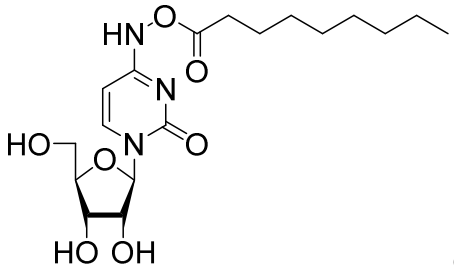
In one aspect, the present disclosure refers to use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

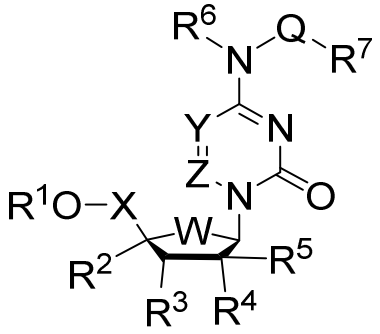
In one aspect, the present disclosure refers to use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula I



Formula I,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

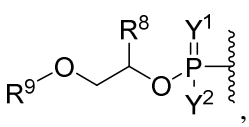
X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is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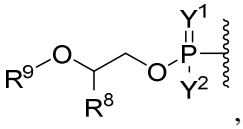
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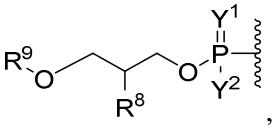
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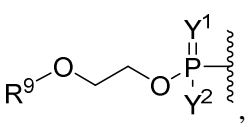
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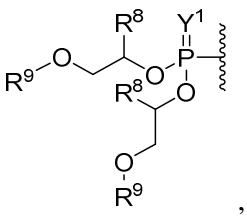
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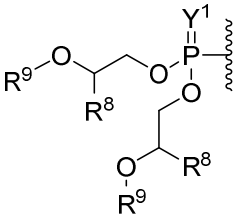
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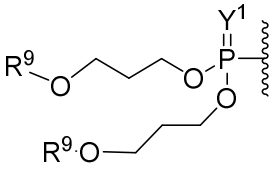
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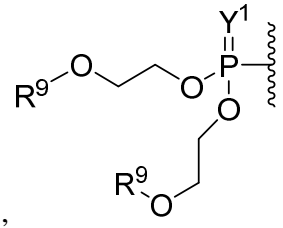
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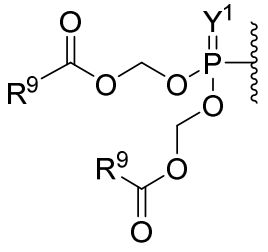
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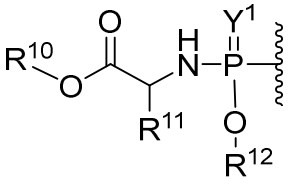
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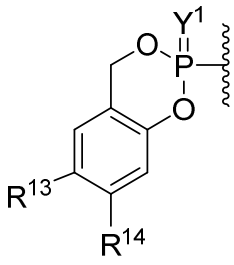
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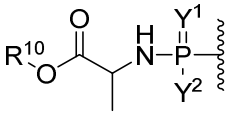
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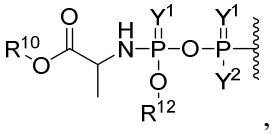
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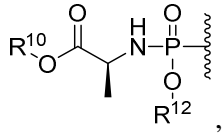
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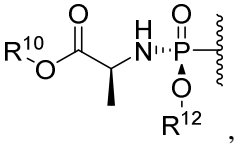
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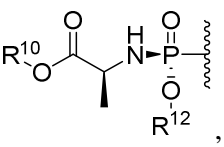
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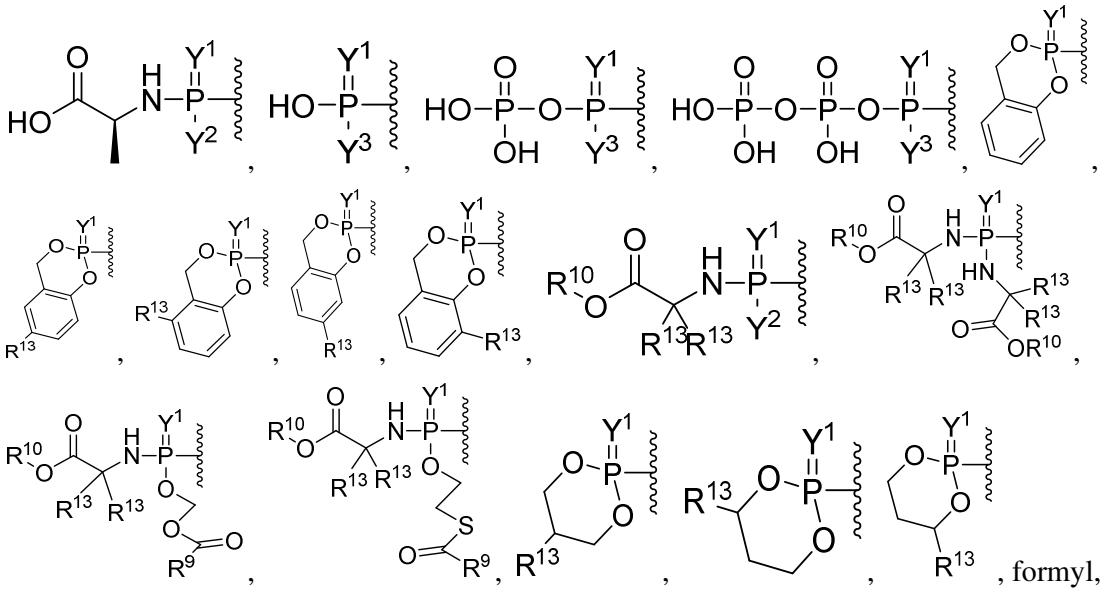


carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, C_{6-10} aryl, heterocyclyl, or phosphoramidyl, or R^1O- is selected from peptide or carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or OOC_{1-2}alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, $C_{1\text{-}10}$ alkoxy, $C_{1\text{-}10}$ alkylthio, $C_{1\text{-}10}$ alkylamino, $(C_{1\text{-}10}$ alkyl$)_2$amino, $C_{1\text{-}10}$ alkylsulfinyl, $C_{1\text{-}10}$ alkylsulfonyl, $C_{6\text{-}12}$ arylsulfonyl, carbocyclyl, $C_{6\text{-}12}$ aryl, or heterocyclyl;

lipid is a $C_{6\text{-}22}$ alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the preparation of β-D-N-hydroxycytidine. a. TBSCl, DMAP, DIPEA, DCM; b. (2,4,6-iPr)$PhSO_2Cl$, DIPEA, DMAP, DCM; c. NH_2OH-HCl, DIPEA, DCM; d. F- source; e. aq NH_2OH, AcOH, 50 ^oC.

Figure 2 illustrates certain embodiments of the disclosure.

Figure 3 illustrates certain embodiments of the disclosure.

Figure 4 shows EIDD-01931 mean plasma concentrations and pharmacokinetic parameters from mice dosed with EIDD-01931

Figure 5 shows EIDD-01931 nucleoside accumulation in mouse organs

Figure 6 shows EIDD-01931 triphosphate accumulation in mouse organs

Figure 7 shows reduction in footpad swelling in CHIKV challenged mice treat with EIDD-01931

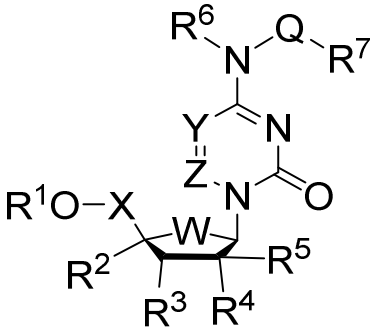
Figure 8 shows reduction of CHIKV RNA copies by PCR in CHIKV challenged mice treated with EIDD-01931

DETAILED DESCRIPTION

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

CLAIMS

1. Use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing human coronavirus, chikungunya, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, MERS coronavirus, Ross River infection, filoviridae virus, Ebola virus, or H5N1 influenza virus, the pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula I



Formula I,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

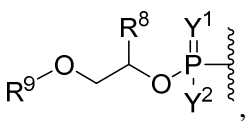
X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is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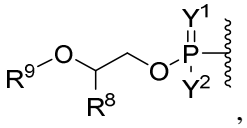
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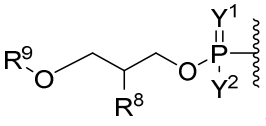
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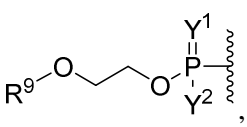
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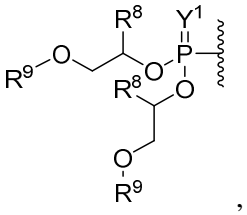
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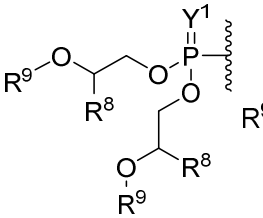
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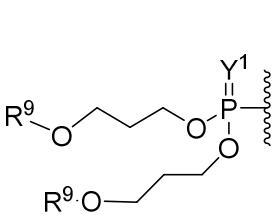
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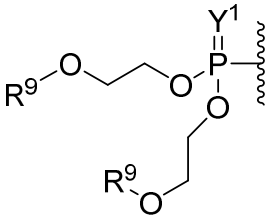
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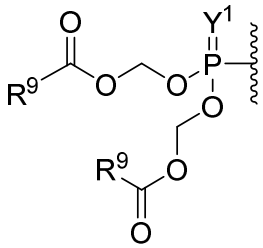
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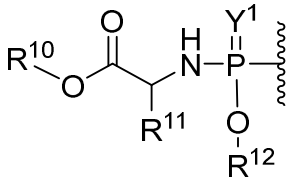
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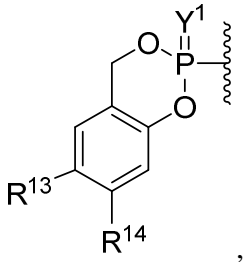
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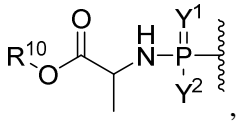
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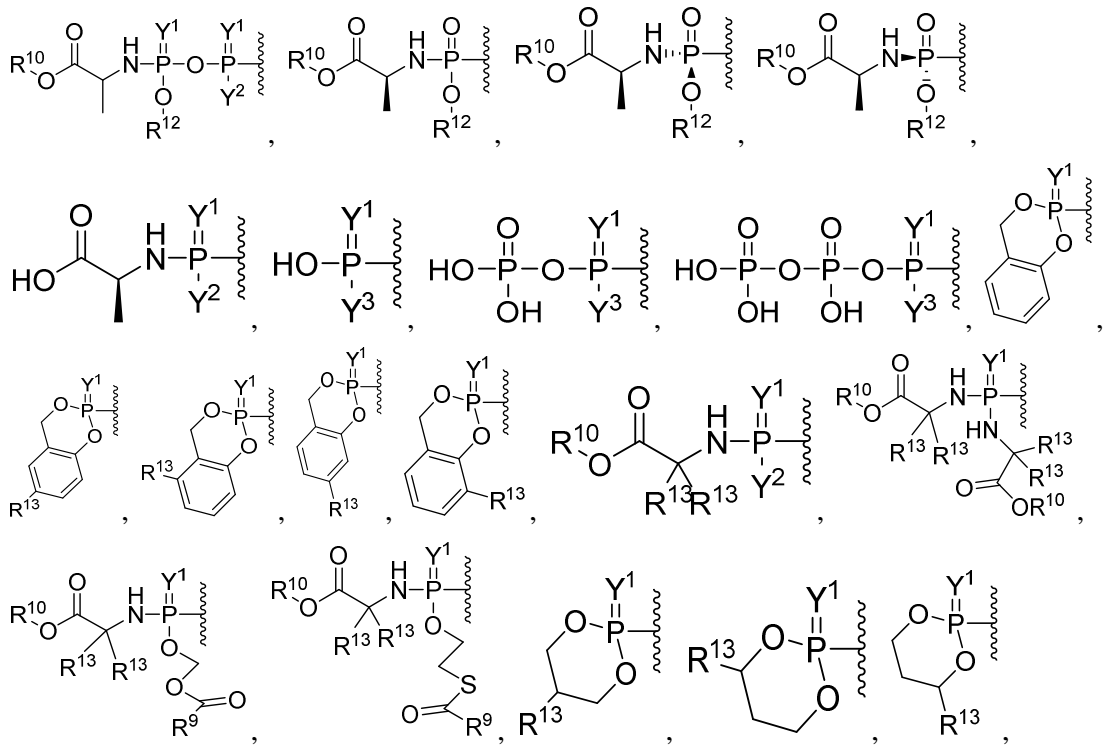


$C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, or R^1O- is selected from peptide or carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OOC_{1\text{-}2}$alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)$OC_{1\text{-}10}$ alkyl, -(C=O)$NHC_{1\text{-}10}$ alkyl, -(C=O)N-$C_{1\text{-}10}$ dialkyl, $C_{1\text{-}10}$ alkyl, $C_{6\text{-}22}$ alkyl, amino, $C_{1\text{-}10}$ alkylamino, $(C_{1\text{-}10}$ alkyl$)_2$amino;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano,

hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

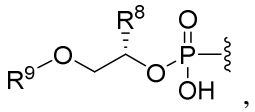
R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, $C_{1\text{-}10}$ alkoxy, $C_{1\text{-}10}$ alkylthio, $C_{1\text{-}10}$ alkylamino, $(C_{1\text{-}10}$ alkyl$)_2$amino, $C_{1\text{-}10}$ alkylsulfinyl, $C_{1\text{-}10}$ alkylsulfonyl, $C_{6\text{-}12}$ arylsulfonyl, carbocyclyl, $C_{6\text{-}12}$ aryl, or heterocyclyl;

lipid is a $C_{6\text{-}22}$ alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

2. The use of claim 1, wherein R^1 is

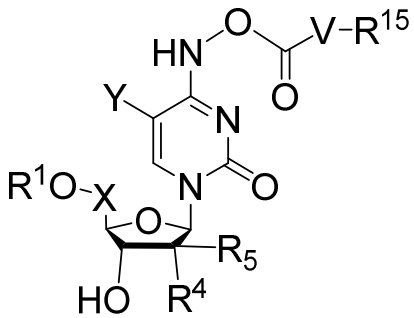


,

R^8 is hydrogen, hydroxy, or benzyloxy, and

R^9 is C_6-C_{22}alkyl.

3. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula IB,



Formula IB,

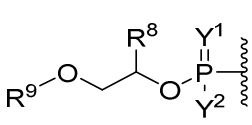
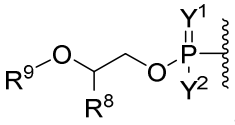
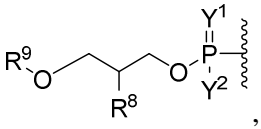
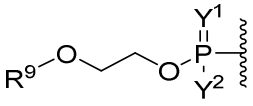
or salts thereof, wherein

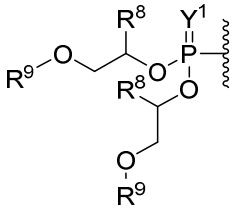
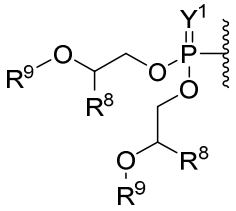
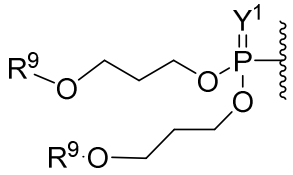
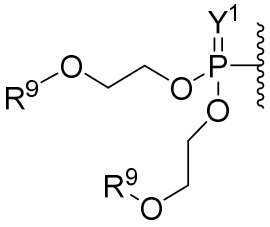
V is O, NH, or NR^{15};

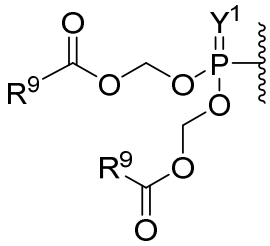
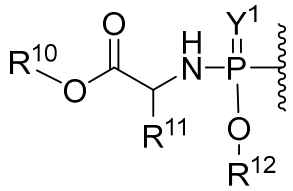
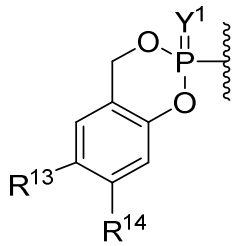
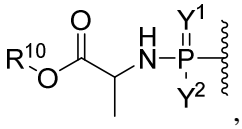
X is CH_2 or CD_2;

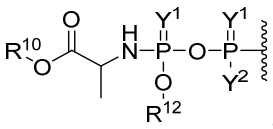
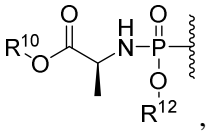
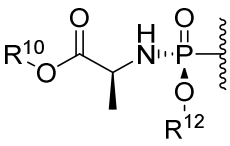
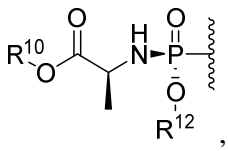
Y is H, D, F, CH_3, CD_3, or CF_3;

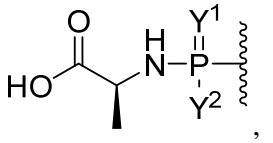
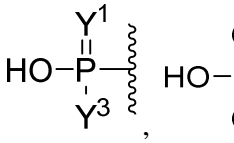
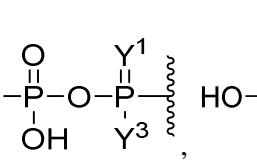
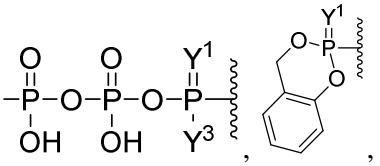
R^1 is hydrogen,

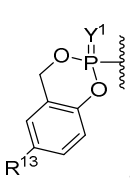
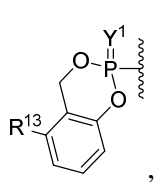
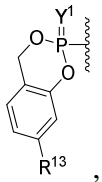
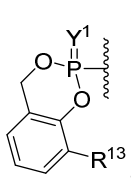
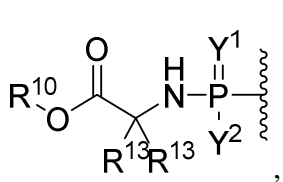
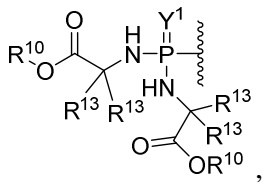
 ,  ,  ,  ,

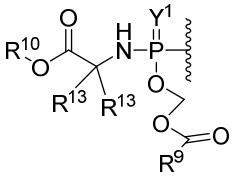
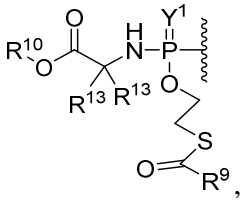
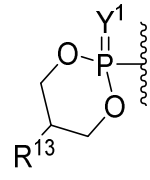
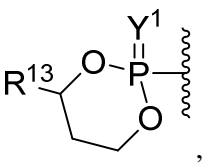
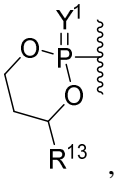
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  , $C_{1\text{-}10}$ alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, $C_{6\text{-}10}$ aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

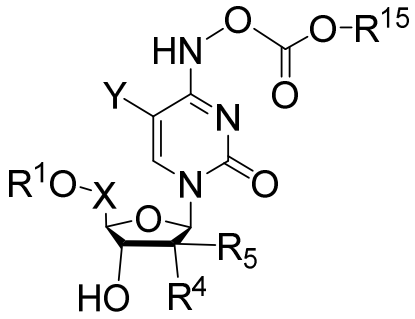
R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

4. The pharmaceutical composition of claim 3, wherein the compound is 1-(3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-((((heptyloxy)carbonyl)oxy)amino)pyrimidin-2-one.

5. The pharmaceutical composition of claim 3, wherein the compound of formula IB has Formula IC,



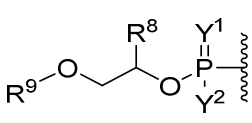
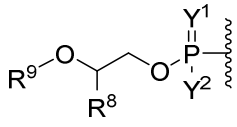
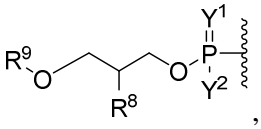
Formula IC,

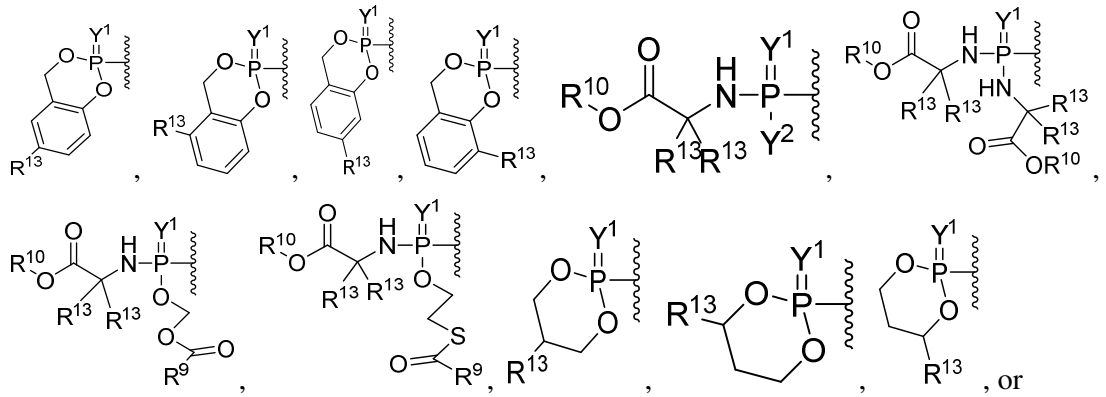
or salts thereof, wherein

X is CH_2 or CD_2;

Y is H, D, F, CH_3, CD_3, or CF_3;

R^1 is,



phosphoramidyl;

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio,

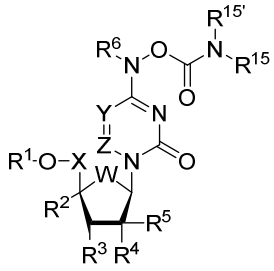
alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

6. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula ID,



Formula ID,

or salt thereof, wherein

W is O;

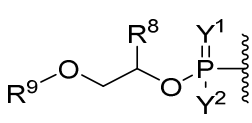
X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is hydrogen,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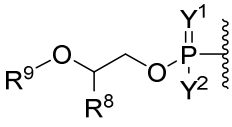
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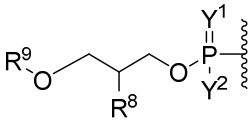
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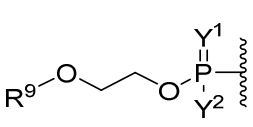
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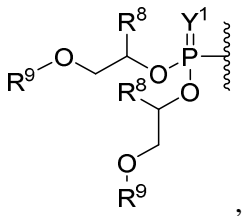
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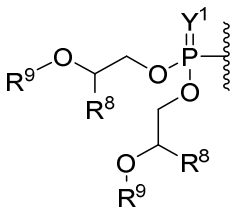
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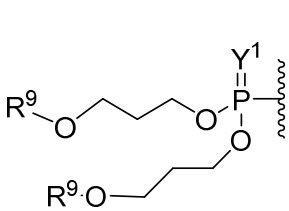
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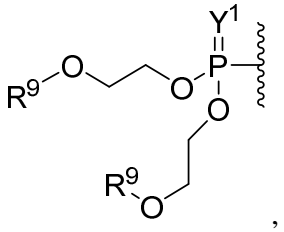
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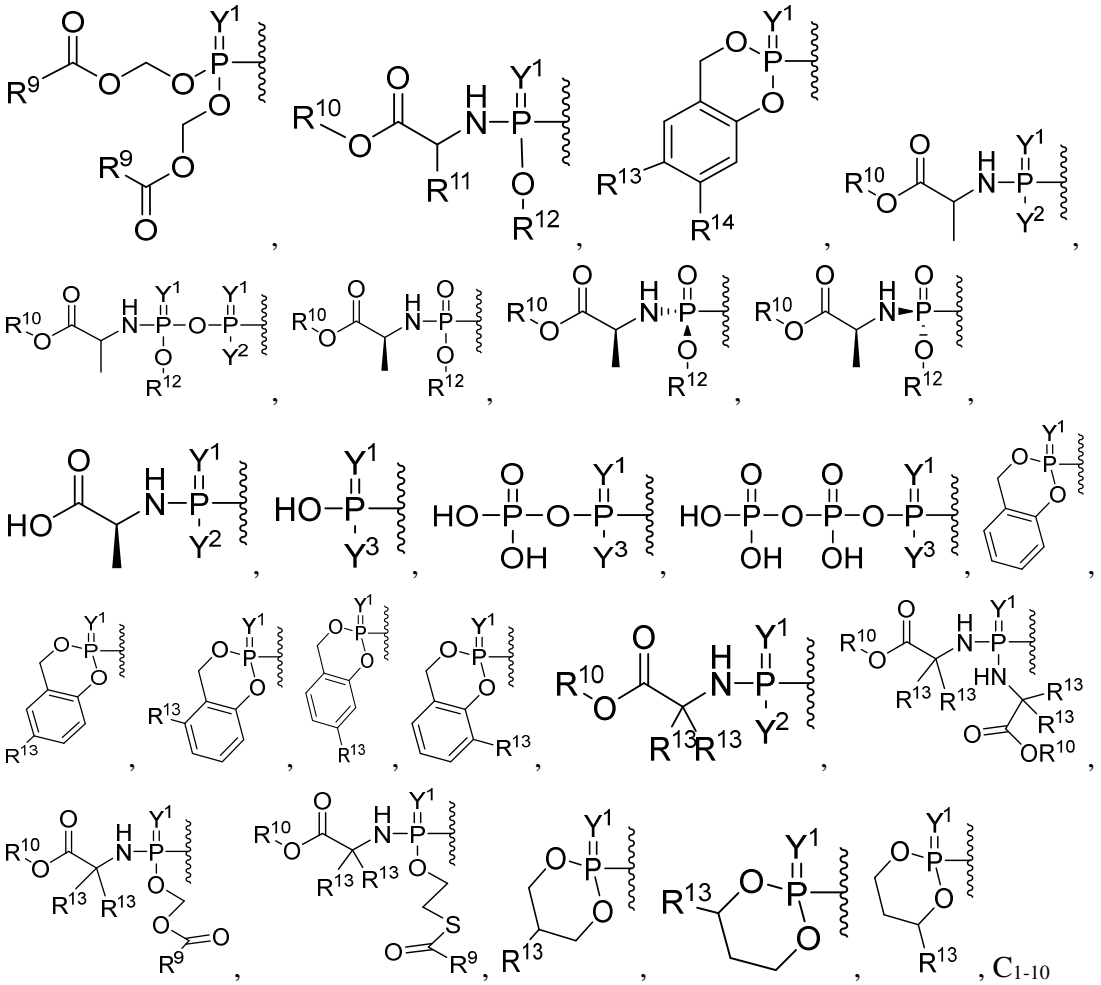


alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, C_{6-10} aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or OC_{1-2} alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl,

alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

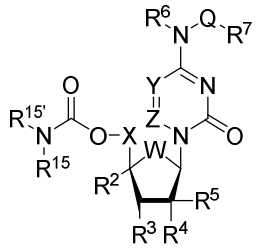
R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

$R^{15'}$ is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

7. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula IE,



Formula IE,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

X is CH_2 or CD_2;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino;

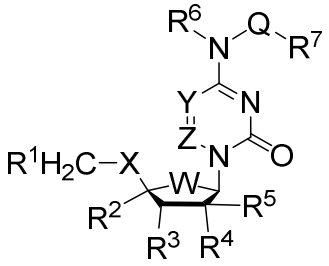
R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

$R^{15'}$ is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is an alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula II,



Formula II,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

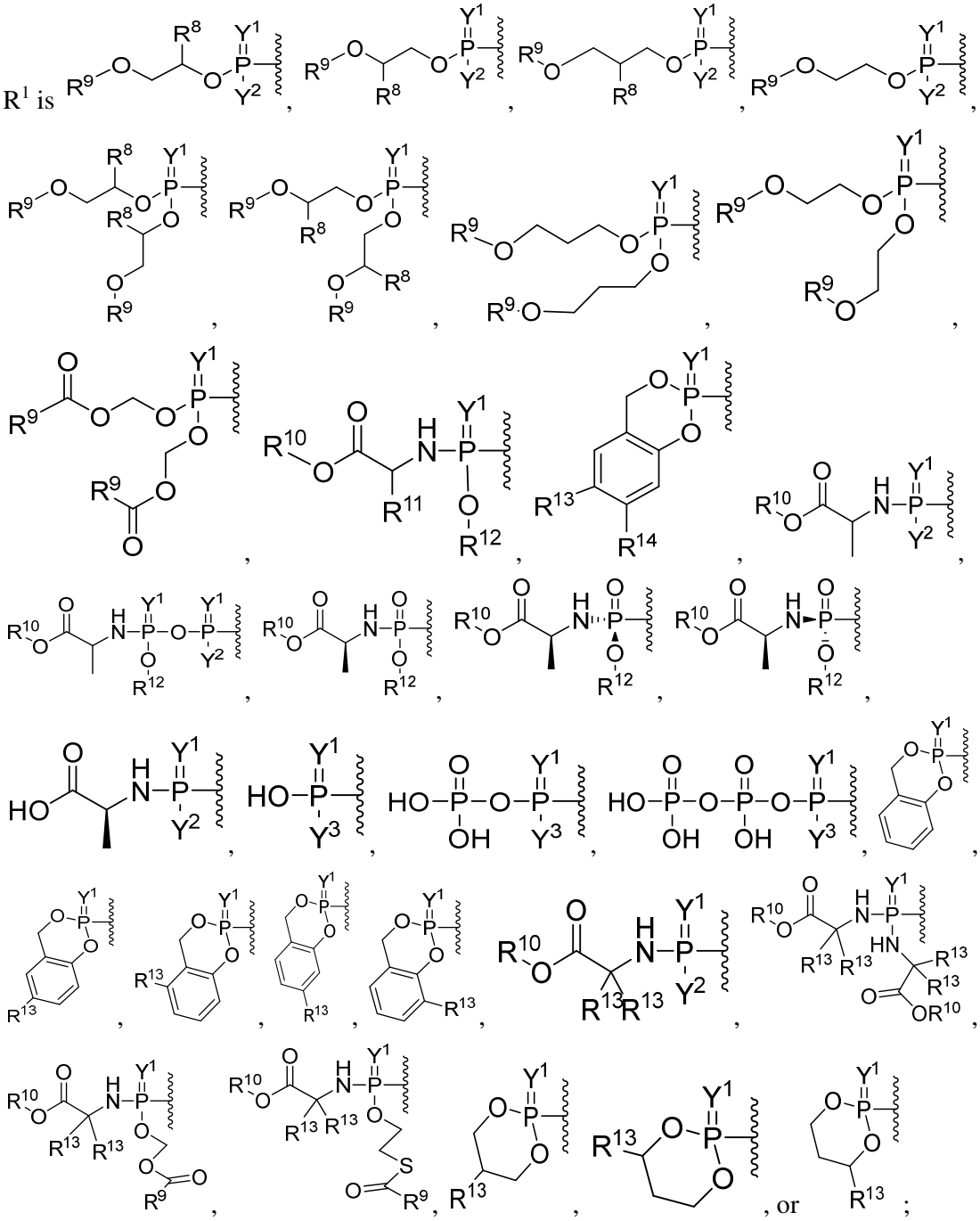
W is O;

X is CH_2 or O;

Y is CR";

Z is CH;

R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

R^1 is 

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$ alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is an alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

9. The use of claim 1 or 2, or the pharmaceutical composition of any one of claims 3-8, wherein the pharmaceutical composition further comprises a propellant.

10. The use or the pharmaceutical composition of claim 9, wherein the propellant is compressed air, ethanol, nitrogen, carbon dioxide, nitrous oxide, hydrofluoroalkanes (HFA), 1,1,1,2,-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or combinations thereof.

11. The use or the pharmaceutical composition of claim 9, wherein when administered, the composition is to be administered from a pressurized container.

12. The use or the pharmaceutical composition of claim 11, wherein the container is a manual pump spray, inhaler, meter-dosed inhaler, dry powder inhaler, nebulizer, vibrating mesh nebulizer, jet nebulizer, or ultrasonic wave nebulizer.

13. Use of a pharmaceutical composition as defined in claim 8, in the manufacture of a medicament for treating or preventing a viral infection in a subject in need thereof.

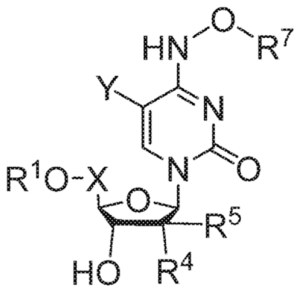
14. The use of claim 13, for treating or preventing human coronavirus, SARS coronavirus, chikungunya, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus (VEEV), MERS coronavirus, Ross River infection, filoviridae virus, Ebola virus, or H5N1 influenza virus.

15. The use of claim 1, wherein the viral infection is an alphavirus or MERS coronavirus.

16. The use of claim 1, wherein the virus is selected from MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Chikungunya virus, and Ross River virus.

17. The use of claim 1, wherein the compound is to be administered through the lungs.

18. The use of claim 1, wherein the compound has a structure according to Formula IA



Formula IA,

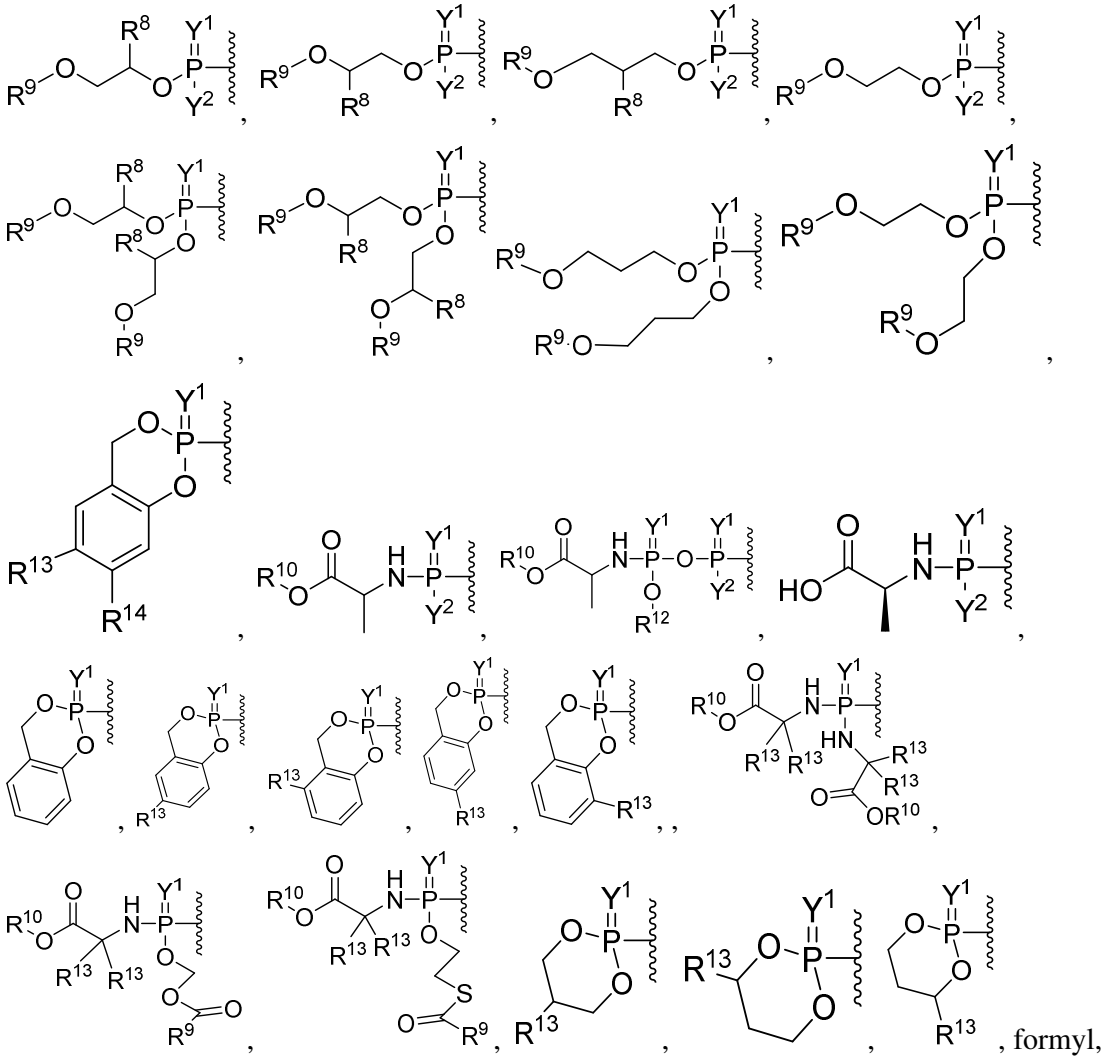
or salt thereof, wherein

R^7 is H,

X is CH_2 or CD_2;

Y is independently selected from is H, D, F, or CH_3;

R^1 is



carboxy, or esteryl, or R^1O- is selected from carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or $OC_{1\text{-}2}$alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, halogen, or fluoro;

R^5 is hydrogen, hydroxy, methoxy, methyl, or ethynyl;

R^8 is hydrogen, deuterium, C_1 alkyl, hydroxy, benzyloxy, carboxy, carbamoyl, azido, C_1 alkoxy, C_1 alkylamino, $(C_1$ alkyl$)_2$amino, carbocyclyl, $C_{6\text{-}10}$ aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, $C_{1\text{-}10}$ alkyl, $C_{6\text{-}22}$ alkyl, cycloalkyl, $C_{1\text{-}10}$ alkoxy, $C_{1\text{-}10}$ alkylamino, $(C_{1\text{-}10}$ alkyl$)_2$amino, carbocyclyl, $C_{6\text{-}12}$ aryl, or heterocyclyl;

R^{10} is hydrogen, $C_{1\text{-}10}$ alkyl, branched $C_{1\text{-}10}$ alkyl, cycloalkyl, lipid methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, $C_{1\text{-}10}$ alkoxy, $C_{6\text{-}12}$ aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, $C_{1\text{-}10}$ alkyl, methyl, hydroxy, $C_{1\text{-}10}$ alkoxy, carbocyclyl, $C_{6\text{-}12}$ aryl, or heterocyclyl;

R^{12} is hydrogen, C_{1-10} alkyl, C_{6-12} aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{6-12} arylsulfonyl, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

R^{20} is deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{6-12} arylsulfonyl, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

lipid is a C_{6-22} alkyl, C_{6-22} alkoxy, polyethylene glycol, or C_{6-12} aryl substituted with a C_{1-10} alkyl group.

19. The use of claim 18, wherein

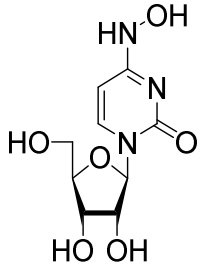
Y is selected from is H, F, or CH_3;

R^1 is carboxy or esteryl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20}, or

R^1O- is selected from carboxylic acid ester.

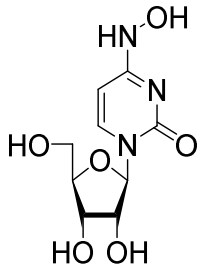
20. The use of claim 18, wherein R^4 is hydroxy and R^5 is hydrogen.

21. Use of a compound with the structure:



or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound, in the manufacture of a medicament for treating or preventing human coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, influenza virus, Ross River virus infection, filoviridae virus or Ebola virus infection in a patient in need thereof, wherein the medicament is to be administered to the lungs or contacted with infected cells.

22. Use of a compound with the structure:



in the manufacture of a medicament for the treatment or prevention of human coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, influenza virus, Ross River virus infection, filoviridae virus or Ebola virus infection in a patient in need thereof, wherein the compound is for administration through the lungs or by contacting with infected cells.

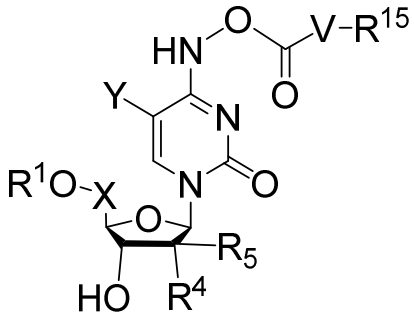
23. The use of claim 21 or 22, wherein the viral infection is selected from human coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Chikungunya virus, Ross River virus, H5N1 influenza virus, filoviridae virus or Ebola virus infection.

24. The use of any one of claims 21-23, wherein administration is to the lungs.

25. The use of any one of claims 21-23, wherein administration is by contacting infected cells.

26. The use of claim 25, wherein administration is selected from intravenous, rectal, transdermal, subcutaneous, intramuscular, intranasal, inhalation, or intraperitoneal.

27. Use of a compound with the formula:



Formula IB,

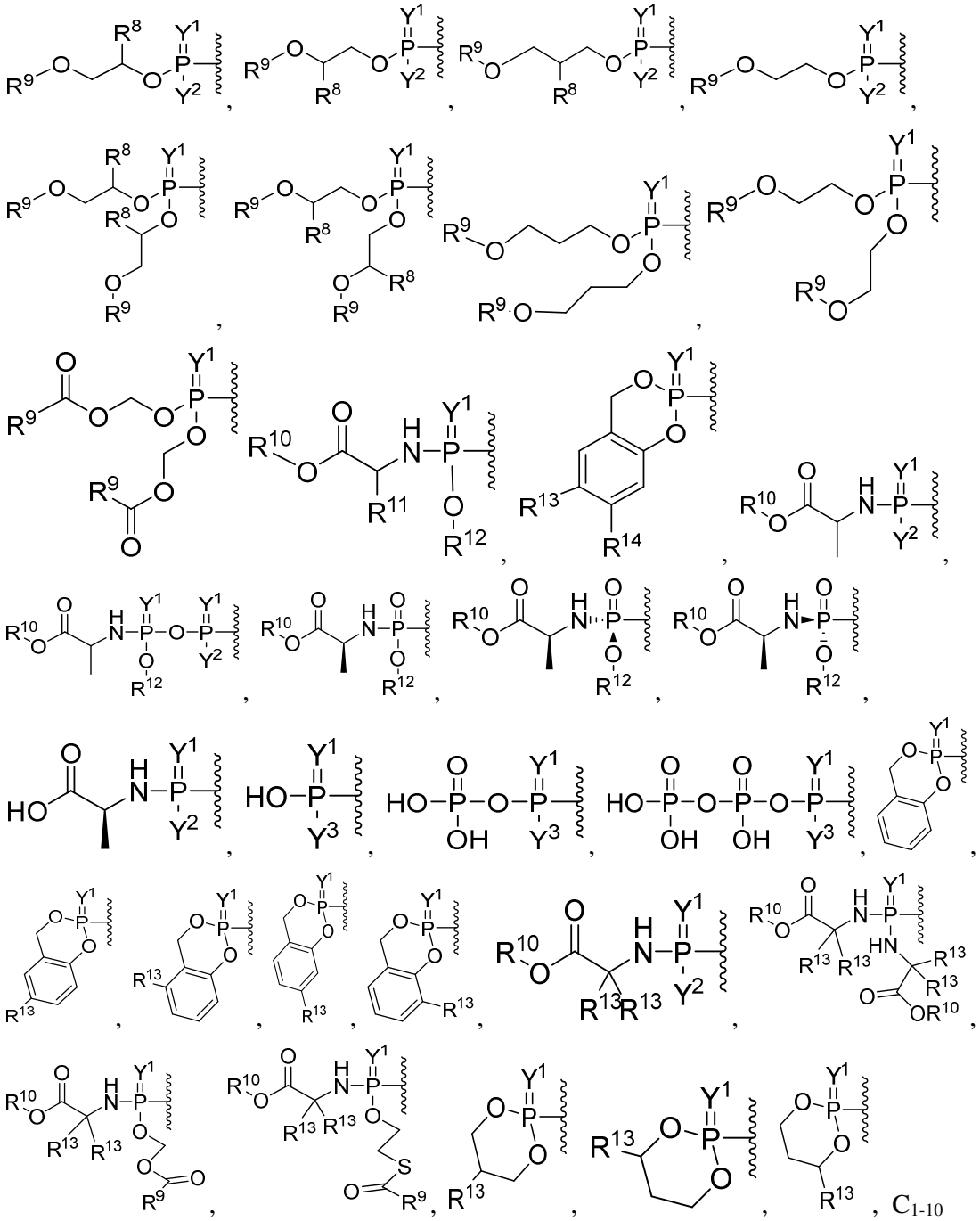
or a salt thereof, wherein

V is O, NH, or NR^{15};

X is CH_2 or CD_2;

Y is H, D, F, CH_3, CD_3, or CF_3;

R^1 is hydrogen,



alkyl, formyl, carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, C_{6-10} aryl, heterocyclyl, or phosphoramidyl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or OC_{1-2} alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6\text{-}C_{16})$alkyl, $(C_6\text{-}C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

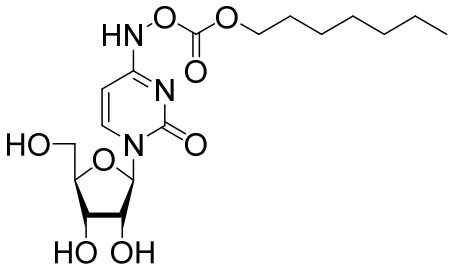
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl; and

lipid is a $C_{6\text{-}22}$ alkyl, alkoxy, polyethylene glycol, or aryl substituted with an alkyl group,

in the manufacture of a medicament for treating or preventing a human coronavirus, SARS coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

28. The use of claim 27, for treating or preventing a human coronavirus selected from SARS coronavirus or MERS coronavirus.

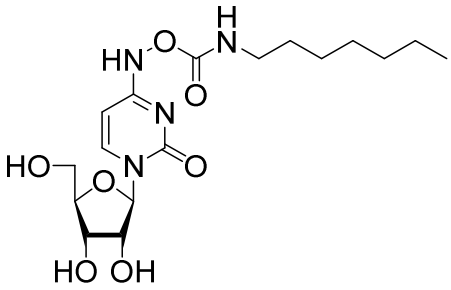
29. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

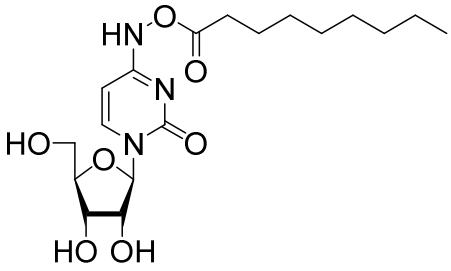
30. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

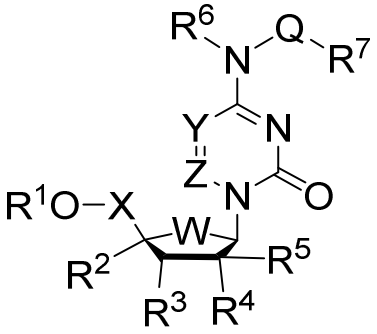
31. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing human coronavirus, MERS coronavirus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Chikungunya virus, Ross River virus infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

32. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound having Formula I



Formula I,

or salt thereof, wherein

Q is O, -O(C=O)V-, or NR^7;

V is O, NH, or NR^7;

W is O;

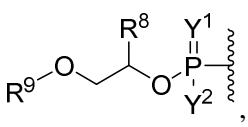
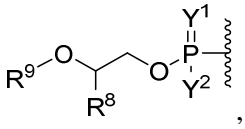
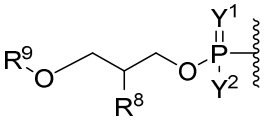
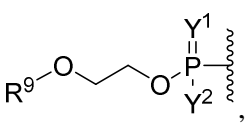
X is CH_2 or CD_2;

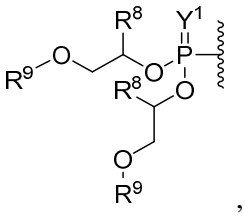
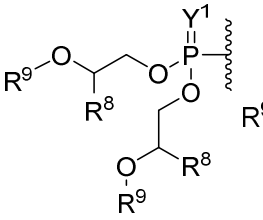
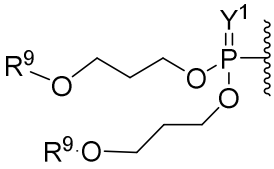
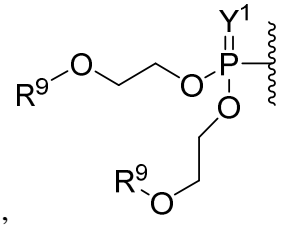
Y is CR";

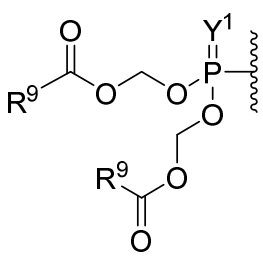
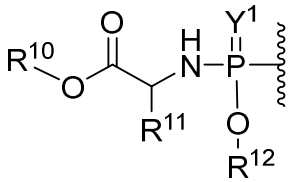
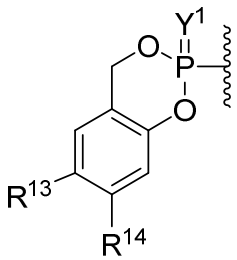
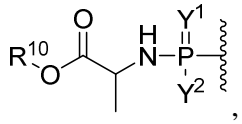
Z is CH;

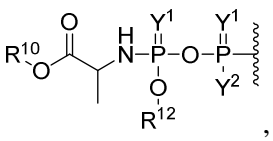
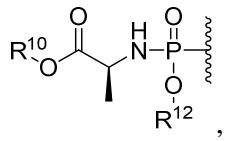
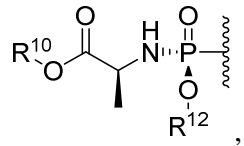
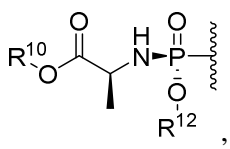
R" is selected from is H, D, F, CH_3, CD_3, or CF_3;

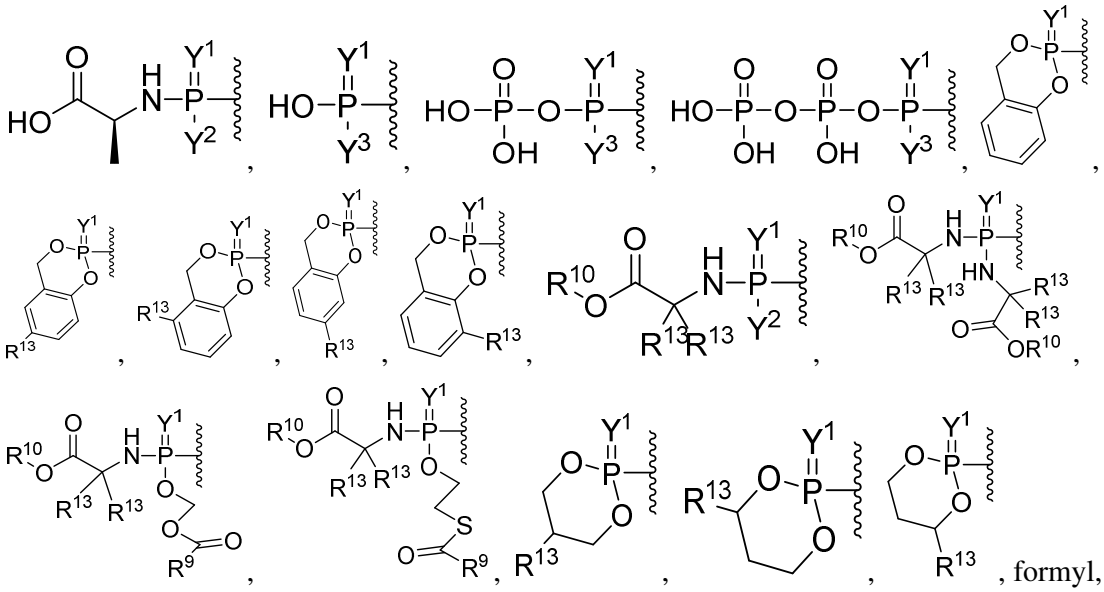
R^1 is

 ,  ,  ,  ,

 ,  ,  , 

 ,  ,  ,  ,

 ,  ,  ,  ,



carboxy, carbamoyl, carbanoyl, esteryl, carbocyclyl, C_{6-10} aryl, heterocyclyl, or phosphoramidyl, or R^1O- is selected from peptide or carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or OOC_{1-2}alkyl;

Y^3 is OH;

R^2 is hydrogen;

R^3 is hydroxy;

R^4 is hydroxy, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^5 is hydrogen, hydroxy, methoxy, methyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, or halogen;

R^6 is hydrogen;

R^7 is selected from absent, hydrogen, -(C=O)OC_{1-10} alkyl, -(C=O)NHC_{1-10} alkyl, -(C=O)N-C_{1-10} dialkyl, C_{1-10} alkyl, C_{6-22} alkyl, amino, C_{1-10} alkylamino, (C_{1-10} alkyl)$_2$amino;

R^8 is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, benzyloxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, alkyl, (C_6-C_{16})alkyl, (C_6-C_{22})alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, cycloalkyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{10} is hydrogen, alkyl, branched alkyl, cycloalkyl, lipid, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, alkyl, methyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{12} is hydrogen, alkyl, aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

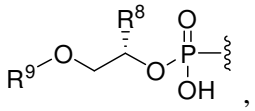
R^{14} is hydrogen, deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^{20} is deuterium, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, $C_{1\text{-}10}$ alkoxy, $C_{1\text{-}10}$ alkylthio, $C_{1\text{-}10}$ alkylamino, $(C_{1\text{-}10}$ alkyl$)_2$amino, $C_{1\text{-}10}$ alkylsulfinyl, $C_{1\text{-}10}$ alkylsulfonyl, $C_{6\text{-}12}$ arylsulfonyl, carbocyclyl, $C_{6\text{-}12}$ aryl, or heterocyclyl;

lipid is a $C_{6\text{-}22}$ alkoxy, polyethylene glycol, or aryl substituted with an alkyl group.

33. The pharmaceutical composition of claim 32, wherein Q-R^7 is OH.

34. The pharmaceutical composition of claim 32, wherein R^1 is

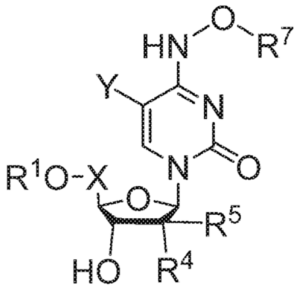


,

R^8 is hydrogen, hydroxy, or benzyloxy, and

R^9 is C_6-C_{22}alkyl.

35. The pharmaceutical composition of claim 32, wherein the compound has a structure according to Formula IA



Formula IA,

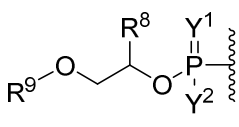
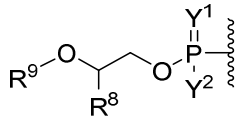
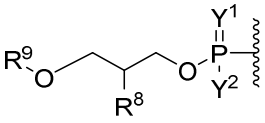
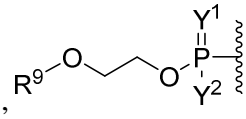
or salt thereof, wherein

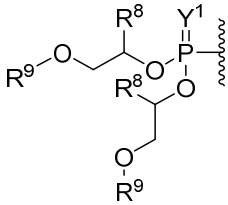
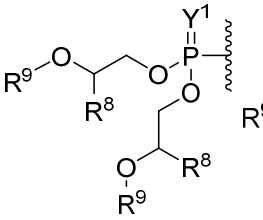
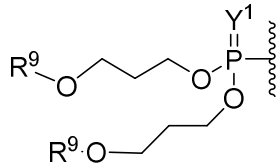
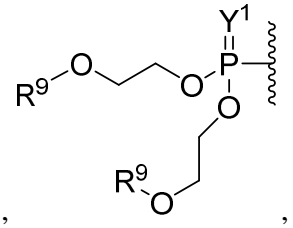
R^7 is H,

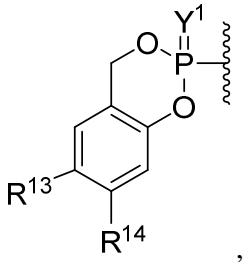
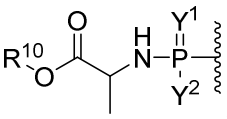
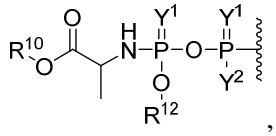
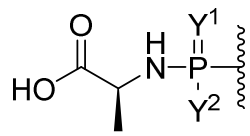
X is CH_2 or CD_2;

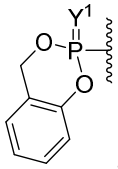
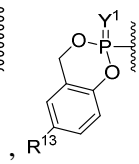
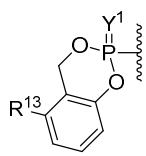
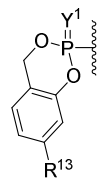
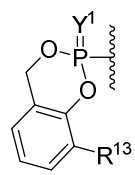
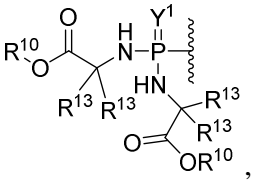
Y is independently selected from is H, D, F, or CH_3;

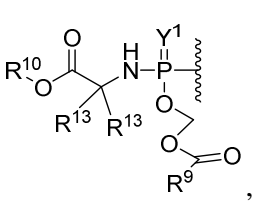
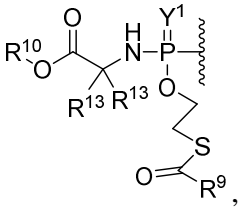
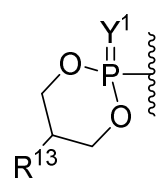
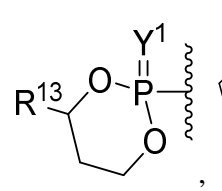
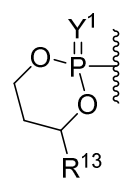
R^1 is

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,  , ,  ,

 ,  ,  ,  ,  , formyl, carboxy, or esteryl, or R^1O- is selected from carboxylic acid ester, wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O;

Y^2 is OH, OR^{12}, or OC_{1-2}alkyl;

Y^3 is OH;

R^4 is hydroxy, methyl, halogen, or fluoro;

R^5 is hydrogen, hydroxy, methoxy, methyl, or ethynyl;

R^8 is hydrogen, deuterium, C_1 alkyl, hydroxy, benzyloxy, carboxy, carbamoyl, azido, C_1 alkoxy, C_1 alkylamino, $(C_1$ alkyl$)_2$amino, carbocyclyl, C_{6-10} aryl, or heterocyclyl;

R^9 is hydrogen, methyl, ethyl, tert-butyl, C_{1-10} alkyl, C_{6-22} alkyl, cycloalkyl, C_{1-10} alkoxy, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

R^{10} is hydrogen, C_{1-10} alkyl, branched C_{1-10} alkyl, cycloalkyl, lipid methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, butyl, pentyl, hexyl, neopentyl, benzyl, C_{1-10} alkoxy, C_{6-12} aryl, or heterocyclyl;

R^{11} is hydrogen, deuterium, C_{1-10} alkyl, methyl, hydroxy, C_{1-10} alkoxy, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

R^{12} is hydrogen, C_{1-10} alkyl, C_{6-12} aryl, phenyl, 1-naphthyl, 2-naphthyl, aromatic, heteroaromatic, 4-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, naphthyl, or heterocyclyl;

R^{13} is hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, lipid, azido, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{6-12} arylsulfonyl, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

R^{20} is deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylamino, $(C_{1-10}$ alkyl$)_2$amino, C_{1-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, C_{6-12} arylsulfonyl, carbocyclyl, C_{6-12} aryl, or heterocyclyl;

lipid is a C_{6-22} alkyl, C_{6-22} alkoxy, polyethylene glycol, or C_{6-12} aryl substituted with a C_{1-10} alkyl group.

36. The pharmaceutical composition of claim 35, wherein

Y is selected from is H, F, or CH_3;

R^1 is carboxy or esteryl, wherein R^1 is optionally substituted with one or more, the same or different, R^{20}, or

R^1O- is selected from carboxylic acid ester.

37. The pharmaceutical composition of claim 35, wherein R^4 is hydroxy and R^5 is hydrogen.