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

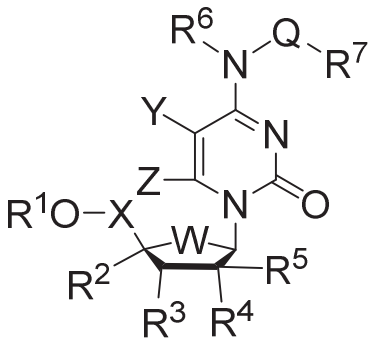
The causative agents for Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE and VEE, respectively) and Chikungunya fever (CHIK) are vector-borne viruses (family *Togaviridae*, genus *Alphavirus*) that can be transmitted to humans through mosquito bites. The equine encephalitis viruses are 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,



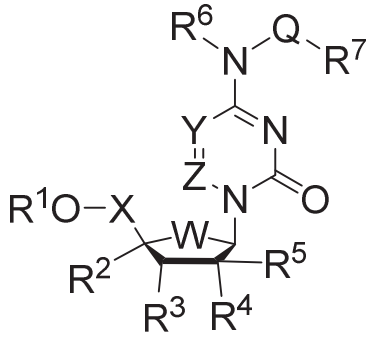
Formula I

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 one aspect, the present disclosure refers to use of a pharmaceutical composition in the manufacture of a medicament for treating or preventing 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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

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

Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is monophosphate, diphosphate, triphosphate,

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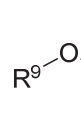
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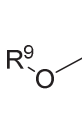
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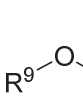
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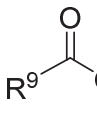
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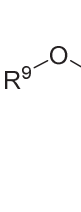
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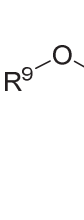
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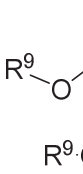
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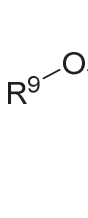
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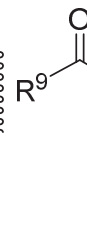
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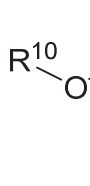
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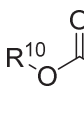
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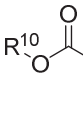
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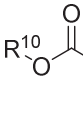
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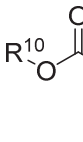
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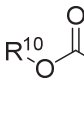
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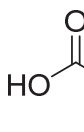
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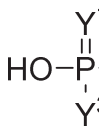
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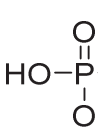
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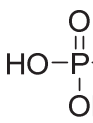
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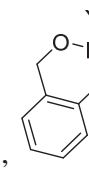
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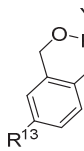
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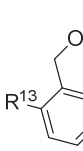
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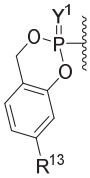
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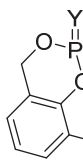
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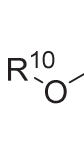
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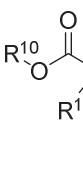
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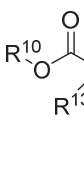
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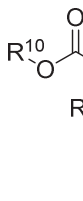
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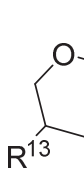
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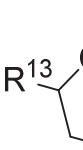
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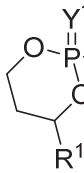
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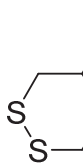
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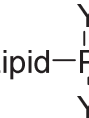

, alkyl, halogen,

nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, -(C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

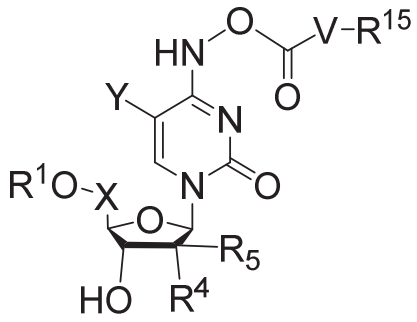
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

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



Formula IB,

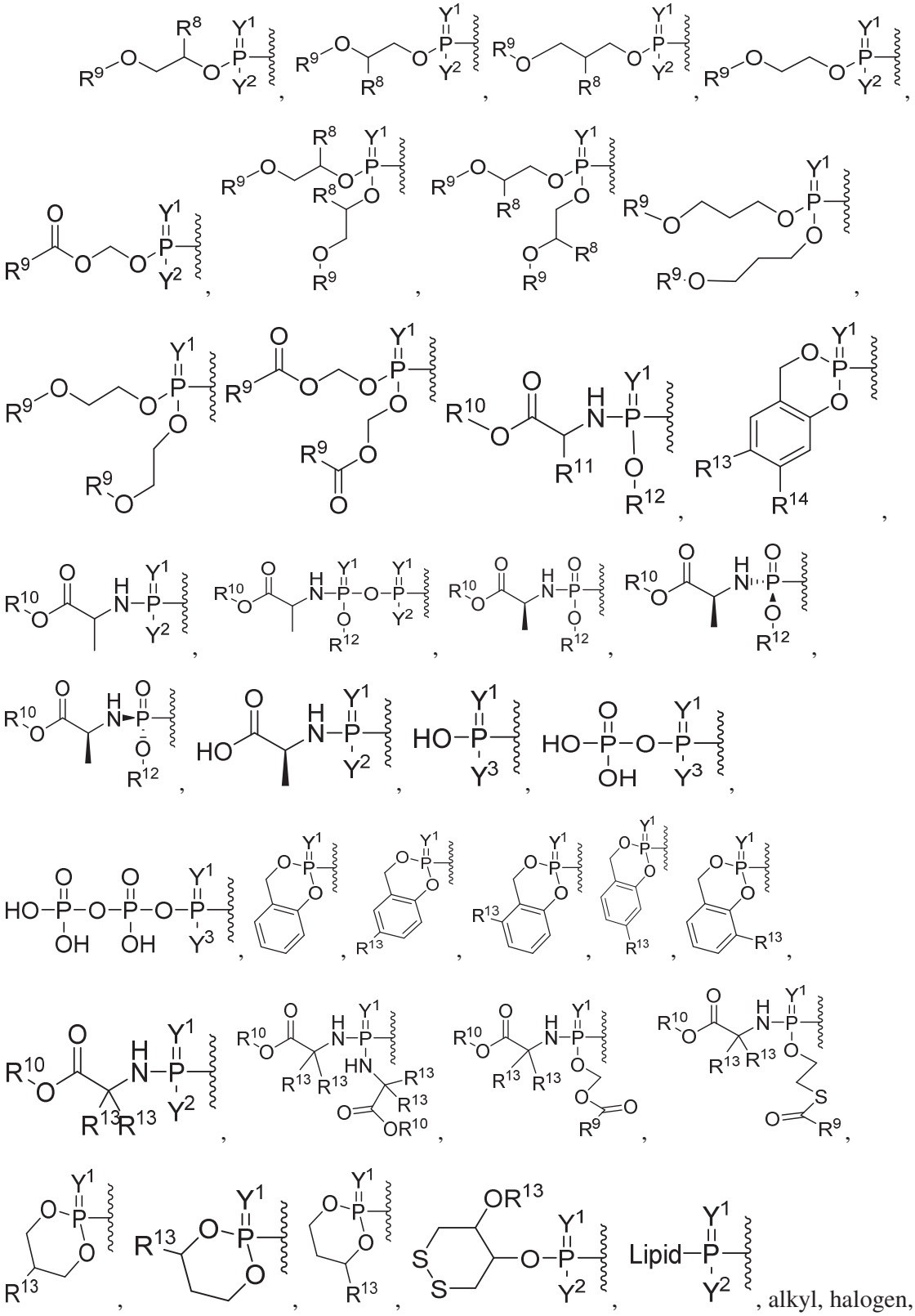
or salts thereof, wherein

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

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

Y is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is hydrogen, monophosphate, diphosphate, triphosphate,



, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl,

carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

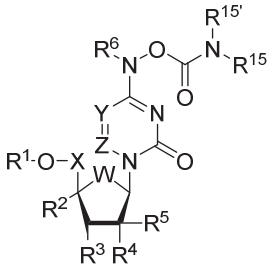
R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

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



Formula ID,

or salt thereof, wherein

W is CH_2, NH, S or O;

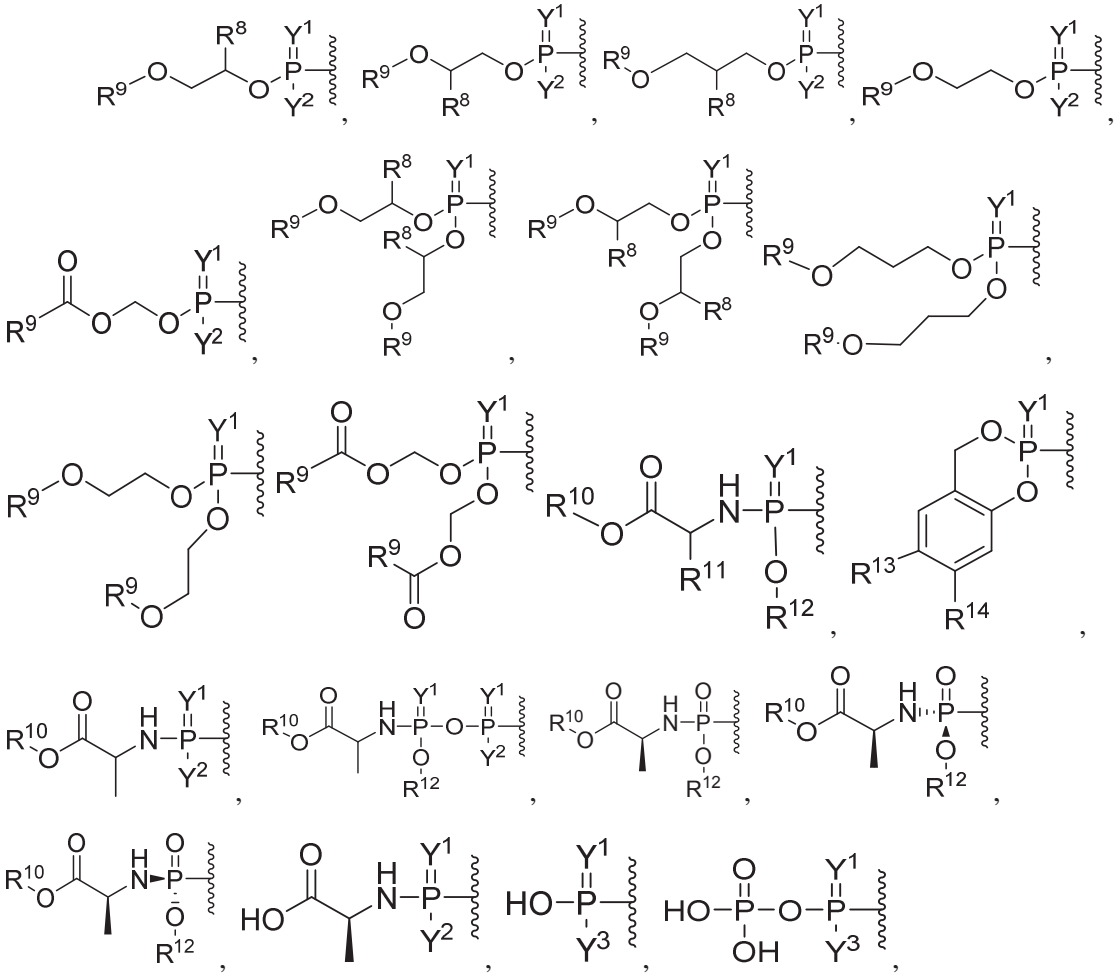
X is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

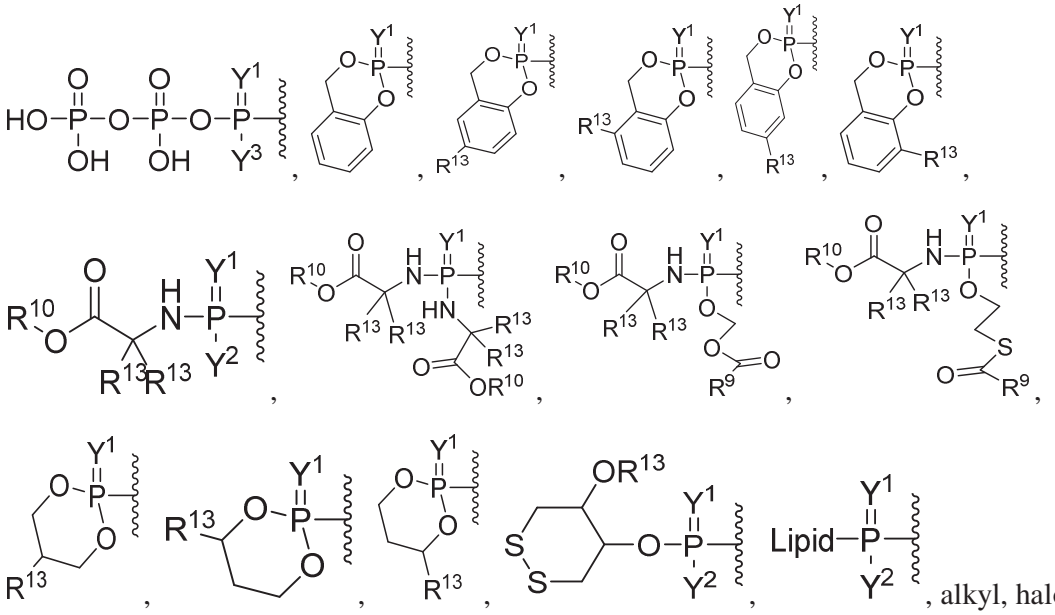
Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is hydrogen, monophosphate, diphosphate, triphosphate,





, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino,

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

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

$R^{15'}$ 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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

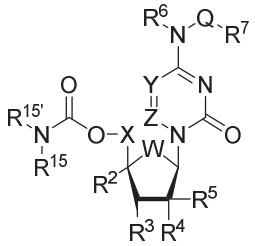
R^{15} and $R^{15'}$ can form a ring that is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

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

Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, -(C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

$R^{15'}$ 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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

R^{15} and $R^{15'}$ can form a ring that is optionally substituted with one or more, the same or different, R^{20};

If Q = -O(C=O)V- and V = NR^7 then the R^7s can together form a ring that is optionally substituted with one or more, the same or different, R^{20};

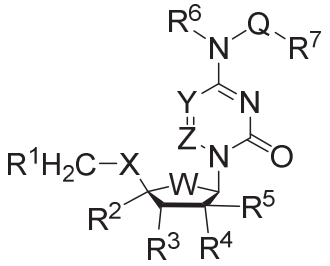
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

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 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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

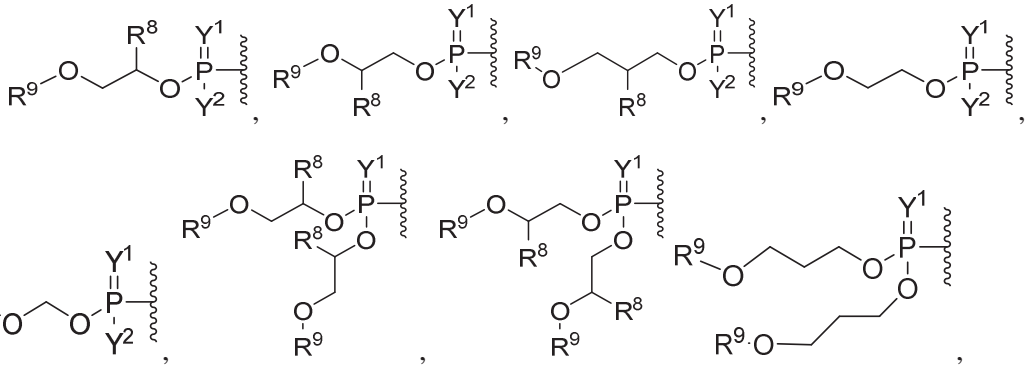
X is CH_2 or O;

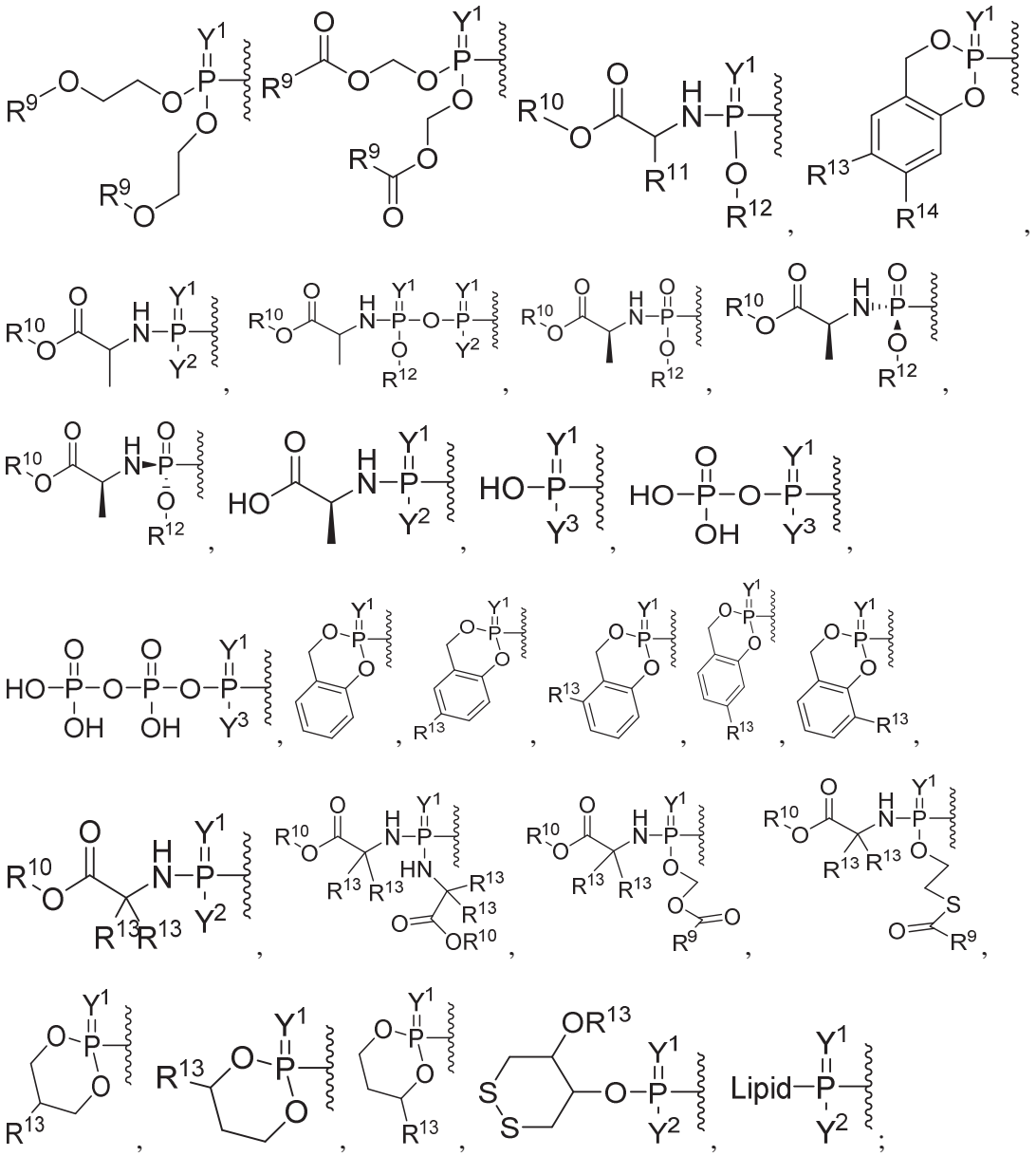
Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is diphosphate, triphosphate,





Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, (C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

If Q = -O(C=O)V- and V = NR^7 then the R^7s can together form a ring that is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

In one example, there is provided a pressurized container comprising a pharmaceutical composition as described herein. 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,

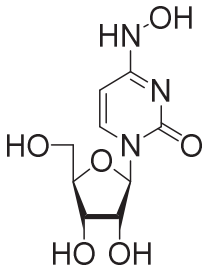
Venezuelan equine encephalitis virus, Ross River virus, Powassan virus, Barmah Forest virus and Chikungunya virus.

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.

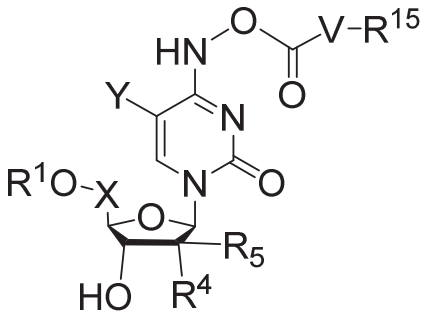
In one aspect, the present disclosure refers to use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating or preventing a viral infection in a subject in need thereof.

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



in the manufacture of a medicament for treating or preventing Ross River virus infection or filoviridae virus or Ebola virus infection in a patient in need thereof.

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

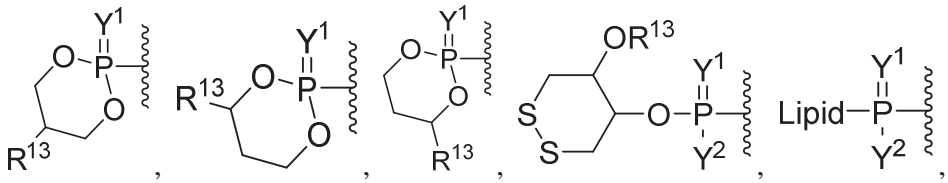


Formula IB,

or a salt thereof, wherein

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

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


, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

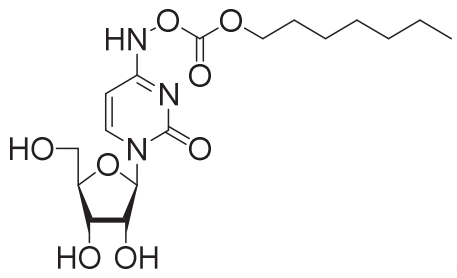
R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

Lipid is a C_{6-22} 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, and Ross River infection, or influenza virus, filoviridae virus or Ebola virus infection in a patient.

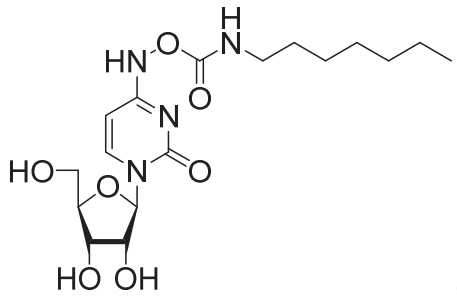
In one aspect, the present disclosure refers to use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing 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.

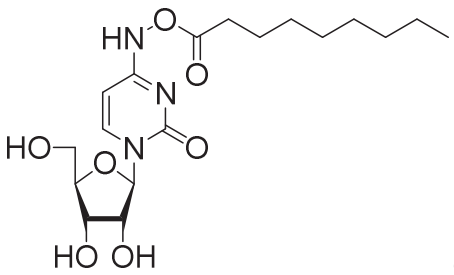
In one aspect, the present disclosure refers to use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing 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 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 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.

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

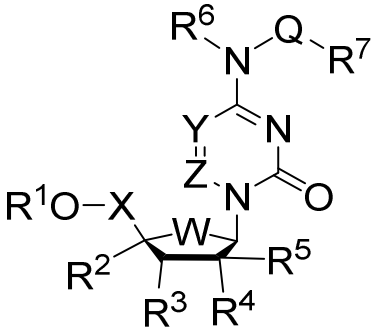
Figure 8 shows reduction of CHIKV RNA copies by PCR in CHIKV challenged mice treated with EIDD-01931

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 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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

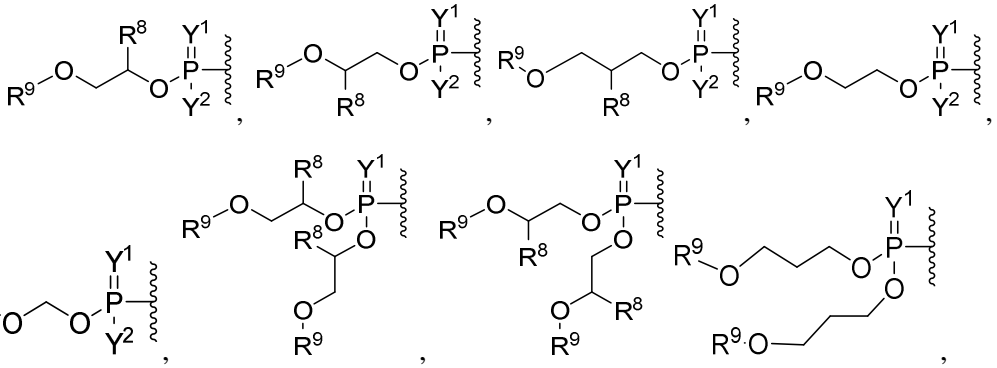
X is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

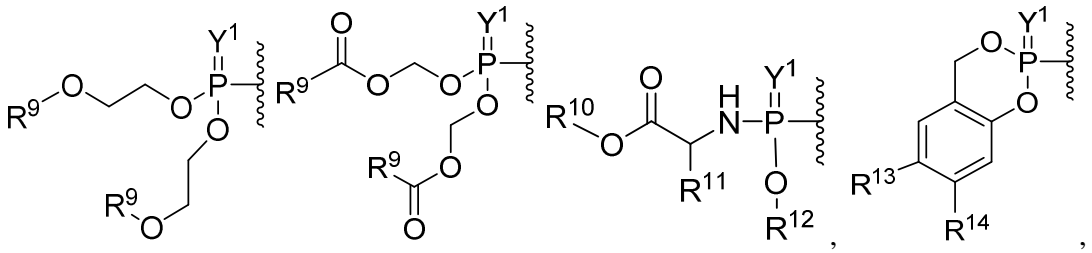
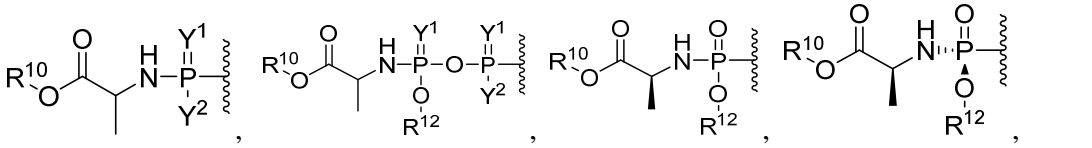
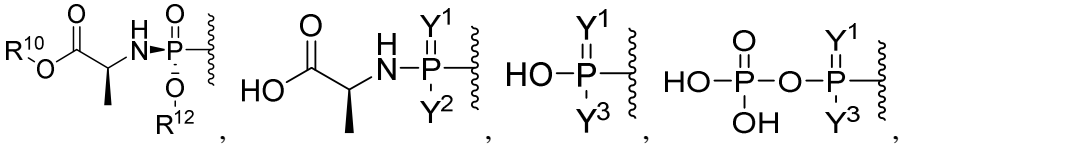
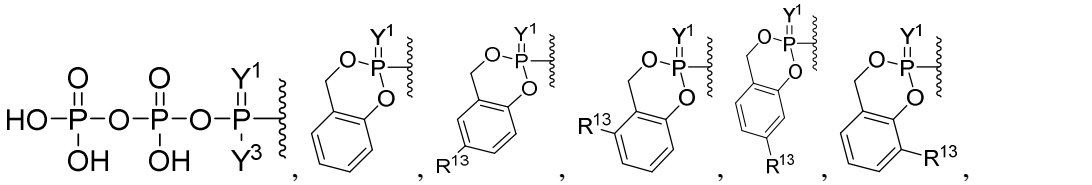
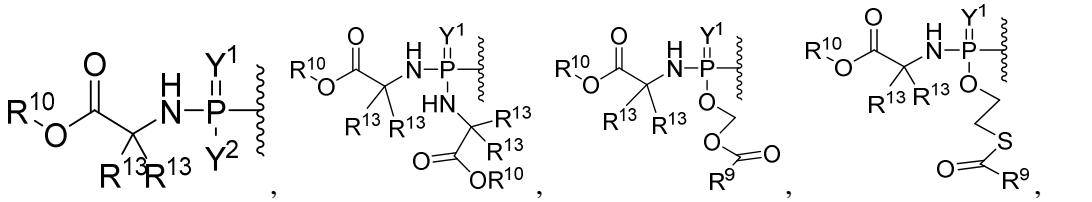
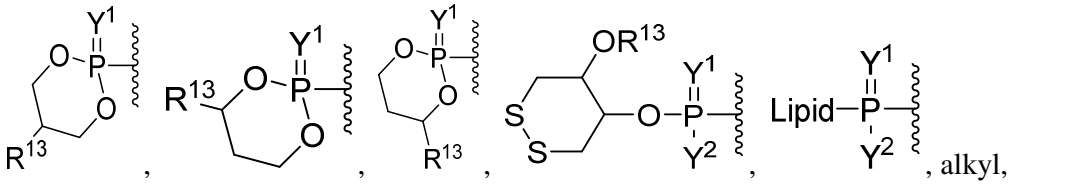
Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is monophosphate, diphosphate, triphosphate,



halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino,

alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, -(C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

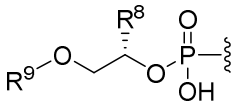
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl,

ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

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

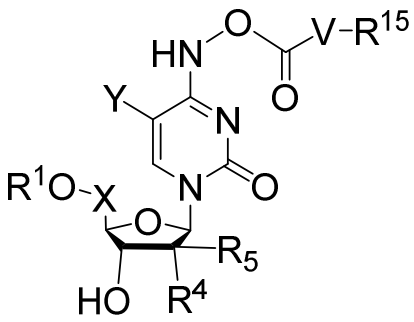


,

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

R^9 is $(C_6\text{-}C_{22})$alkyl.

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



Formula IB,

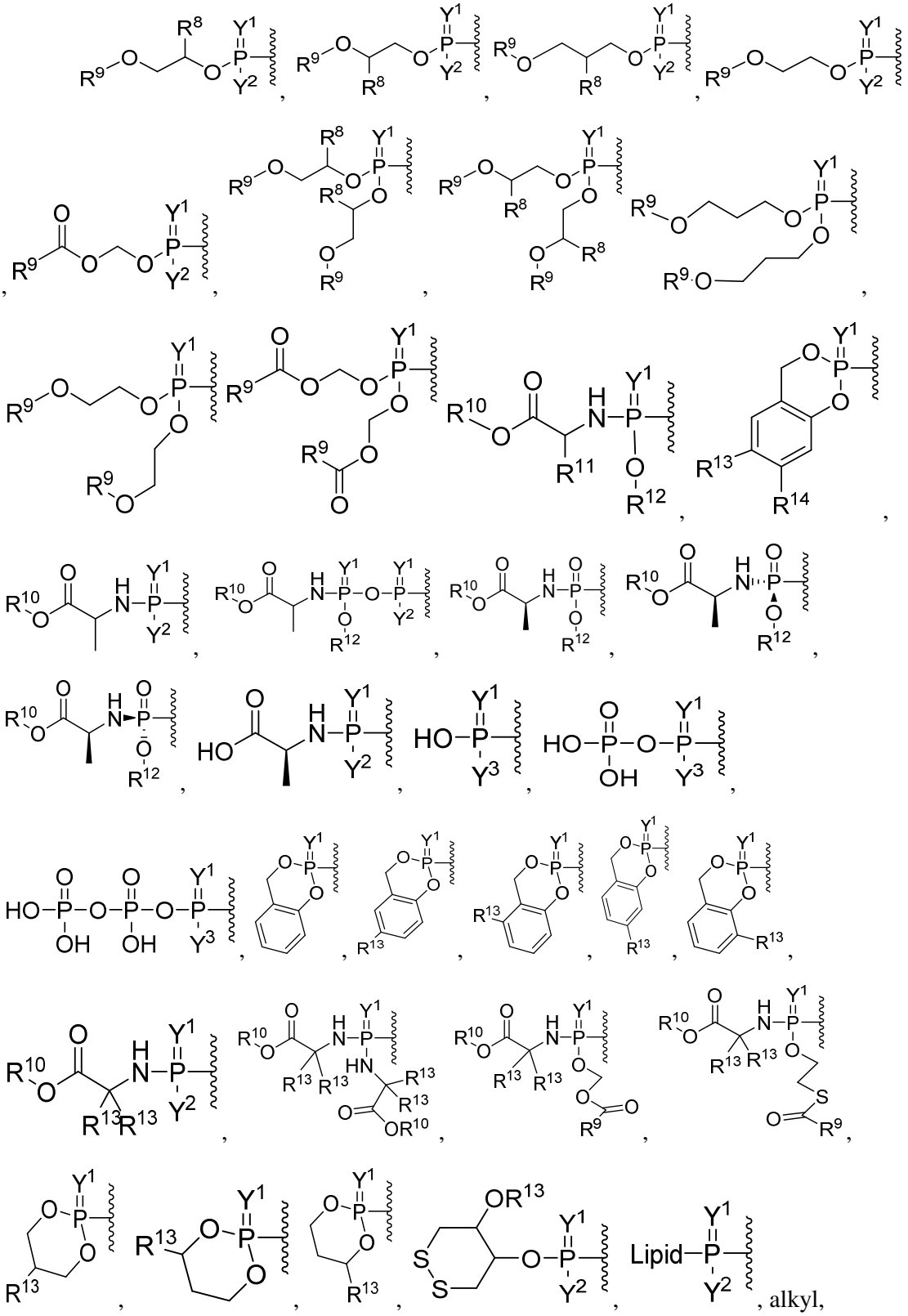
or salts thereof, wherein

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

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

Y is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is hydrogen, monophosphate, diphosphate, triphosphate,



halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl,

arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

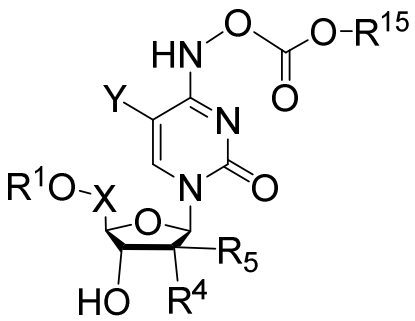
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

4. The 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,



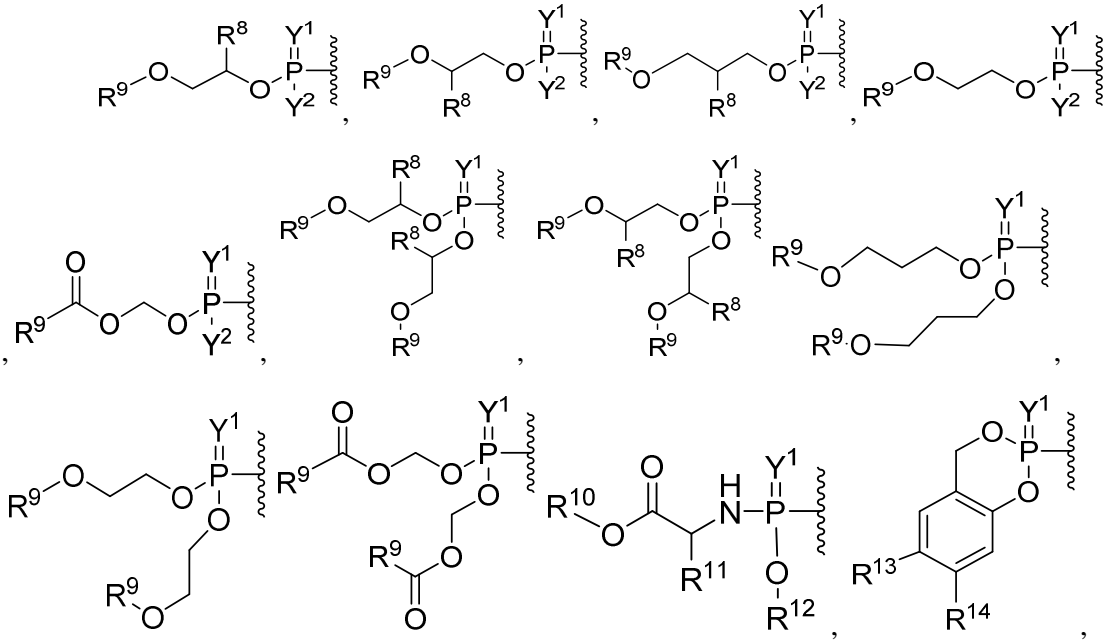
Formula IC,

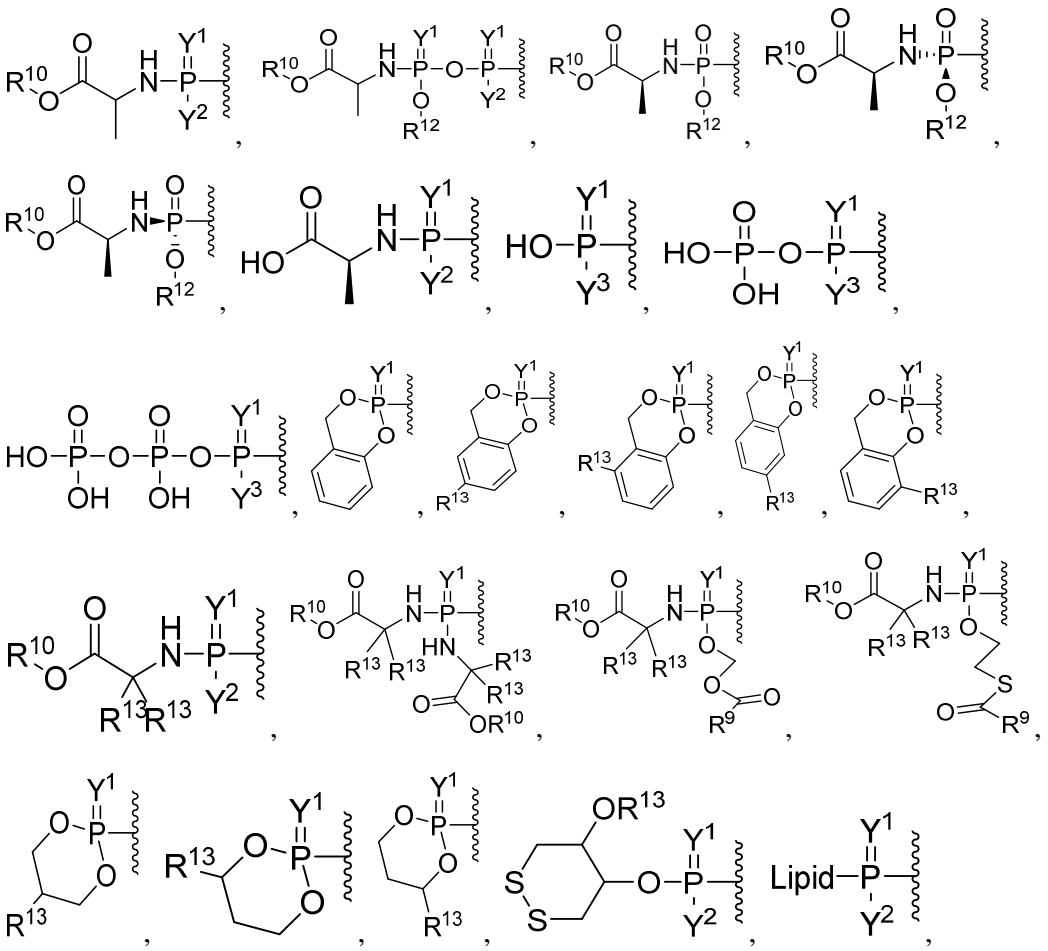
or salts thereof, wherein

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

Y is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is, monophosphate, diphosphate, triphosphate,





phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

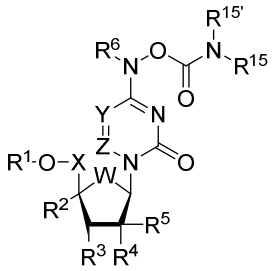
R^{15} is hydrogen, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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 CH_2, NH, S or O;

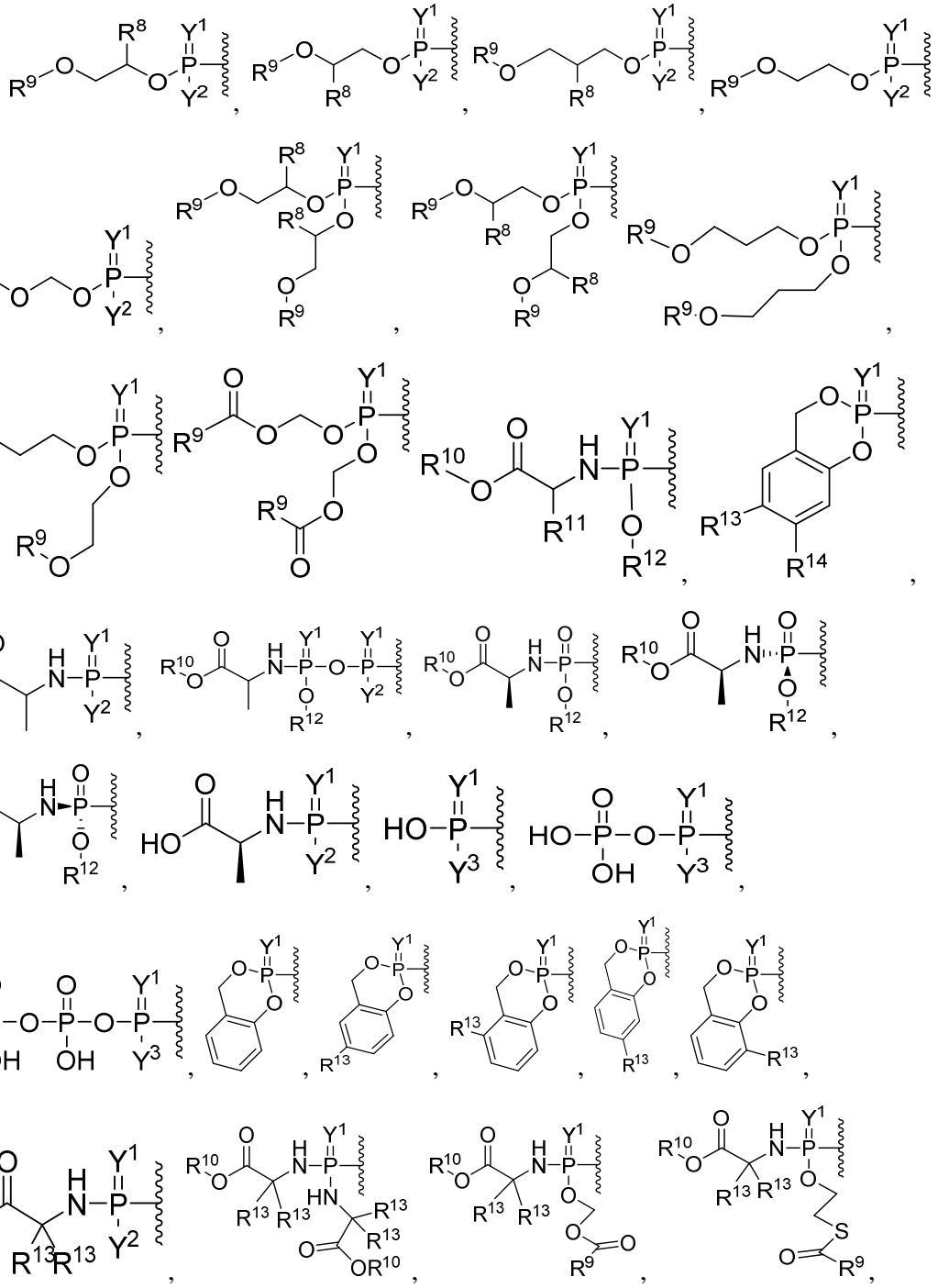
X is CH_2, CHMe, CMe_2, CHF, CF_2, or CD_2;

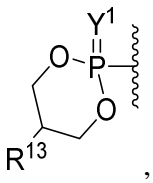
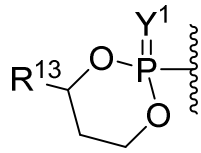
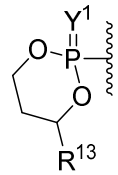
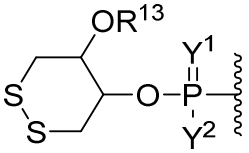
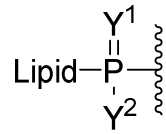
Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is hydrogen, monophosphate, diphosphate, triphosphate,



 ,  ,  ,  ,  , alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

$R^{15'}$ 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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

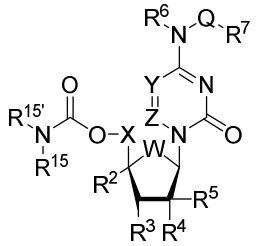
R^{15} and $R^{15'}$ can form a ring that is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

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

Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino,

alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, -(C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

$R^{15'}$ 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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

R^{15} and $R^{15'}$ can form a ring that is optionally substituted with one or more, the same or different, R^{20};

If Q = -O(C=O)V- and V = NR^7 then the R^7s can together form a ring that is optionally substituted with one or more, the same or different, R^{20};

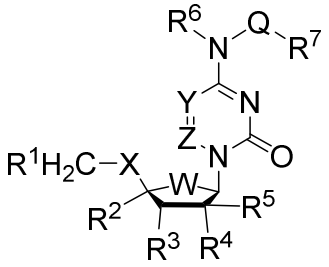
R^{20} is deuterium, alkyl, alkenyl, alkynyl, halogen, nitro, cyano, hydroxy, amino, amido, mercapto, formyl, carboxy, carbamoyl, azido, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-

diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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)Lipid, -O(C=O)V-, NH, or NR^7;

V is O, NH, NR^7, S, CH_2, or CHR^7;

W is CH_2, NH, S or O;

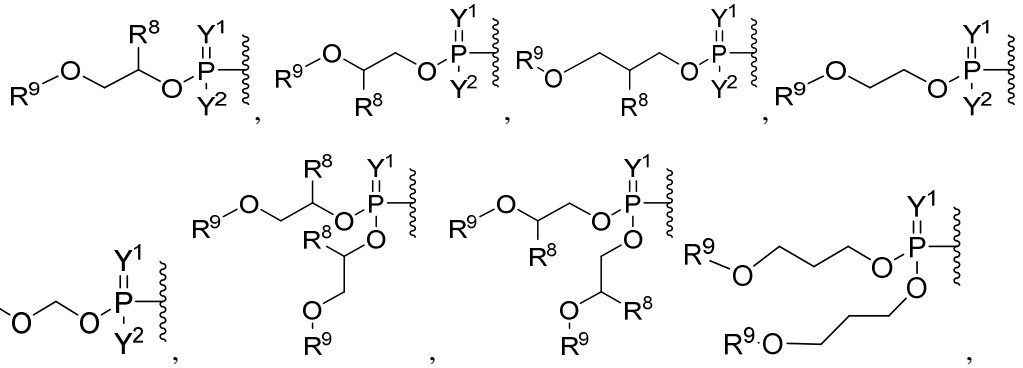
X is CH_2 or O;

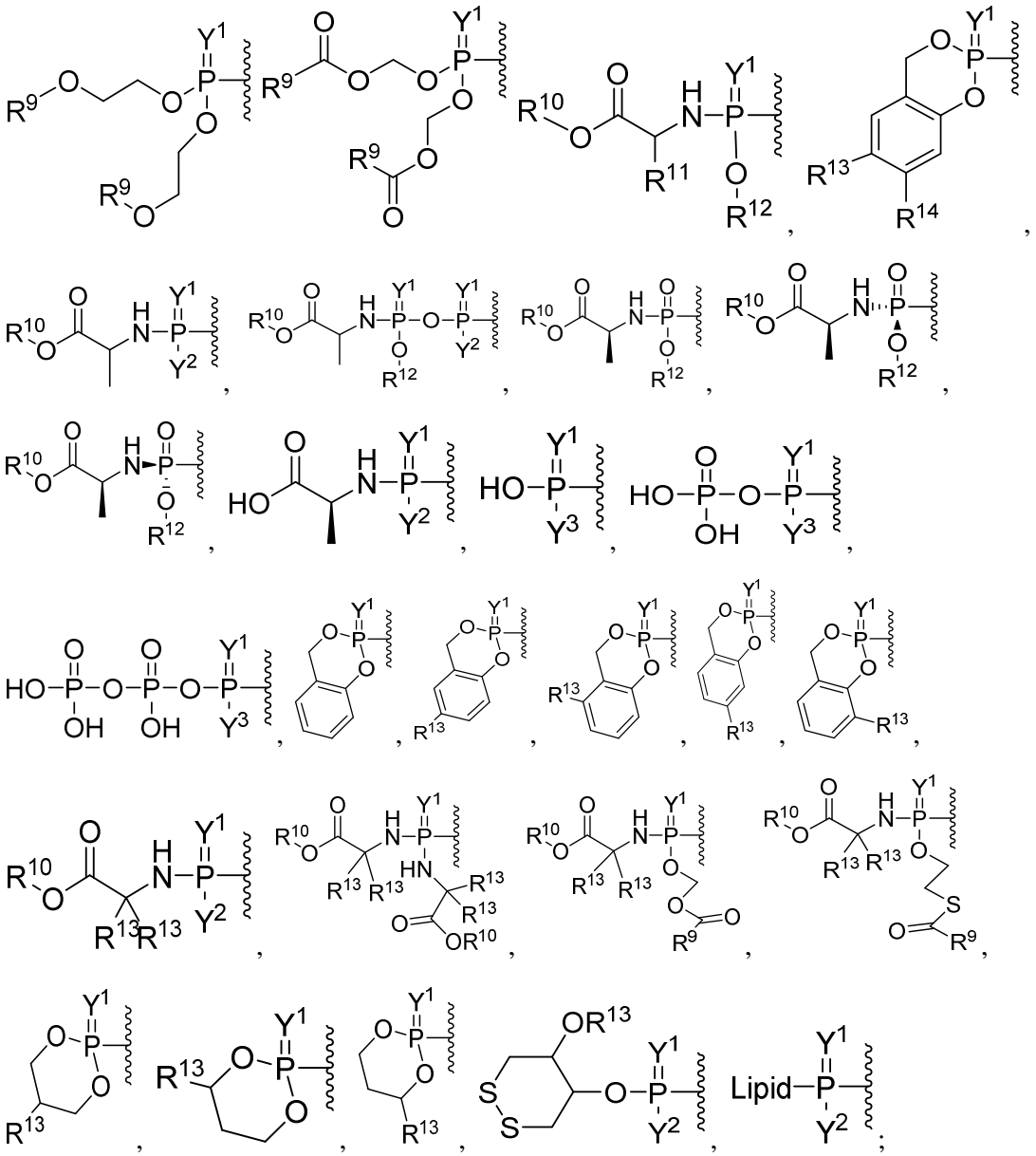
Y is N or CR";

Z is N or CR";

each R" is independently selected from is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is diphosphate, triphosphate,





Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^2 is hydrogen, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, azido, or heterocyclyl;

R^3 is hydrogen, hydroxy, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl,

alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^6 is hydrogen, hydroxy, alkoxy, alkyl, ethynyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

each R^7 is independently selected from absent, (C=O)Oalkyl, -(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, wherein each R^7 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

If Q = -O(C=O)V- and V = NR^7 then the R^7s can together form a ring that is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl,

N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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

9. The use of the pharmaceutical composition of claim 1 or claim 8, wherein the pharmaceutical composition further comprises a propellant.

10. The use of 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 of the pharmaceutical composition of claim 1, wherein when administered, the composition is to be administered from a pressurized container comprising a pharmaceutical composition of claim 1.

12. The use 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.

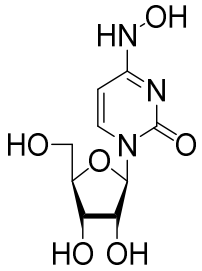
13. Use of a pharmaceutical composition as defined in claim 8 in the manufacture of a medicament for treating or preventing a viral infection in a subject in need thereof.

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

15. 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.

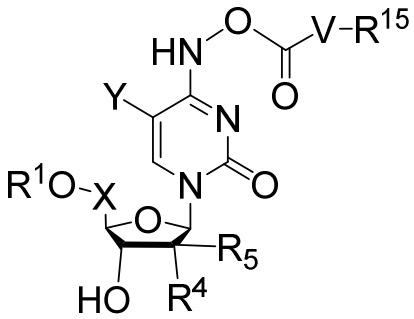
16. The use of claim 1 wherein the compound is to be administered through the lungs.

17. Use of a compound with the structure:



in the manufacture of a medicament for treating or preventing Ross River virus infection or filoviridae virus or Ebola virus infection in a patient in need thereof.

18. Use of a compound with the formula:



Formula IB,

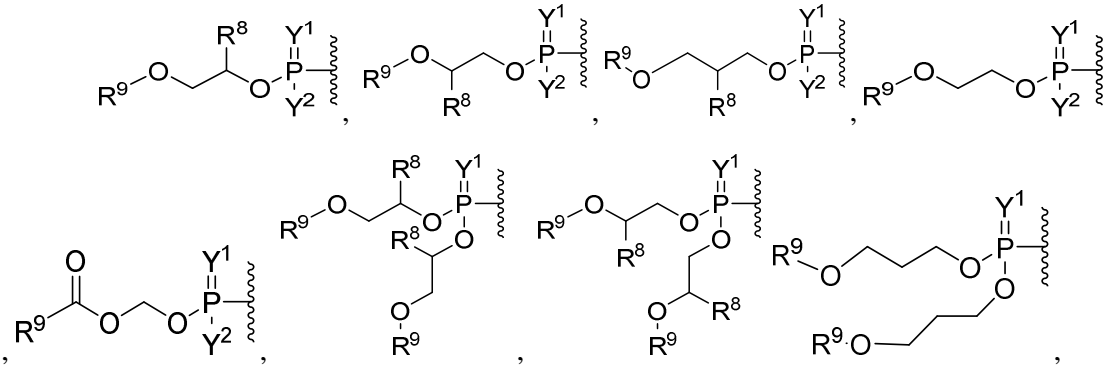
or a salt thereof, wherein

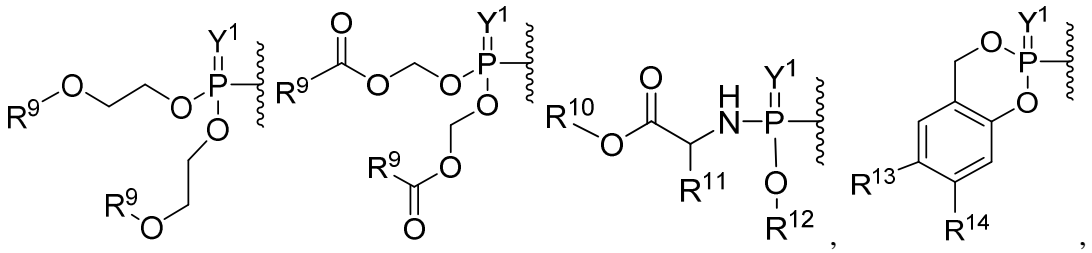
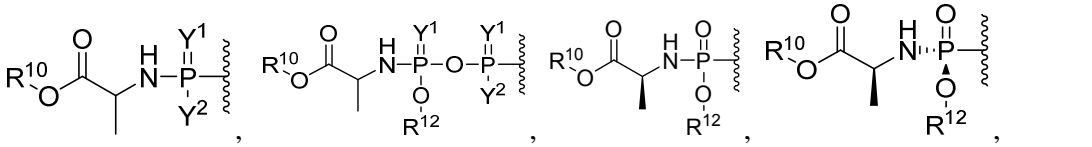
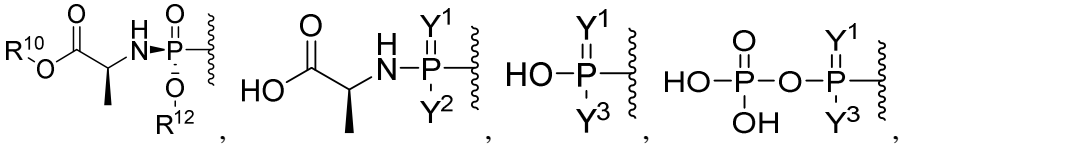
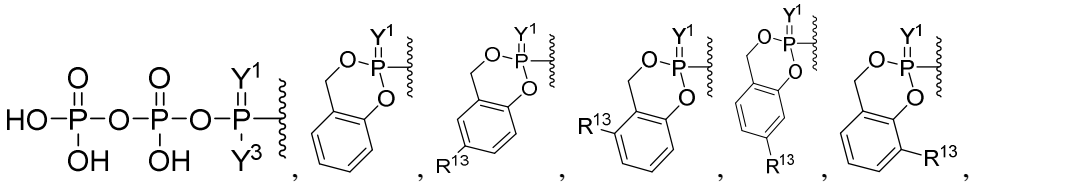
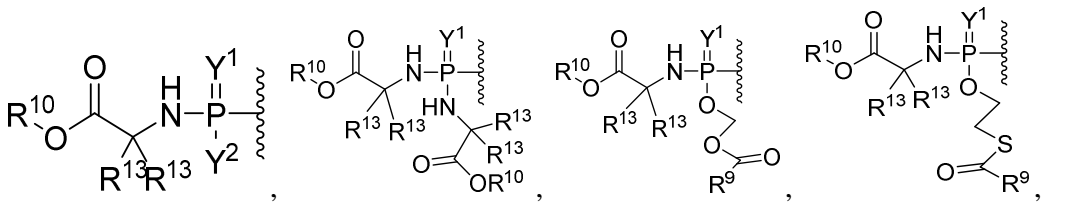
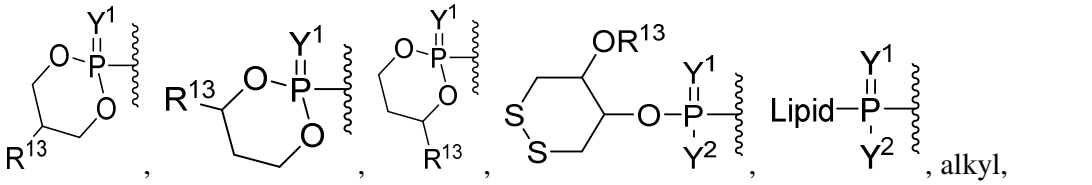
V is O, NH, NR^{15} or S;

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

Y is H, D, F, Cl, Br, I, CH_3, CD_3, CF_3, alkyl, acyl, alkenyl, alkynyl, hydroxyl, formyl or SCH_3;

R^1 is hydrogen, monophosphate, diphosphate, triphosphate,



halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, carbanoyl, esteryl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, phosphoramidyl, or phosphate wherein R^1 is optionally substituted with one or more, the same or different, R^{20};

Y^1 is O or S;

Y^2 is OH, OR^{12}, OAlkyl, or $BH_3^-M^+$;

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

R^4 is hydrogen, hydroxy, alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl,

arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

R^5 is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, ethynyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, allenyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl;

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, wherein R^8 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^9 is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{10} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{11} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{12} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{13} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{14} is optionally substituted with one or more, the same or different, R^{20};

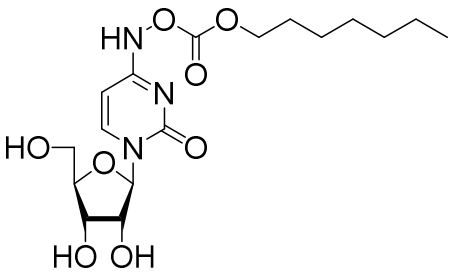
R^{15} is hydrogen, Lipid, -(C=O)Oalkyl, -(C=O)alkyl, -(C=O)NHalkyl, -(C=O)N-dialkyl, -(C=O)Salkyl, hydroxy, alkoxy, alkyl, $(C_6$-$C_{16})$alkyl, $(C_6$-$C_{22})$alkyl, halogen, nitro, cyano, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{20};

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, wherein R^{20} is optionally substituted with one or more, the same or different, R^{21}; and

R^{21} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

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.

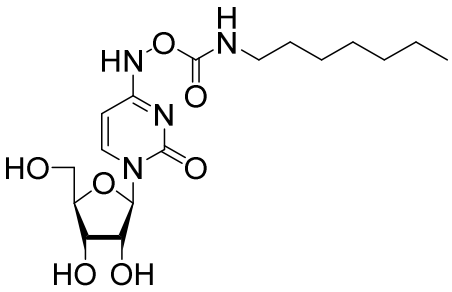
19. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing 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.

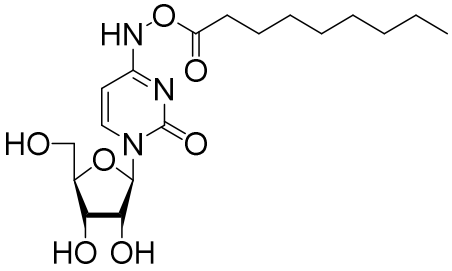
20. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing 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.

21. Use of a compound with the formula:



or a salt thereof

in the manufacture of a medicament for treating or preventing 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.

22. The use of claim 1, for treating or preventing chikungunya, Venezuelan equine encephalitis virus (VEEV), or MERS coronavirus.

23. 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.