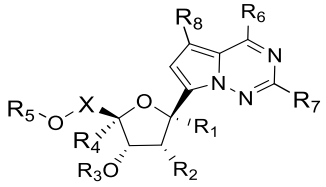
Claims

1. A compound of formula (I), or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof:



(I)

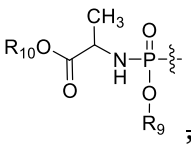
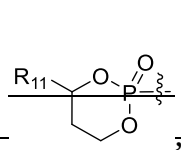
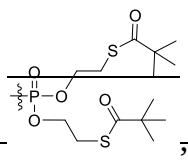
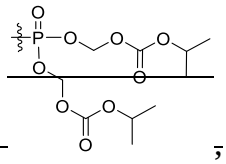
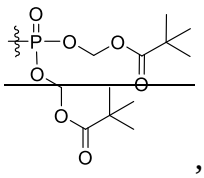
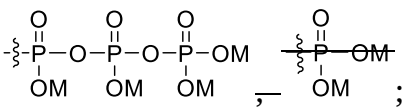
wherein,

R_1 is selected from hydrogen, deuterium~~, halogen~~, cyano~~, azido, amino, amino substituted with C_{1-6}alkyl~~, C_{1-6}acyl~~, C_{1-6}alkyl, C_{1-6}alkoxy, amino substituted with C_{1-6}alkanoyl, halogenated C_{1-6}alkyl~~, C_{2-6}alkenyl~~, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{2-6}alkynyl~~, C_{3-6}cycloalkyl~~, halogenated C_{3-6}cycloalkyl~~, carbamoyl, hydroxymethyl~~, cyanomethyl (-CH_2CN), guanyl, guanidyl, carbamido, thiocyanato (-SCN), cyanato (-OCN)~~;

R_2 is selected from ~~hydrogen, halogen, OR$_3$, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

R_3 is selected from hydrogen, C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl, C_{1-6}alkyl amino-C_{1-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, α-amino acid, and the carboxyl of the α-amino acid is attached to the hydroxyl on the furan ring via ester bond;

R_4 is selected from hydrogen, deuterium, halogen~~, azido, cyano, C_{1-6}alkyl, halogenated C_{1-6}alkyl, azidoC_{1-6}alkyl, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl, guanyl, guanidyl, carbamido, thiocyanato, cyanato~~;

R_5 is selected from R_3, , , , , , ;

R_6 is selected from amino, hydroxy~~, halogen, cyano, cyanato, thiocyanato, C_{1-6}alkoxy, C_{1-6}alkylamino~~, NHOH~~, NHCOR$_{12}$, NHOCOR$_{12}$~~, NHCOOR$_{12}$;

R_7 is selected from hydrogen, deuterium, halogen~~, amino, methyl, NHCOR$_{12}$, NHCOOR$_{12}$~~;

R_8 is selected from hydrogen, deuterium, halogen, cyano~~, carbamoyl, carbamoyl substituted with C_{1-6}alkyl, C_{1-6}alkoxyamido, C_{1-6}alkoxycarbonyl, hydroxy, hydroxyC_{1-6}alkyl, amino, amino substituted with C_{1-6}alkanoyl, amino substituted with C_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

X is selected from $-CH_2-$, $-CD_2-$~~, -CHD -~~;

R_9 is ~~selected from C_{1-6}alkyl, C_{3-6}cycloalkyl,~~ C_{6-20}aryl~~, 5-15 membered heteroaryl~~;

R_{10} is ~~selected from~~ C_{1-18}alkyl~~, methyleneC_{6-20}aryl~~;

~~R_{11} is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-20}aryl, 5-15 membered heteroaryl;~~

R_{12} is ~~selected from~~ C_{1-20}alkyl;

M is each independently selected from hydrogen, metal, ~~$-NH_4$,~~ or protonated organic amines.

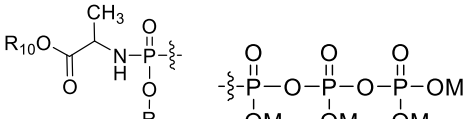
2. The compound of formula (I) of claim 1, or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof, wherein,

R_1 is cyano;

R_2 is selected from OR_3, C_{1-6}alkoxy;

R_3 is selected from hydrogen, C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl, C_{1-6}alkylamino-C_{1-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, α-amino acid, and the carboxyl of the α-amino acid is attached to the hydroxyl on the furan ring via ester bond;

R_4 is hydrogen;

R_5 is selected from R_3, ;

R_6 is amino;

R_7 is hydrogen;

R_8 is selected from hydrogen, deuterium, halogen, cyano;

X is selected from $-CH_2-$, $-CD_2-$;

R_9 is C_{6-20}aryl;

R_{10} is C_{1-18}alkyl;

M is each independently selected from hydrogen, metal, or protonated organic amines.

3. The compound of formula (I) of claim 1, or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof, wherein,

R_1 is cyano;

R_2 is selected from OR_3, C_{1-6}alkoxy;

R_3 is selected from hydrogen, C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl;

R_4 is hydrogen;

R_5 is selected from C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl;

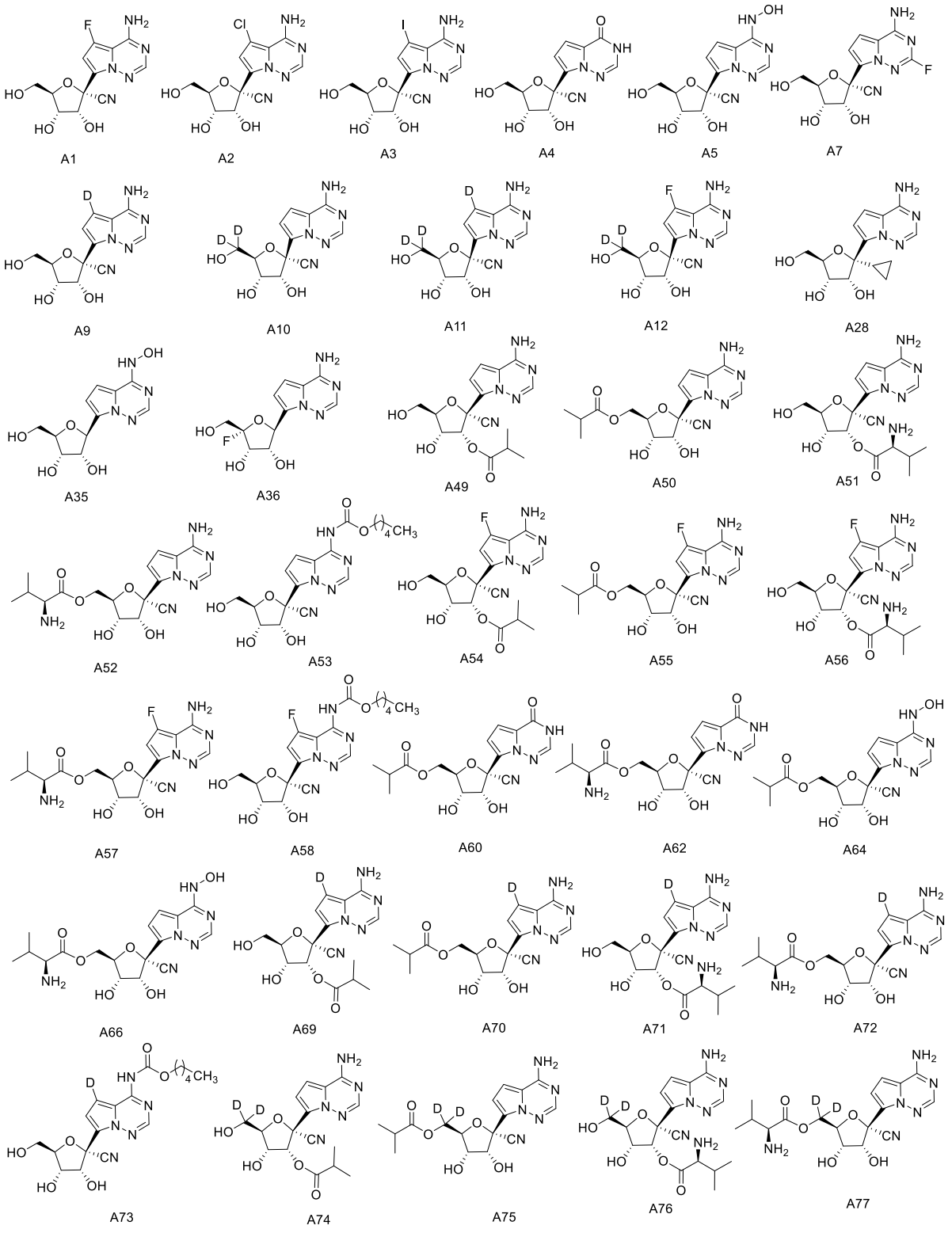
R_6 is amino;

R_7 is hydrogen;

R_8 is selected from hydrogen, deuterium, halogen;

X is selected from $-CH_2-$, $-CD_2-$.

4. The compound of formula (I) claim 1, or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof, wherein the compound is any one of compounds selected from the following group, or the combination thereof: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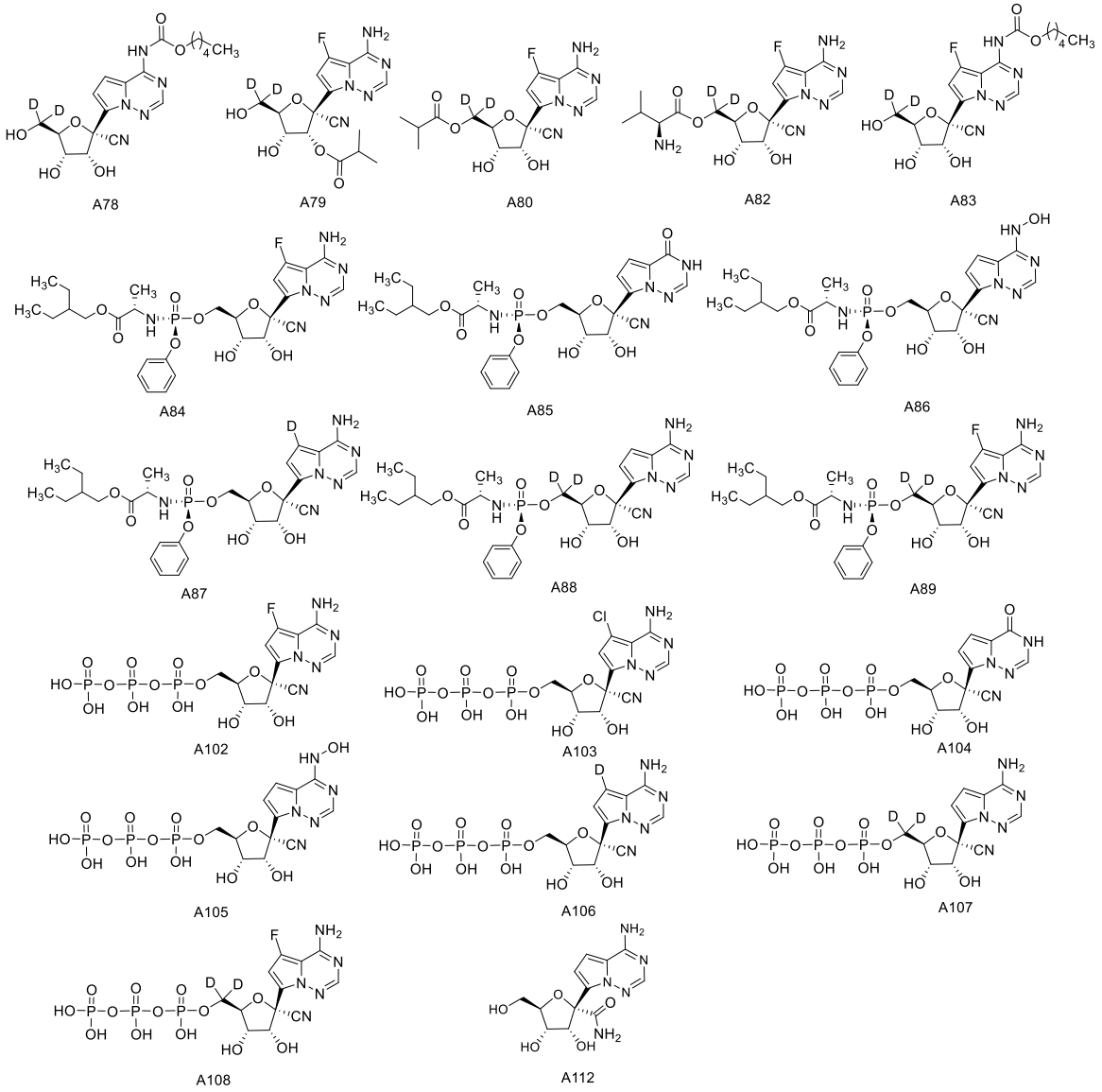
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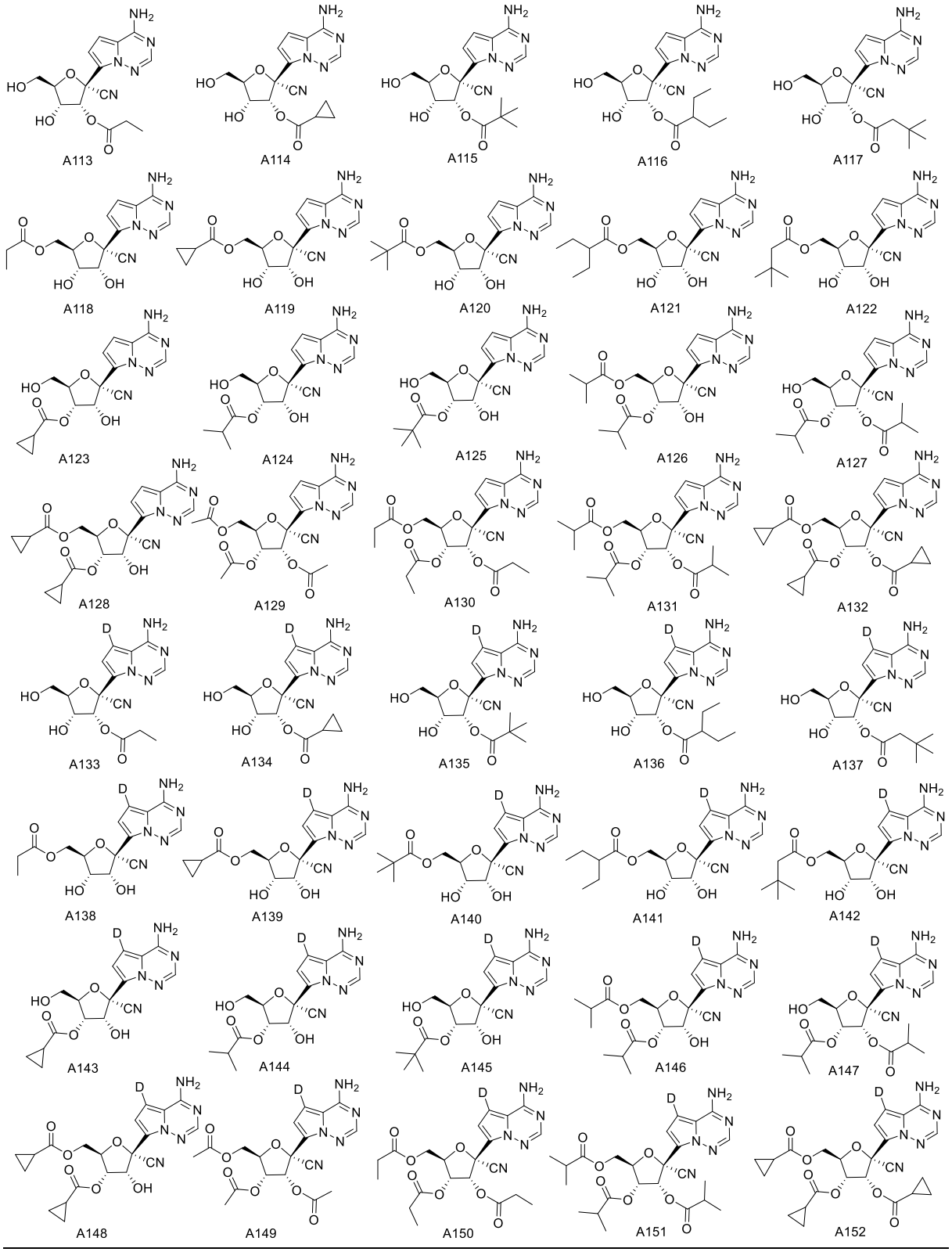
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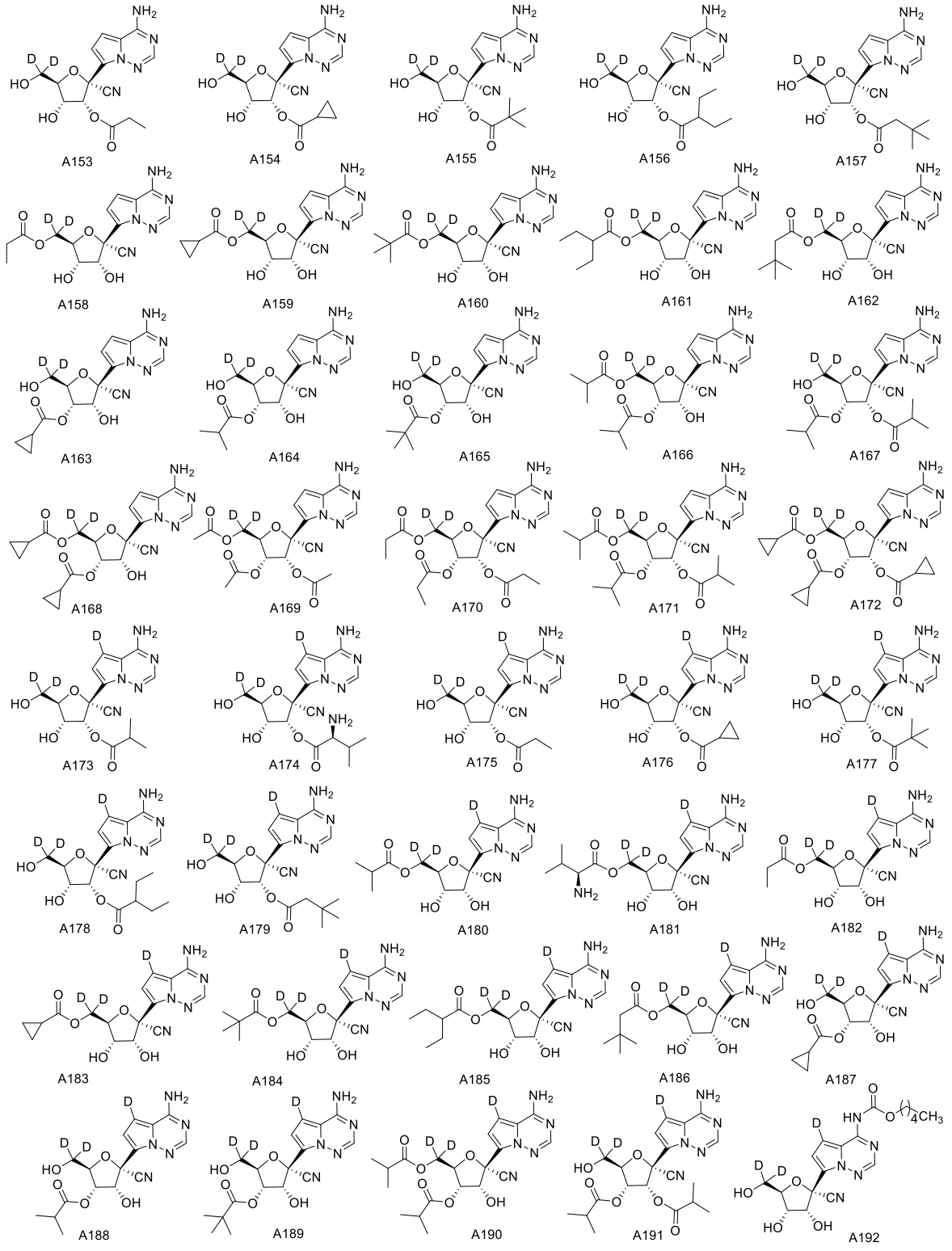
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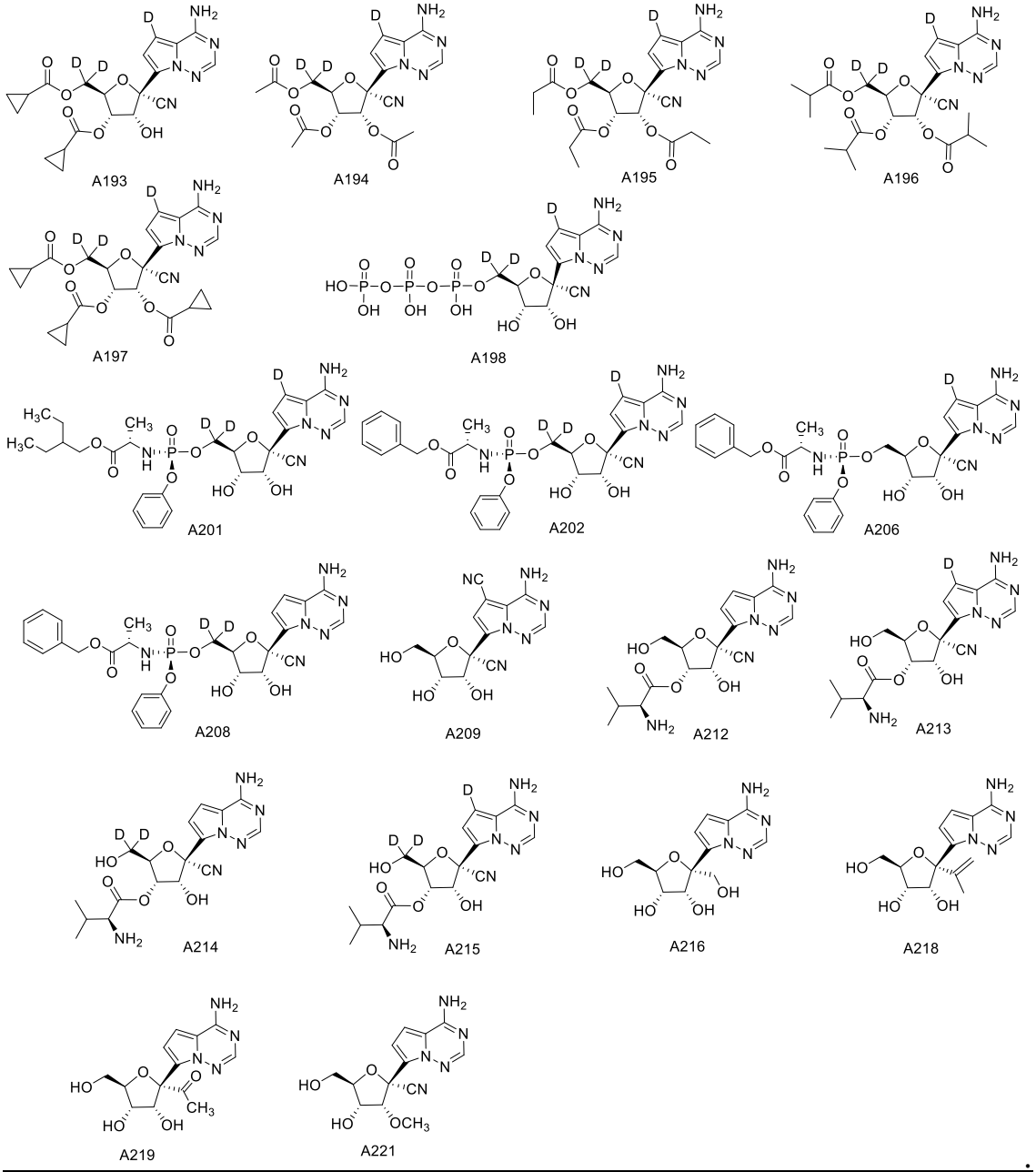
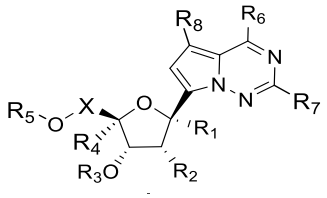


5. The compound of formula (I) of claim 4, or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof, wherein the compound is any one of the compounds as follows, or combinations thereof:

A1, A5, A9, A10, A11, A12, A28, A35, A36, A49, A50, A51, A52, A53, A54, A55, A57, A58, A69, A70, A71, A72, A73, A74, A75, A76, A77, A78, A79, A80, A84, A87, A88, A89, A102, A105, A106, A107, A108, A113, A114, A115, A116, A117, A118, A119, A120, A121, A122, A123, A124, A125, A126, A127, A128, A129, A130, A131, A132, A133, A134, A135, A136, A137, A138, A139, A140, A141,

A142, A143, A144, A145, A146, A147, A148, A149, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A160, A161, A162, A163, A164, A165, A166, A167, A168, A169, A170, A171, A172, A173, A174, A175, A176, A177, A178, A179, A180, A181, A182, A183, A184, A185, A186, A187, A188, A189, A190, A191, A192, A193, A194, A195, A196, A197, A198, A201, A202, A206, A208, A209, A212, A213, A214, A215, A216, A218, A219, A221, or the combination thereof.

~~2~~6. A use of an active ingredient or a formulation containing the said active ingredient, wherein the active ingredient is a compound of formula (I) or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof:



(I)

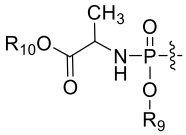
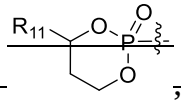
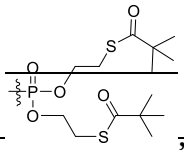
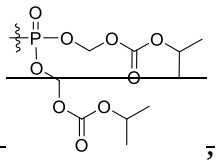
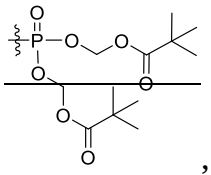
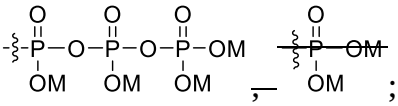
wherein,

R_1 is selected from hydrogen, deuterium~~, halogen~~, cyano~~, azido, amino, amino substituted with C_{1-6}alkyl~~, C_{1-6}acyl~~, C_{1-6}alkyl, C_{1-6}alkoxy, amino substituted with C_{1-6}alkanoyl, halogenated C_{1-6}alkyl~~, C_{2-6}alkenyl~~, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{2-6}alkynyl~~, C_{3-6}cycloalkyl~~, halogenated C_{3-6}cycloalkyl~~, carbamoyl, hydroxymethyl~~, cyanomethyl (-CH_2CN), guanyl, guanidyl, carbamido, thiocyanato (-SCN), cyanato (-OCN)~~;

R_2 is selected from~~ hydrogen, halogen, OR_3, cyano~~, C_{1-6}alkyl~~, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

R_3 is selected from hydrogen, C_{1-20}alkanoyl~~, aminoC_{1-20}alkanoyl, C_{1-6}alkylamino-C_{1-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, α-amino acid, and the carboxyl of the α-amino acid is attached to the hydroxyl on the furan ring via ester bond~~;

R_4 is selected from hydrogen, deuterium~~, halogen, azido, cyano, C_{1-6}alkyl, halogenated C_{1-6}alkyl, azidoC_{1-6}alkyl, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl, guanyl, guanidyl, carbamido, thiocyanato, cyanato~~;

R_5 is selected from R_3, , , , , , ;

R_6 is selected from amino, hydroxy~~, halogen, cyano, cyanato, thiocyanato, C_{1-6}alkoxy, C_{1-6}alkylamino~~, NHOH~~, $NHCOR_{12}$, $NHOCOR_{12}$~~, $NHCOOR_{12}$;

R_7 is selected from hydrogen, deuterium, halogen~~, amino, methyl, $NHCOR_{12}$, $NHCOOR_{12}$~~;

R_8 is selected from hydrogen, deuterium, halogen, cyano~~, carbamoyl, carbamoyl substituted with C_{1-6}alkyl, C_{1-6}alkoxyamido, C_{1-6}alkoxycarbonyl, hydroxy, hydroxyC_{1-6}alkyl, amino, amino substituted with C_{1-6}alkanoyl, amino substituted with C_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

X is selected from $-CH_2-$, $-CD_2-$~~, $-CHD-$~~;

R_9 is selected from ~~C_{1-6}alkyl, C_{3-6}cycloalkyl,~~ C_{6-20}aryl~~, 5-15 membered heteroaryl~~;

R_{10} is selected from C_{1-18}alkyl~~, methyleneC_{6-20}aryl~~;

~~R_{11} is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-20}aryl, 5-15 membered heteroaryl;~~

R_{12} is selected from C_{1-20}alkyl;

M is each independently selected from hydrogen, metal~~, $-NH_4$~~, or protonated organic amines~~;~~

and the active ingredient or the formulation containing the said active ingredient, is used for preparing (a) inhibitors for inhibiting viral replication; and/or (b) medicaments for treating and/or preventing, alleviating diseases associated with viral infections.

~~3~~7. The use of Claim ~~2~~6, wherein the virus is selected from:

(1) coronavirus infecting human: severe acute respiratory syndrome coronavirus (SARS-CoV), 2019 novel coronavirus (2019-nCoV or SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV);

(2) coronavirus causing the common cold: the coronavirus causing the common cold is ~~preferably~~ selected from the group consisting of: Human coronavirus OC43, Human coronvirus 229E, Human coronvirus NL63, and Human coronvirus HKUL;

(3) human respiratory syncytial virus (RSV);

(4) human influenza virus: influenza A virus, influenza B virus and influenza C virus;

(5) flaviviridae virus: hepatitis C virus (HCV), dengue virus (DENV), Zika virus (Zika);

(6) filoviridae virus: Marburg virus (MBV) and Ebola virus (EBV);

(7) coronavirus infecting other mammals: porcine epidemic diarrhea virus (PEDV).

~~4~~8. The use of Claim ~~2~~6, wherein the related diseases caused by the viruses are selected from the group consisting of

(D1) common cold, high-risk symptom infection, respiratory tract infection, pneumonia and the complications thereof caused by human coronavirus infection;

(D2) common cold, high-risk symptom infection, respiratory tract infection, pneumonia and the complications thereof caused by human respiratory syncytial virus (RSV) infection;

(D3) common cold, high-risk symptom infection, respiratory tract infection, pneumonia and the complications thereof caused by human influenza virus infection;

(D4) chronic hepatitis C and the complications thereof caused by hepatitis C virus (HCV);

(D5) dengue fever and the complications thereof caused by dengue virus (DENV);

(D6) infection and the complications thereof caused by Zika virus (Zika);

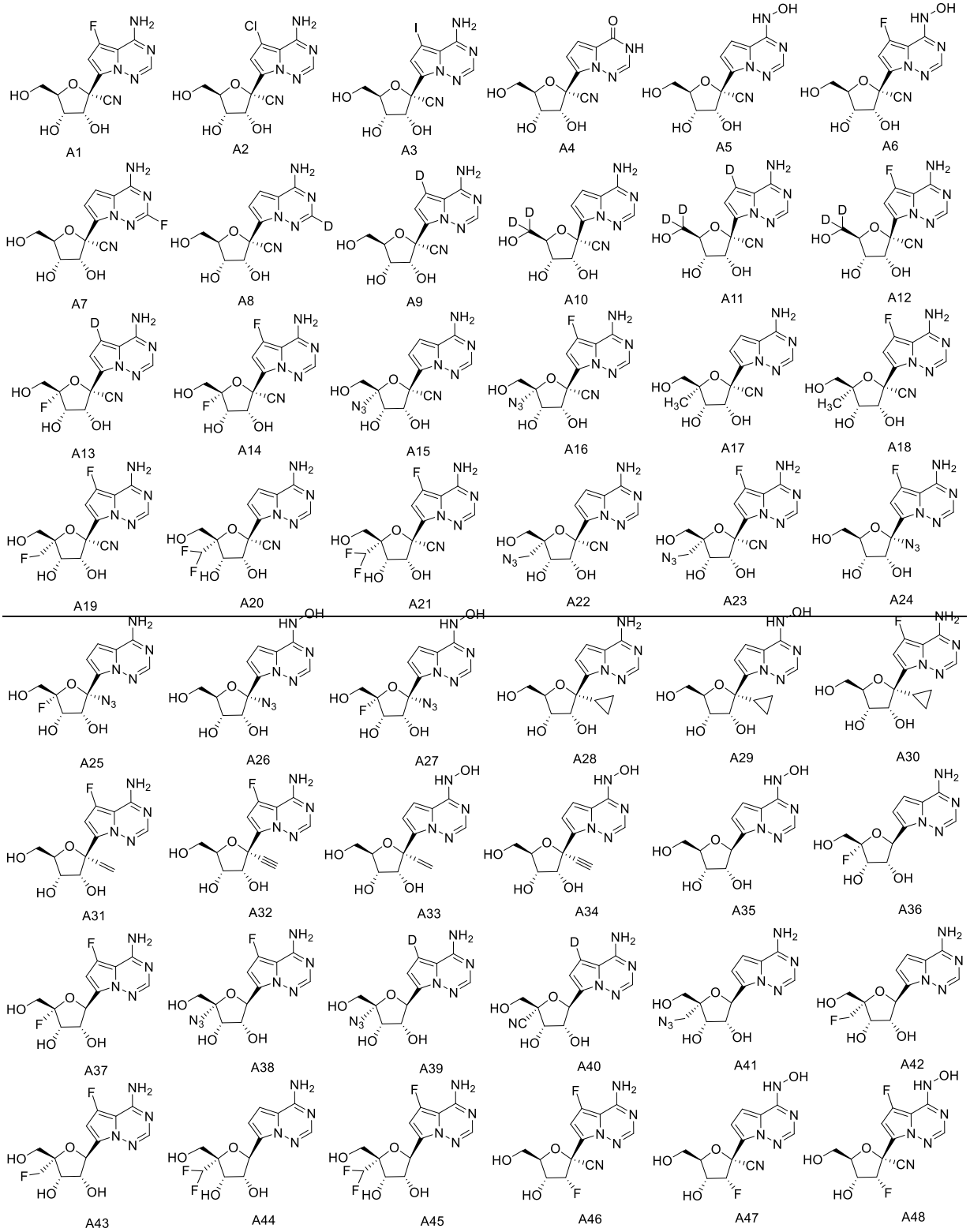
(D7) hemorrhagic fever and the complications thereof caused by Marburg virus (MBV) and Ebola virus (EBV);

(D8) novel coronavirus pneumonia (Corona Virus Disease 2019，COVID-19) caused by SARS-CoV-2 (COVID-19);

(D9) Porcine epidemic diarrhea caused by porcine epidemic diarrhea virus (PEDV);

(D10) any combination of the above diseases.

~~5~~9. The use of any one of Claims 6 to 8~~2~~, wherein the active ingredient is the compound of formula (I) according to any one of claims 2 to 5, or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof~~is any one of Compound A1 to A221 having the following structure, or the combination thereof:~~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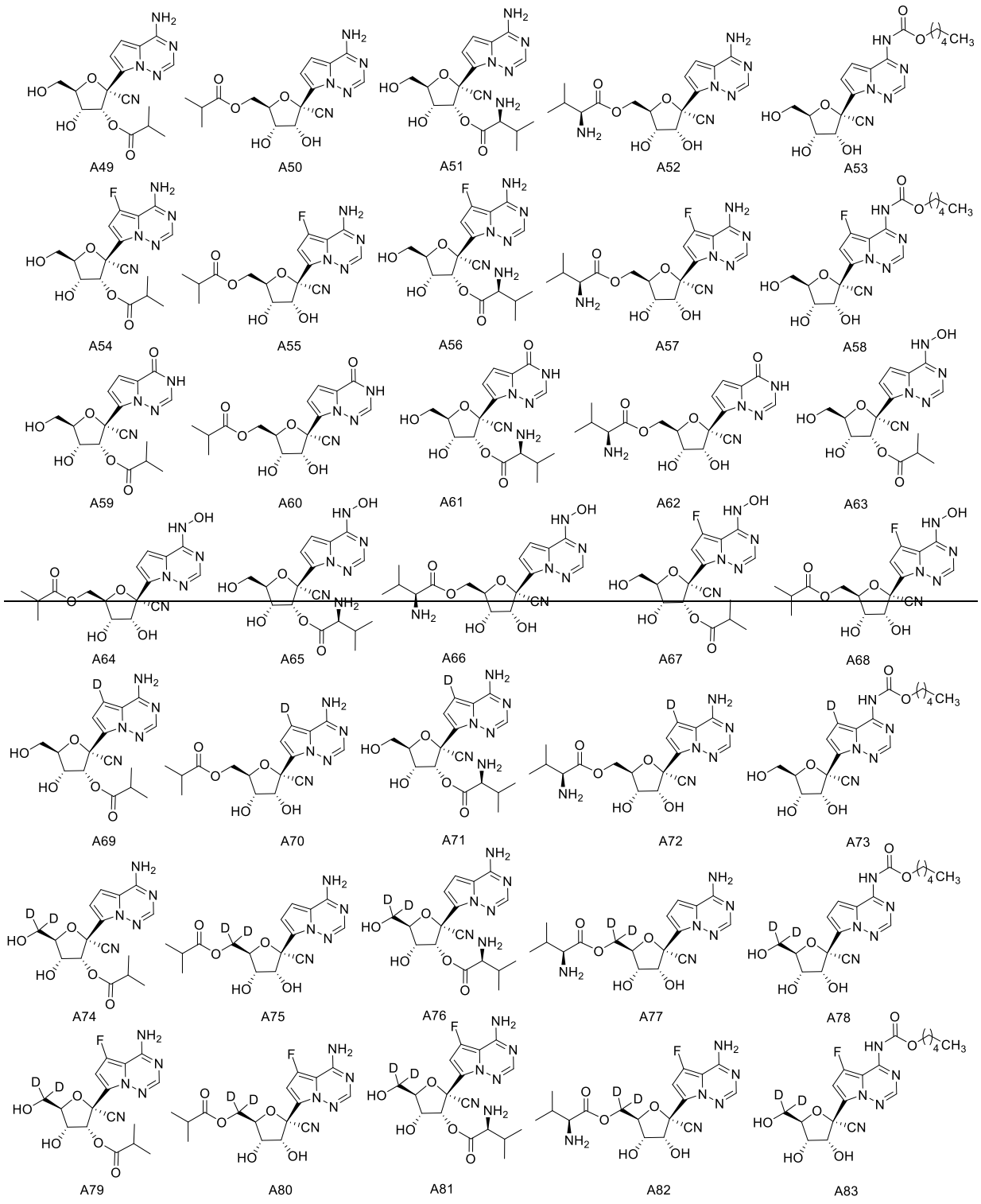
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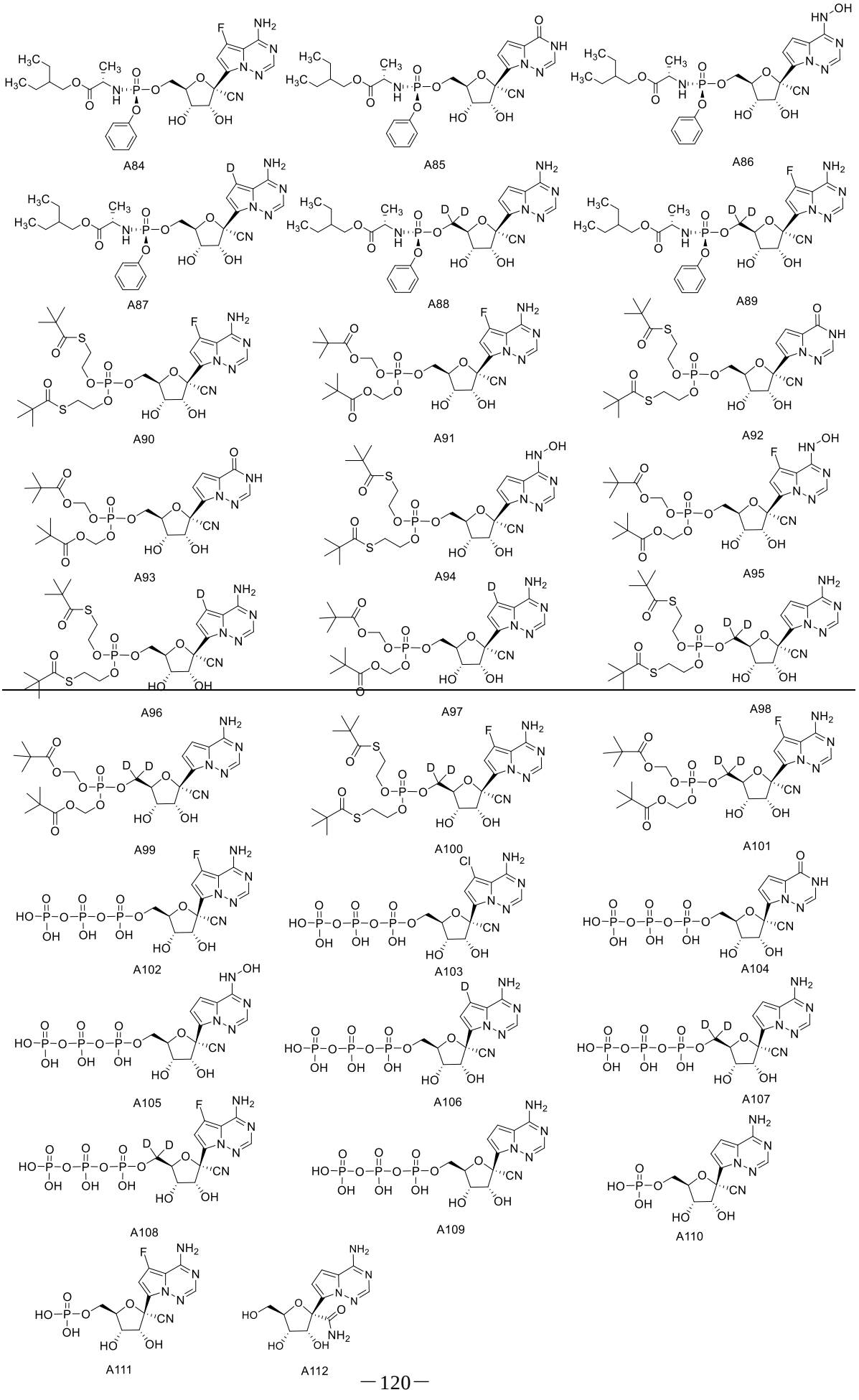
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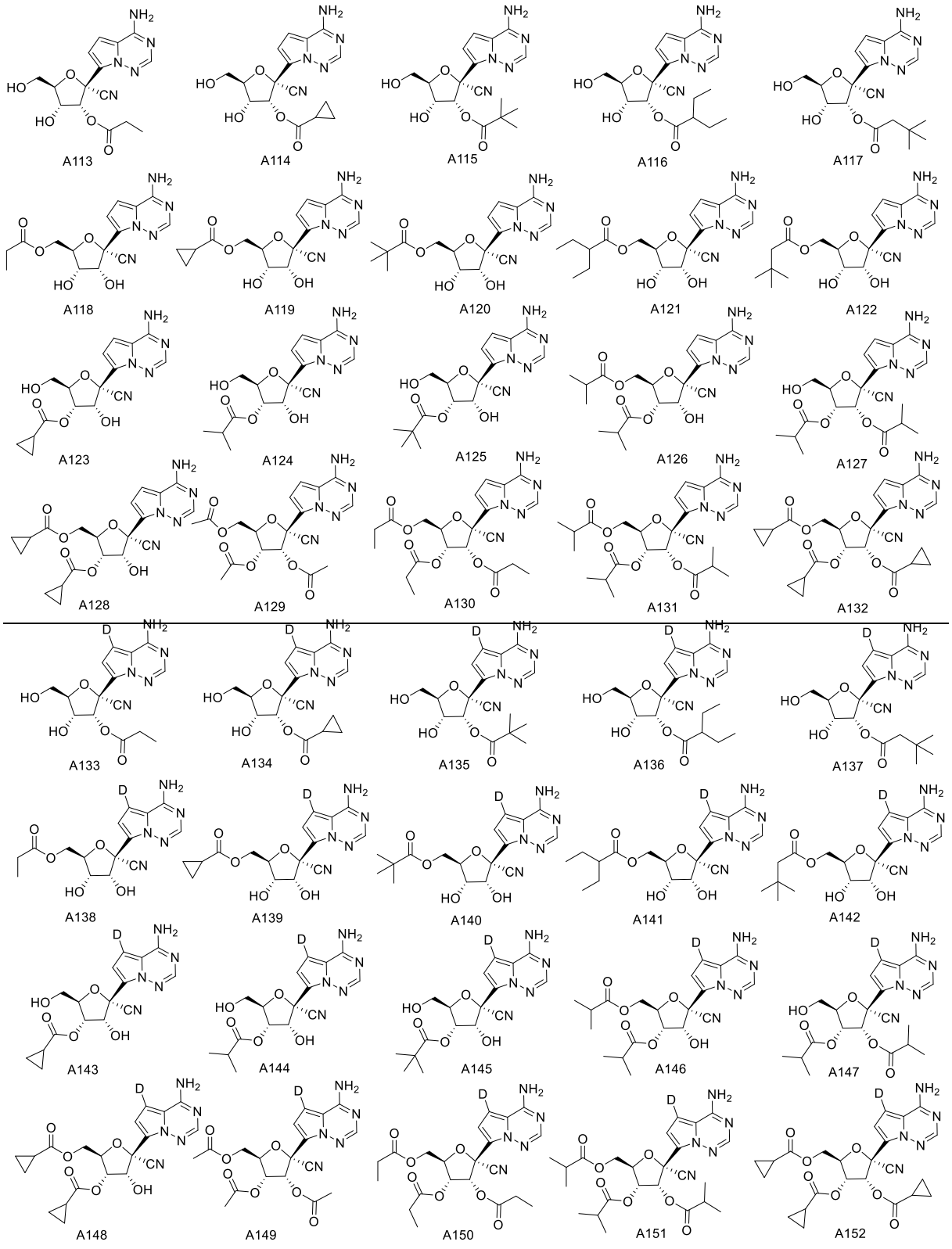
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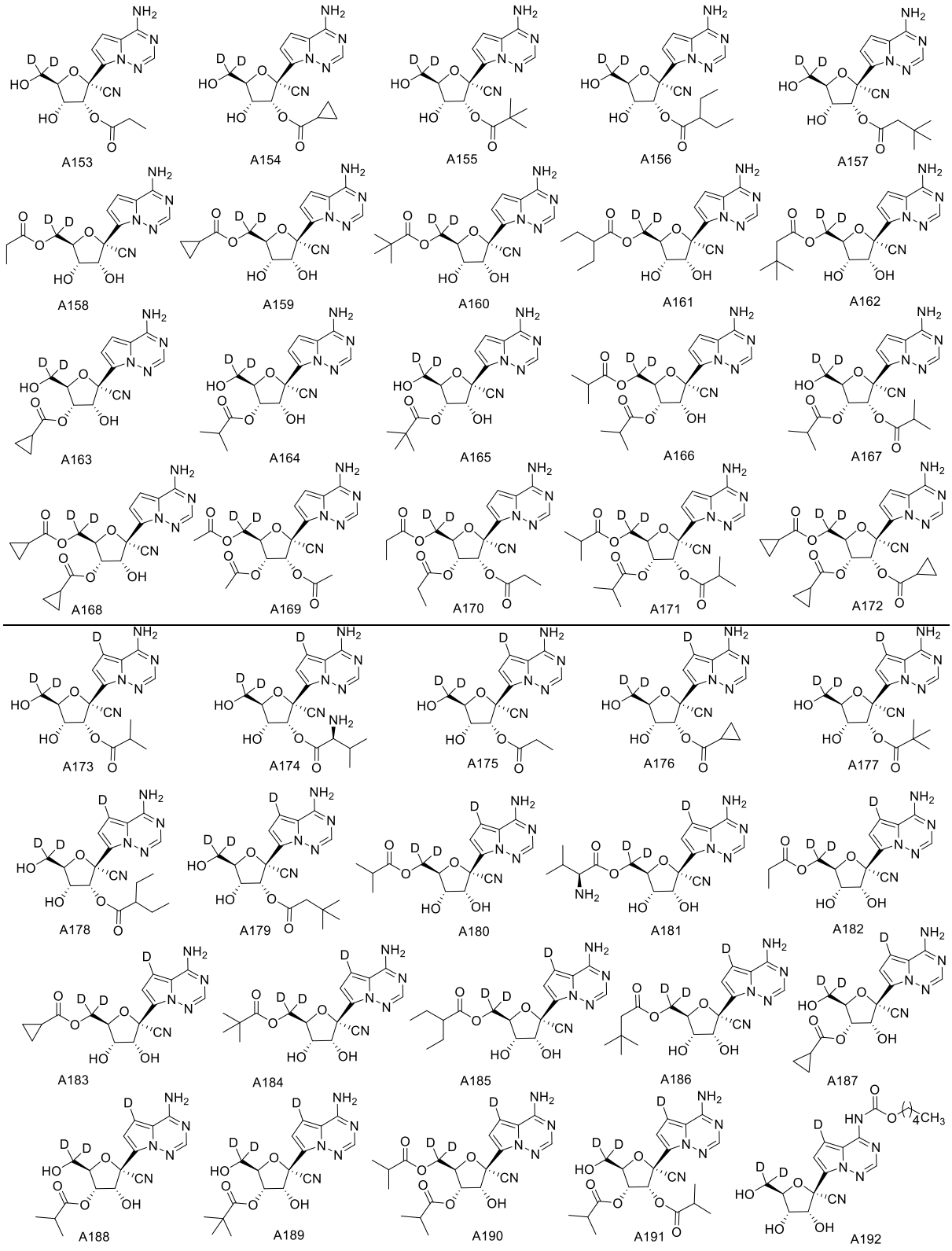
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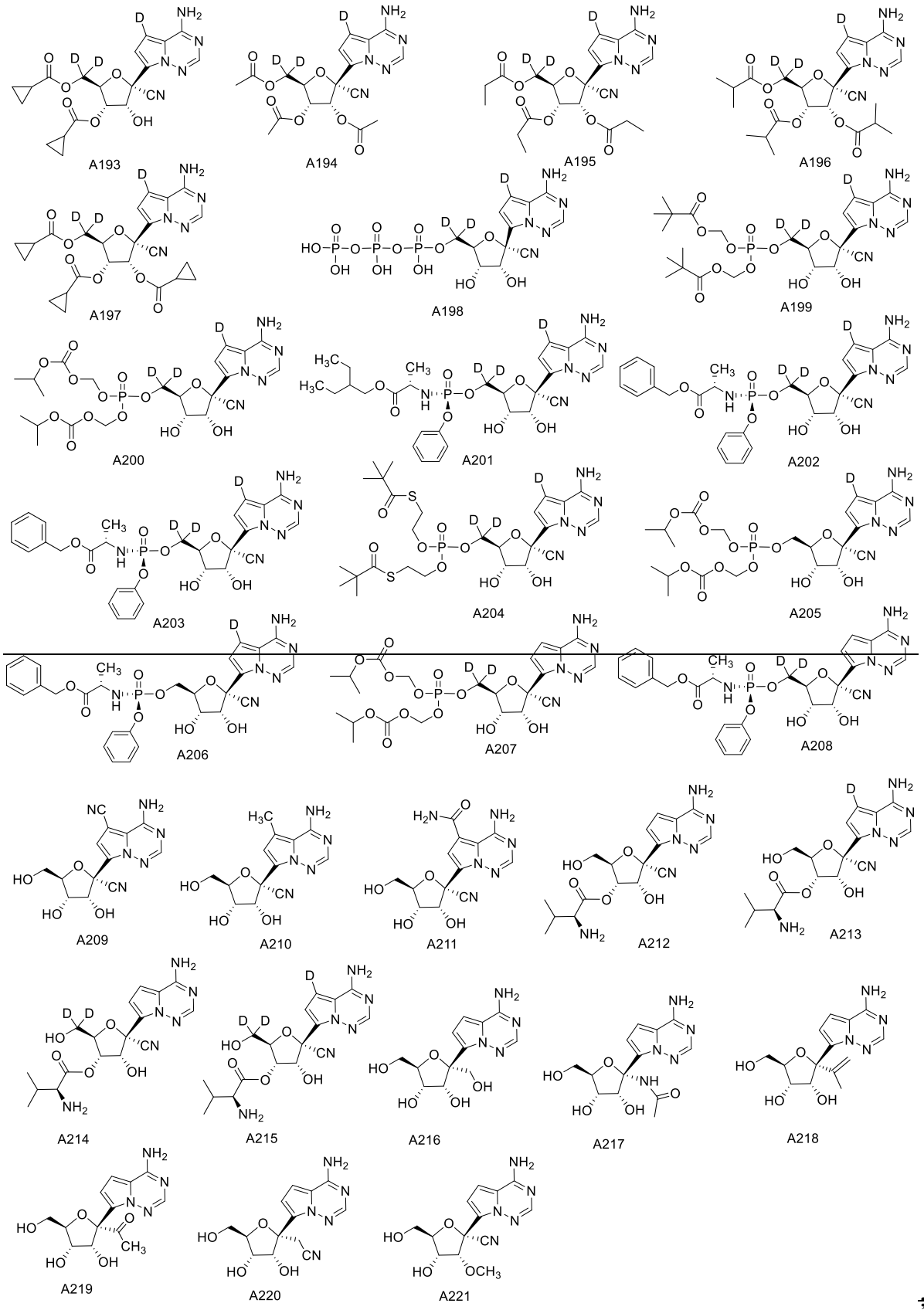


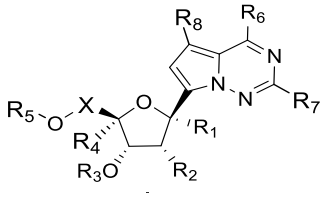
;

~~preferably, the active ingredient is a nucleoside analog selected from the following group, or the pharmaceutically acceptable salts thereof or crystalline hydrate thereof or the solvate thereof or the prodrug thereof:~~

~~A1, A5, A6, A8, A9, A10, A11, A12, A13, A14, A28, A30, A35, A36, A37, A38, A39, A40, A41, A42, A43, A44, A45, A46, A49, A50, A51, A52, A53, A54, A55, A57, A58, A63, A69, A70, A71, A72, A73, A74, A75, A76, A77, A78, A79, A80, A81, A84, A86, A87, A88, A89, A91, A95, A97, A99, A101, A102, A105, A106, A107, A108, A109, A110, A111, A113, A114, A115, A116, A117, A118, A119, A120, A121, A122, A123, A124, A125, A126, A127, A128, A129, A130, A131, A132, A133, A134, A135, A136, A137, A138, A139, A140, A141, A142, A143, A144, A145, A146, A147, A148, A149, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A160, A161, A162, A163, A164, A165, A166, A167, A168, A169, A170, A171, A172, A173, A174, A175, A176, A177, A178, A179, A180, A181, A182, A183, A184, A185, A186, A187, A188, A189, A190, A191, A192, A193, A194, A195, A196, A197, A198, A199, A200, A201, A202, A203, A204, A205, A206, A207, A208, A209, A210, A211, A212, A213, A214, A215, A216, A217, A218, A219, A220, A221, or the combination thereof~~.

~~6~~10. A pharmaceutical composition comprising

(a~~1~~) first active ingredient, the first active ingredient is a compound of formula (I), and the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof:



(I)

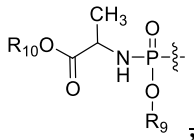
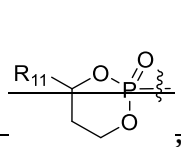
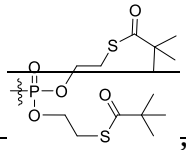
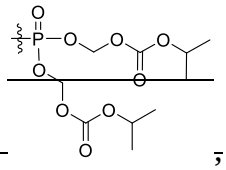
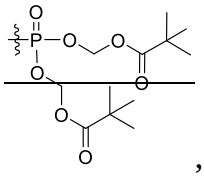
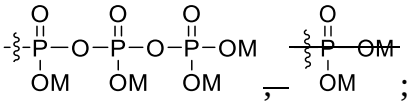
wherein,

R_1 is selected from hydrogen, deuterium, ~~halogen,~~ cyano~~, azido, amino, amino substituted with C_{1-6}alkyl~~, C_{1-6}acyl~~, C_{1-6}alkyl, C_{1-6}alkoxy, amino substituted with C_{1-6}alkanoyl, halogenated C_{1-6}alkyl~~, C_{2-6}alkenyl~~, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{2-6}alkynyl, C_{3-6}cycloalkyl, halogenated C_{3-6}cycloalkyl~~, carbamoyl, hydroxymethyl~~, cyanomethyl (-CH_2CN), guanyl, guanidyl, carbamido, thiocyanato (-SCN), cyanato (-OCN)~~;

R_2 is selected from ~~hydrogen, halogen,~~ OR_3, ~~cyano, C_{1-6}alkyl,~~ C_{1-6}alkoxy~~, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

R_3 is selected from hydrogen, C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl, (C_{1-6}alkyl)aminoC_{1-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, α-amino acid, and the carboxy of the α-amino acid is attached to the hydroxyl on the furan ring via ester bond;

R_4 is selected from hydrogen, deuterium, halogen~~, azido, cyano, C_{1-6}alkyl, halogenated C_{1-6}alkyl, azidoC_{1-6}alkyl, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl, guanyl, guanidyl, carbamido, thiocyanato, cyanato~~;

R_5 is selected from R_3, , , , , , ;

R_6 is selected from amino, hydroxy~~, halogen, cyano, cyanato, thiocyanato, C_{1-6}alkoxy, C_{1-6}alkylamino~~, NHOH~~, $NHCOR_{12}$, $NHOCOR_{12}$~~, $NHCOOR_{12}$;

R_7 is selected from hydrogen, deuterium, halogen~~, amino, methyl, $NHCOR_{12}$, $NHCOOR_{12}$~~;

R_8 is selected from hydrogen, deuterium, halogen, cyano~~, carbamoyl, carbamoyl substituted with C_{1-6}alkyl, C_{1-6}alkoxyamido, C_{1-6}alkoxycarbonyl, hydroxy, hydroxyC_{1-6}alkyl, amino, amino substituted with C_{1-6}alkanoyl, amino substituted with C_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

X is selected from CH_2, CD_2~~, CHD~~;

R_9 is ~~selected from C_{1-6}alkyl, C_{3-6}cycloalkyl,~~ C_{6-20}aryl~~, 5-15 membered heteroaryl~~;

R_{10} is ~~selected from~~ C_{1-18}alkyl~~, methyleneC_{6-20}aryl~~;

~~R_{11} is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-20}aryl, 5-15 membered heteroaryl;~~

R_{12} is ~~selected from~~ C_{1-20}alkyl;

M is each independently selected from hydrogen, metal, ~~NH_4,~~ or protonated organic amines;

and (b) pharmaceutically acceptable carriers.

~~7~~11. The pharmaceutical composition of Claim ~~6~~10, wherein the compound of formula (I) is defined as in any one of ~~C~~claims 2 to 5~~any one of Compound A1 to A221, or the combination thereof~~.

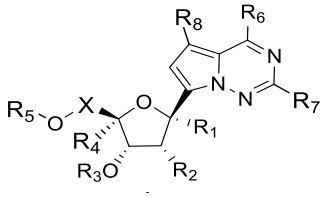
~~8~~12. A use of pharmaceutical composition of any one of Claims ~~6~~ 10 ~~to~~ 11 in

preparing (a) inhibitors that inhibit the replication of coronavirus, influenza virus, respiratory syncytial virus, flaviviridae virus, filoviridae virus and/or porcine epidemic diarrhea virus (PEDV); and/or (b) medicaments for treating and/or preventing, alleviating related diseases caused by coronavirus, influenza virus, respiratory syncytial virus, flaviviridae virus, filoviridae virus and/or porcine epidemic diarrhea virus (PEDV) infection.

~~9~~13. A method for inhibiting virus replication, wherein comprises the step of

contacting a first active ingredient or a formulation containing the first active ingredient with a virus, thereby inhibiting the replication of the virus;

wherein the first active ingredient is a compound of formula (I) or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof:



(I)

wherein,

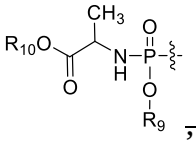
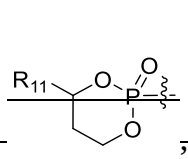
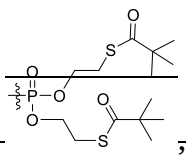
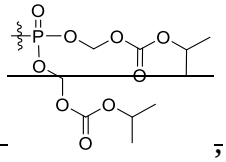
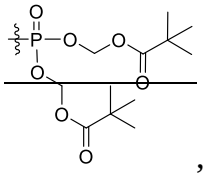
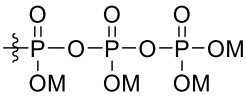
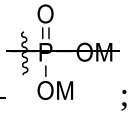
R_1 is selected from hydrogen, deuterium~~, halogen~~, cyano~~, azido, amino, amino substituted with C_{1-6}alkyl~~, C_{1-6}acyl~~, C_{1-6}alkyl, C_{1-6}alkoxy, amino substituted with C_{1-6}alkanoyl, halogenated C_{1-6}alkyl~~, C_{2-6}alkenyl~~, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{2-6}alkynyl~~, C_{3-6}cycloalkyl~~, halogenated C_{3-6}cycloalkyl~~, carbamoyl, hydroxymethyl~~, cyanomethyl (-CH_2CN), guanyl, guanidyl, carbamido, thiocyanato (-SCN), cyanato (-OCN)~~;

R_2 is selected from~~ hydrogen, halogen,~~ OR_3~~, cyano, C_{1-6}alkyl~~, C_{1-6}alkoxy~~, C_{2-6}alkenyl, C_{2-6}alkynyl~~;

R_3 is selected from hydrogen, C_{1-20}alkanoyl, aminoC_{1-20}alkanoyl, C_{1-6}alkylaminoC_{1-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, α-amino acid, and the carboxyl of the α-amino acid is attached to the hydroxyl on the furan ring via ester bond~~; preferably, the α-amino acid is selected from alanine, valine, isoleucine, tryptophan, phenylalanine~~;

R_4 is selected from hydrogen, deuterium, halogen~~, azido, cyano, C_{1-6}alkyl, halogenated C_{1-6}alkyl, azidoC_{1-6}alkyl, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{2-6}alkenoxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, guanyl, guanidyl,~~

~~carbamido, thiocyanato, cyanato~~;

R_5 is selected from R_3, , , , , , , ;

R_6 is selected from amino, hydroxy, ~~halogen, cyano, cyanato, thiocyanato, C_{1-6}alkoxy, C_{1-6}alkylamino,~~ NHOH, ~~$NHCOR_{12}$, $NHOCOR_{12}$,~~ $NHCOOR_{12}$;

R_7 is selected from hydrogen, deuterium, halogen, amino, methyl, $NHCOR_{12}$, $NHCOOR_{12}$;

R_8 is selected from hydrogen, deuterium~~, halogen, cyano, carbamoyl, carbamoyl substituted with C_{1-6}alkyl, C_{1-6}alkoxyamido, C_{1-6}alkoxycarbonyl, hydroxy, hydroxyC_{1-6}alkyl, amino, amino substituted with C_{1-6}alkanoyl, amino substituted with C_{1-6}alkyl, C_{1-6}alkyl, C_{2-6} C_{1-6}alkoxy, alkenyl, C_{2-6}alkynyl~~;

X is selected from -CH_2-, -CD_2-~~, CHD~~;

R_9 is ~~selected from C_{1-6}alkyl, C_{3-6}cycloalkyl,~~ C_{6-20}aryl~~, 5-15 membered heteroaryl~~;

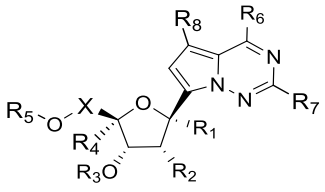
R_{10} is ~~selected from~~ C_{1-18}alkyl~~, methyleneC_{6-20}aryl~~;

~~R_{11} is selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{6-20}aryl, 5-15 membered heteroaryl;~~

R_{12} is ~~selected from~~ C_{1-20}alkyl;

M is each independently selected from hydrogen, metal~~, NH_4~~, or protonated organic amines.

~~10~~14. A method for (a) inhibiting viral replication and/or (b) treating and/or preventing, alleviating related diseases caused by viral infection, wherein comprises the step of administrating safe and effective amount of a compound of formula (I), or the pharmaceutically acceptable salts thereof or the crystalline hydrate thereof or the solvate thereof or the prodrug thereof to the subject in need thereof:



(I)

wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and X are defined as in Claim 1.