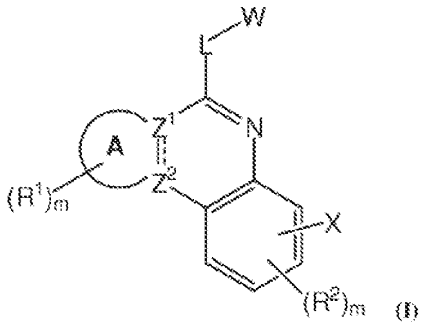
Claims

WHAT IS CLAIMED IS:

1. A method for treating an RNA viral infection in a human comprising administering a therapeutically effective amount of a compound having a structure of Formula (I):



(I)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S; each R^1, R^2, R^3, R^4 and R^5 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group, or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2, wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl, and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O; and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted; and R^4 and R^5, when on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0-3;

or a pharmaceutically acceptable salt or ester thereof.

2. The method of claim 1, wherein L is NH or NMe.

3. The method of claim 1, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

4. The method of claim 1, wherein Z^1 and Z^2 are C and ----- represents a double bond.

5. The method of claim 1, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

6. The method of claim 1, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

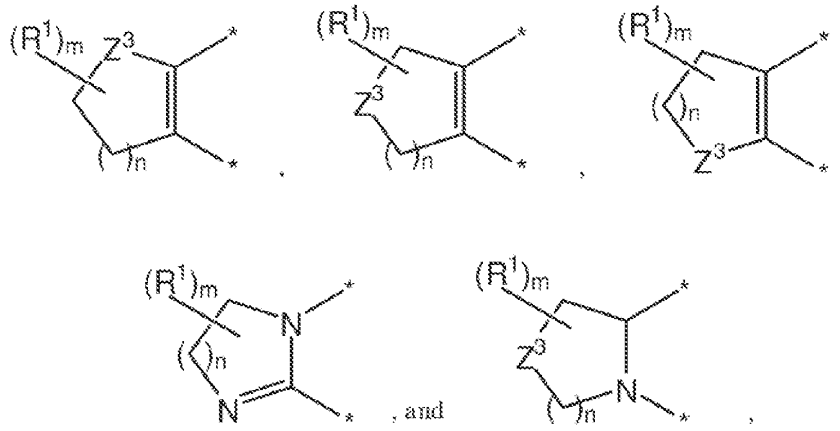
7. The method of claim 1, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and $-NR''_2$, where each R'' is independently H or optionally substituted C1-C6 alkyl; and two R'' taken together with the N to which they are attached can be linked together to form an optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

8. The method of claim 1, wherein L is NH or NMe.

9. The method of claim 7, wherein W comprises at least one group of the formula $-(CH_2)_p-NR^x_2$, where p is 1-4, R^x is independently at each occurrence H or optionally substituted alkyl; and two R^x taken together with the N to which they are attached can be linked together to form an

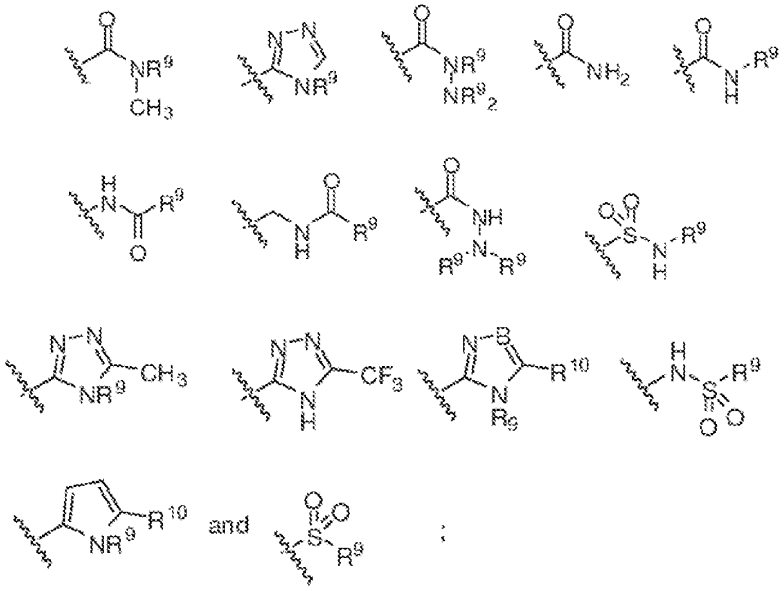
optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

10. The method of claim 1, wherein A is selected from the group consisting of:



wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O; n is 1-3; and p is 0-2.

11. The method of claim 1, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,

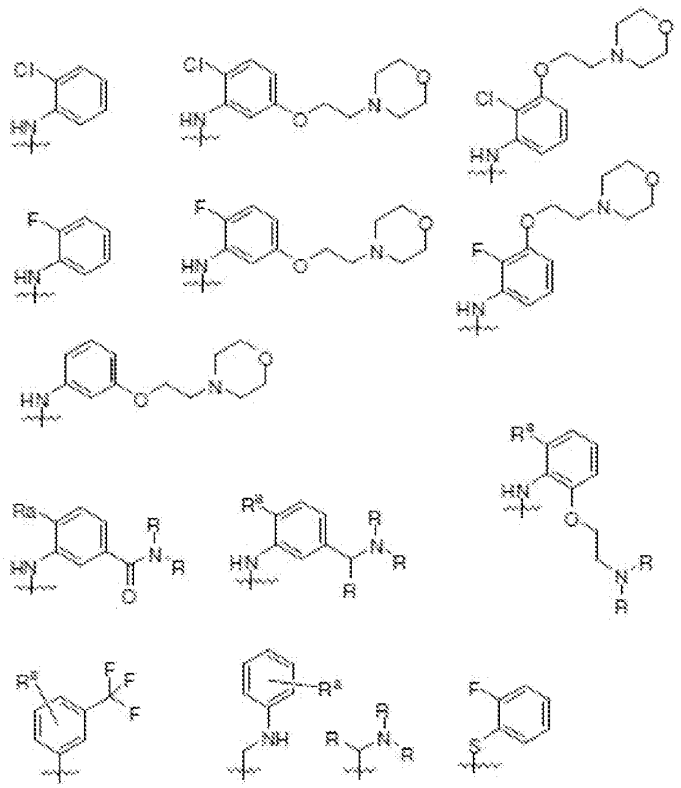


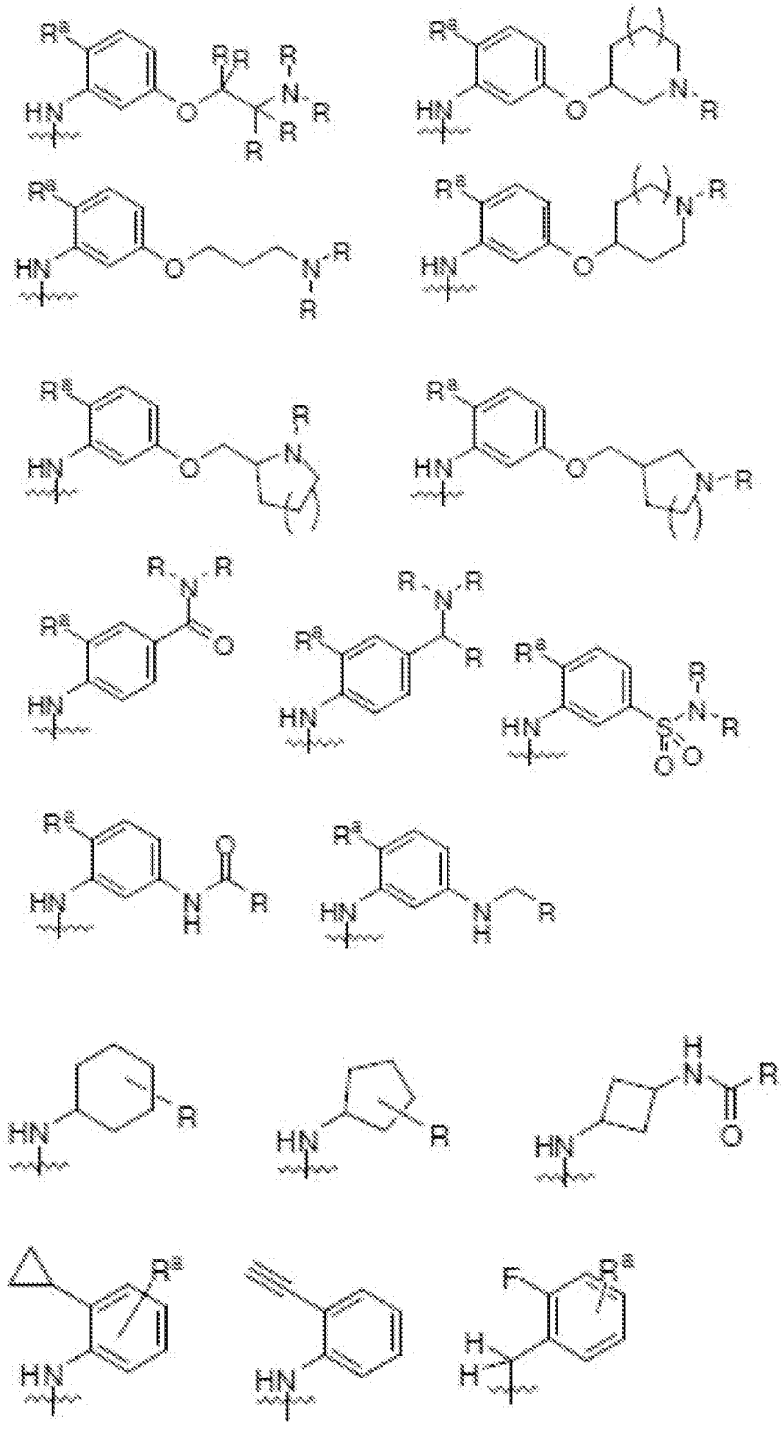
wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl, and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member; R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;
and B is N or CR^{10}.

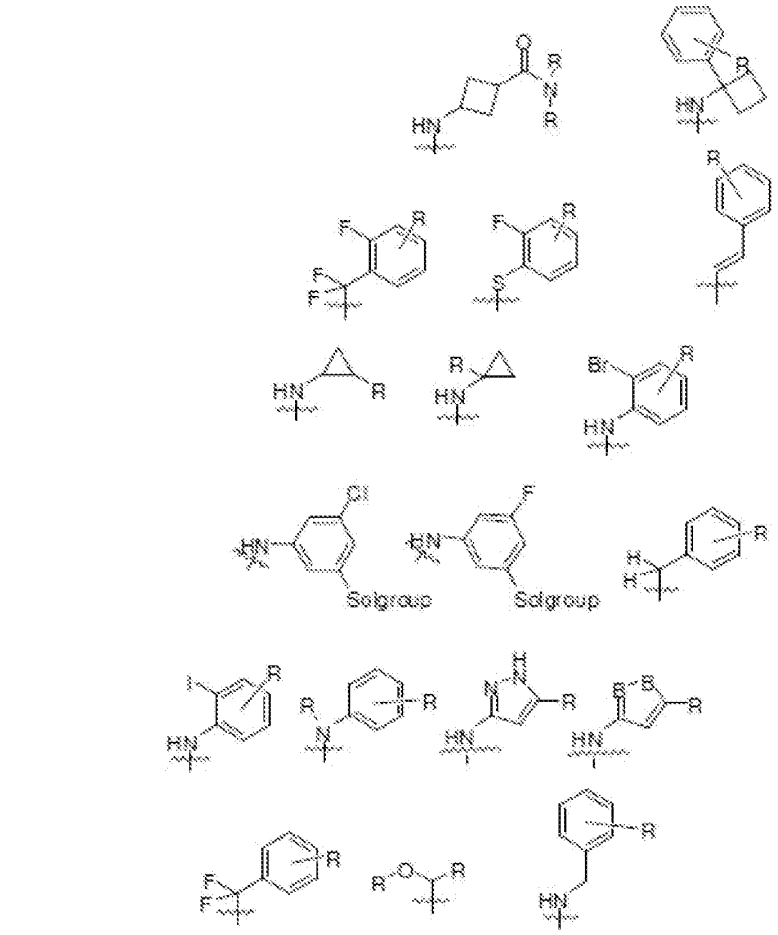
12. The method of claim 1, wherein the polar substituent X is located at position 3 on the phenyl ring.

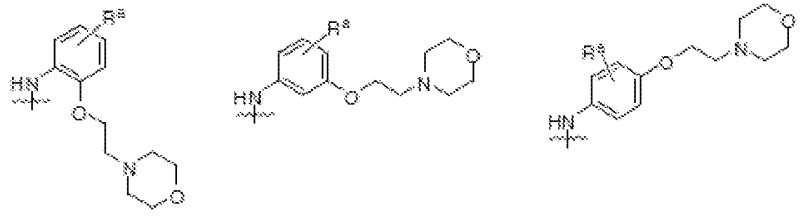
13. The method of claim 1, wherein the polar substituent X is located at position 4 on the phenyl ring.

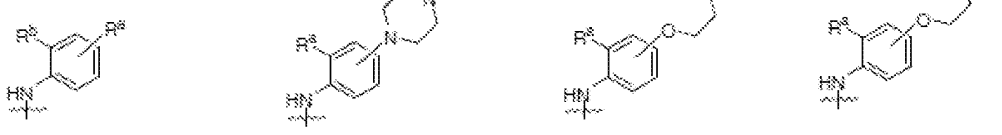
14. The method of claim 1, wherein –L-W is selected from:






Sdgroup
Sdgroup





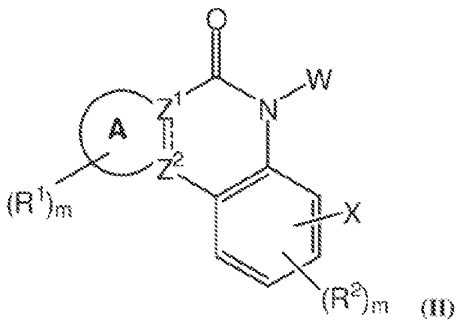
wherein each R^a is independently H, Cl or F;

each R^b is independently Me, F, or Cl; each R is independently selected from H, halo, C1-C4 alkyl, C1-C4 alkoxy, and

C1-C4 haloalkyl, and two R groups on the same or adjacent connected atoms can optionally be linked together to form a 3-8 membered ring;

each B is N or CR; and each Solgroup is a solubility-enhancing group.

15. A method of claim 1, wherein the compound is one having a structure of Formula (II):



(II)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

------ represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ------ represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ------ represents a double bond;

each of R^1 and R^2 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group, or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from

halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2, wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0-3;

or a pharmaceutically acceptable salt or ester thereof.

16. The method of claim 15, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

17. The method of claim 15, wherein Z^1 and Z^2 are C and ----- represents a double bond.

18. The method of claim 15, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

19. The method of claim 15, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

20. The method of claim 15, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and $-NR"_2$,

where each R" is independently H or optionally substituted C1-C6 alkyl;

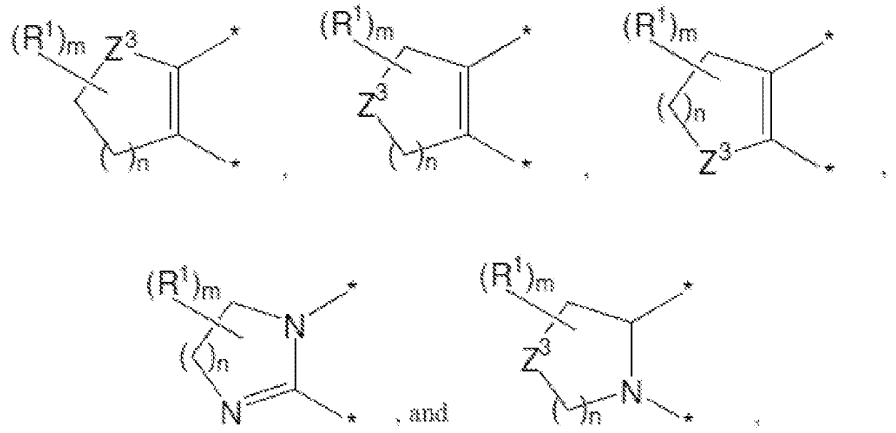
and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

21. The method of claim 20, wherein W comprises at least one group of the formula $-(CH_2)_p-NR^x_2$, where p is 1-4,

R^x is independently at each occurrence H or optionally substituted alkyl;

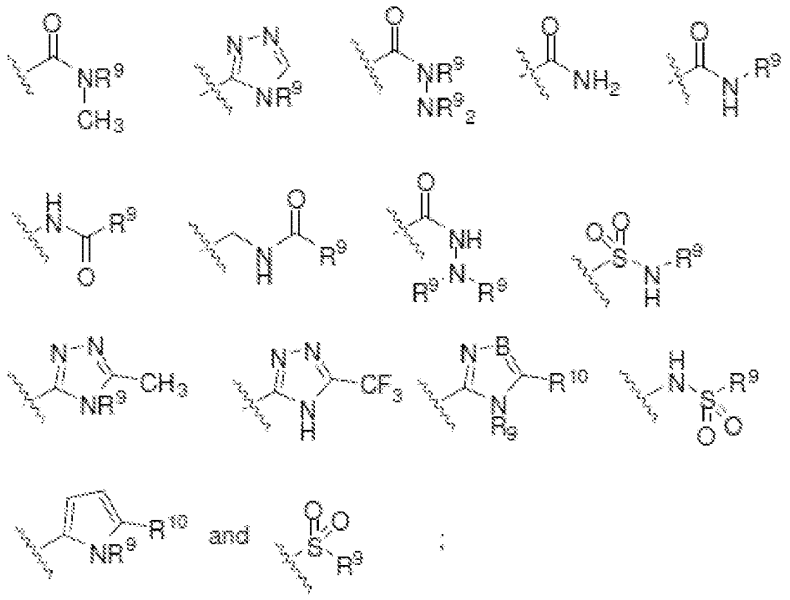
and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3-8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

22. The method of any one of claims 15, wherein A is selected from the group consisting of:



wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O; n is 1-3; and p is 0-2.

23. The method of claim 15, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,



wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

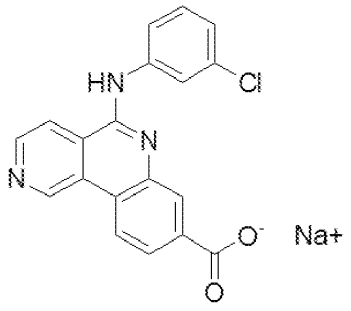
and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member; R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

and B is N or CR^{10}.

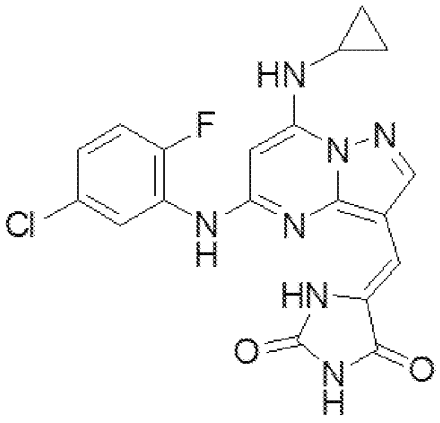
24. The method of claim 23, wherein the polar substituent X is located at position 3 on the phenyl ring.

25. The method of claim 23, wherein the polar substituent X is located at position 4 on the phenyl ring.

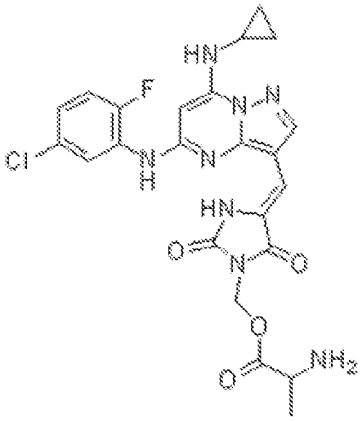
26. The method of claim 1, wherein the compound is selected from the group consisting of the following compounds:



Compound A;

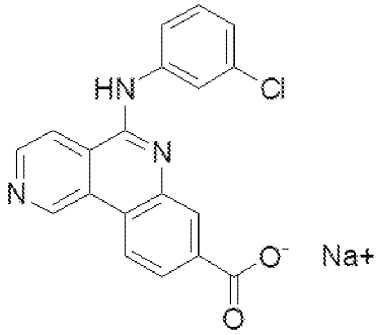


Compound B; and

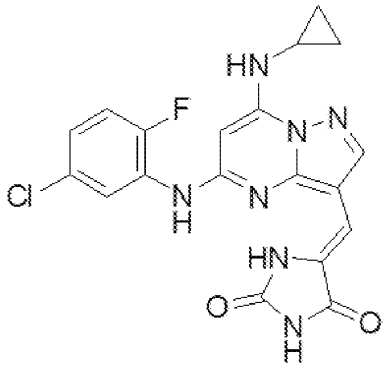


Compound C.

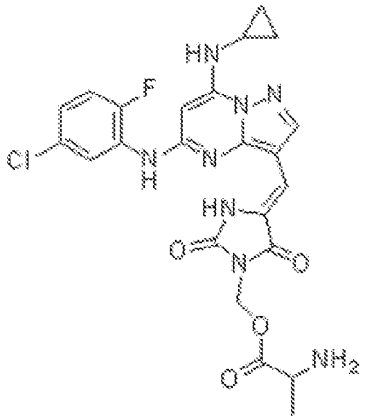
27. The method of claim 1, wherein the compound is Compound A having the structure of



28. The method of claim 1, wherein the compound is Compound B having the structure of



29. The method of claim 1, wherein the compound is Compound C having the structure of



30. The method of claim 1, wherein the RNA virus is severe acute respiratory syndrome-related coronavirus (SARS-CoV), or SARS-CoV-2.

31. The method of claim 1, wherein the RNA viral infection is COVID-19.

32. A pharmaceutical composition for treating an RNA viral infection, comprising a compound set forth in any one of claims 1-29 and a pharmaceutically acceptable excipient.

33. The pharmaceutical composition of claim 32, wherein the compound is Compound A.

34. The pharmaceutical composition of claim 32, wherein the compound is Compound B.

35. The pharmaceutical composition of claim 32, wherein the compound is Compound C.

36. The pharmaceutical composition of claim 32, wherein the RNA virus is SARS-CoV-2.

37. The pharmaceutical composition of claim 32, wherein the RNA viral infection is COVID-19.

38. A use of a compound as described in any one of claims 1-29, or a pharmaceutically acceptable salt or ester thereof, in the preparation of a medicament for treating an RNA viral infection.

39. The use of claim 38, wherein the RNA viral infection is COVID-19.