INHIBITORS OF NOROVIRUS AND CORONAVIRUS REPLICATION

FIELD OF THE DISCLOSURE

[0001] This disclosure relates generally to inhibitors of norovirus and coronavirus replication, and methods of treating or preventing norovirus and coronavirus infections by administering the inhibitors to a patient in need of treatment thereof.

BACKGROUND

[0002] Noroviruses are important enteric pathogens involved in non-bacterial gastroenteritis outbreaks worldwide. Noroviruses mainly occur from person to person via the fecal-oral route but also through contaminated food or water. Indirect contamination is also possible owing to the persistence of the virus in the environment. Human noroviruses belong to the genus Norovirus, family Caliciviridae and are non-enveloped viruses with a positive-sense, single-stranded RNA genome. Norovirus strains are classified into seven groups. Viruses belonging to groups GI, GII, and GIV infect humans, while groups GII, GIII, GIV, GV, GVI and GVII NoVs have been described in animals.

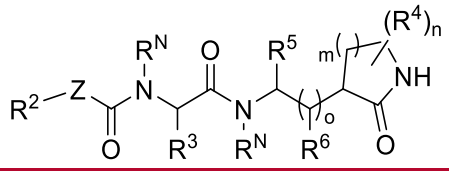
[0003] Coronaviruses are a family of common viruses that cause a range of illnesses in humans from the common cold to severe acute respiratory syndrome (SARS). Coronaviruses can also cause a number of diseases in animals. Coronaviruses are enveloped, positive-stranded RNA viruses whose name derives from their characteristic crown-like appearance in electron micrographs. Coronaviruses are classified as a family within the Nidovirales order, viruses that replicate using a nested set of mRNAs. The coronavirus subfamily is further classified into four genera: alpha, beta, gamma, and delta coronaviruses. The human coronaviruses (HCoVs) are in two of these genera: alpha coronaviruses (including HCoV-229E and HCoV-NL63) and beta coronaviruses (including HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome coronavirus (MERS-CoV), the severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2).

[0004] In 2012, a novel coronavirus emerged in Saudi Arabia and became known as Middle East Respiratory Syndrome coronavirus (MERS-CoV). About half of reported cases of MERS-CoV infection have resulted in death and a majority of reported cases have occurred in older to middle age men. Only a small number of reported cases involved subjects with mild respiratory illness. Human to human transmission of MERS-CoV has been found to be possible, but very limited. Another novel coronavirus emerged in Wuhan, China in late 2019. This virus is known as SARS-CoV-2, 2019-nCoV, or Wuhan coronavirus, and it the cause of a worldwide pandemic in late 2019 and 2020.

[0005] Given the widespread transmission and potential health effects of these viruses, there is a need for drugs for treating norovirus and coronavirus infections.

SUMMARY

[0005a] In one aspect of the present disclosure, there is provided a compound having a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

Z is O, NR^1, or a bond;

each R^N is independently H or C_{1-6}alkyl;

R^1 is C_{5-8}carbocyclyl optionally substituted with C_{1-6}alkylene-C_{6-10}aryl, or 5- to 8-membered N-heterocycle, wherein the ring nitrogen is optionally substituted with COO-C_{1-6}alkyl;

R^2 is C_{1-6}alkyl, C_{1-6}alkylene-C_{5-8}carbocycyl, 4-10 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O, and S, C_{1-6}alkylene-C_{6-10}aryl, or C_{0-6}alkylene-5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, wherein C_{1-6}alkylene is optionally substituted with 1-3 R^7, and the carbocyclyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-C_{6-10}aryl, O-C_{1-6}alkylene-C_{6-10}aryl, and CO_2C_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{5-8}carbocyclyl, C_{0-6}alkylene-C_{6-10}aryl optionally substituted with 1-2 halo, or an amino acid side chain;

each R^4 is independently halo, OH, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyl-OH, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}alkyloxyalkyl, oxo (=O), $NR^ASO_2R^B$, $SO_2NR^AR^B$, $COOR^A$, C_{0-4}alkylene-C_{6-10}aryl, C_{0-4}alkylene-(5-12 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S), or C_{0-4}alkylene-(4-12 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S); and the aryl, heteroaryl, and heterocycle is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl, or

two R^4 with the carbon or carbons to which they are attached combine to form a spiro or fused 3-12 membered carbocyclic or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkylene-O-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, SO_2-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl;

R^5 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, -$[C(O)]_{1-2}$-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S), -$[C(O)]_{1-2}$-NR^NR^N, C(O)-Y-H, or -$[C(O)]_{1-2}$-NR^N-Y-X-A, wherein A is H, C_{3-8}carbocyclyl, 4-12-membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, C_{6-10}aryl, or 5-8-membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl;

Y is a bond, C_{1-6}alkylene, C_{1-6}alkylene-O-C_{1-6}alkylene, or C_{1-6}alkenylene, wherein C_{1-6}alkylene and C_{1-6}alkenylene are optionally substituted with 1-3 substituents independently selected from halo, OH, NR^NR^N, and C_{1-6}alkoxy;

X is a bond, NR^NR^N, C(O), SO_2, or OC(O);

each R^6 is independently H, C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, CHO, or C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O,

and S);

each R^7 is independently halo, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{3-5}carbocycyl, or C_{0-6}alkylene-C_{6-10}aryl, and C_{6-10}aryl is optionally substituted with 1-2 halo, or

two R^7 with the carbon or carbons to which they are attached combine to form a spiro or fused C_{3-6}carbocyclyl ring;

R^A and R^B are each independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{0-6}alkylene-C_{6-10}aryl, C_{0-6}alkylene-5-8 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S;

n is 0-3;

m is 0-5; and

o is 0-5.

[0005b] In another aspect of the present disclosure, there is provided a compound as recited in Table A, or a pharmaceutically acceptable salt thereof.

[0005c] In a further aspect of the present disclosure, there is provided a compound as recited in Table B, or a pharmaceutically acceptable salt thereof.

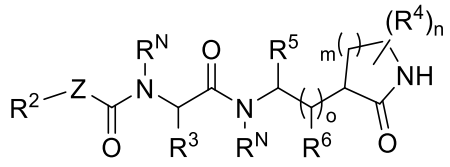
[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical formulation comprising the compound or salt disclosed herein and a pharmaceutically acceptable excipient.

[0005e] In a further aspect of the present disclosure, there is provided a use of the compound or salt disclosed herein in the manufacture of a medicament for treating or preventing a viral infection in a host.

[0005f] In another aspect of the present disclosure, there is provided a compound or salt disclosed herein, for use in therapy.

[0006] The present disclosure generally relates to methods of treating norovirus and coronavirus infections, to methods of inhibiting the replication of noroviruses and coronaviruses, to methods of reducing the amount of noroviruses and coronaviruses, and to compounds and compositions that can be employed for such methods.

[0007] The disclosure provides compounds of Formula (I), and pharmaceutically acceptable salts thereof:



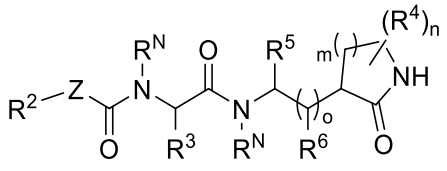
(I),

wherein

Z is O, NR^1, or a bond; each R^N is independently H or C_{1-6}alkyl; R^1 is C_{5-8}carbocyclyl optionally substituted with C_{1-6}alkylene-C_{6-10}aryl, or 5- to 8-membered N-heterocycle, wherein the ring nitrogen is optionally substituted with COO-C_{1-6}alkyl; R^2 is C_{1-6}alkyl, C_{1-6}alkylene-C_{5-8}carbocycyl, 4-10 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O, and S, C_{1-6}alkylene-C_{6-10}aryl, or C_{0-6}alkylene-5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, wherein C_{1-6}alkylene is optionally substituted with 1-3 R^7, and the carbocyclyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-C_{6-10}aryl, O-C_{1-6}alkylene-C_{6-10}aryl, and CO_2C_{1-6}alkyl; R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{5-8}carbocyclyl, C_{0-6}alkylene-C_{6-10}aryl optionally substituted with 1-2 halo, or an amino acid side chain; each R^4 is independently halo, OH, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyl-OH, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}alkyloxyalkyl, oxo (=O), $NR^ASO_2R^B$, $SO_2NR^AR^B$, $COOR^A$, C_{0-4}alkylene-C_{6-10}aryl, C_{0-4}alkylene-(5-12 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S), or C_{0-4}alkylene-(4-12 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S); and the aryl, heteroaryl, and heterocycle is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl, or two R^4 with the carbon or carbons to which they are attached combine to form a spiro or fused 3-12 membered carbocyclic or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkylene-O-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, SO_2-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl; R^5 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, -$[C(O)]_{1-2}$-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S), -$[C(O)]_{1-2}$-NR^NR^N, C(O)-Y-H, or -$[C(O)]_{1-2}$-NR^N-Y-X-A, wherein A is H, C_{3-8}carbocyclyl, 4-12-membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, C_{6-10}aryl, or 5-8-membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl; Y is a bond, C_{1-6}alkylene, C_{1-6}alkylene-O-C_{1-6}alkylene, or C_{1-6}alkenylene, wherein C_{1-6}alkylene and C_{1-6}alkenylene are optionally substituted with 1-3 substituents independently selected from halo, OH, NR^NR^N, and C_{1-6}alkoxy; X is a bond, NR^NR^N, C(O), SO_2, or OC(O); each R^6 is independently H, C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, CHO, or C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S); each R^7 is independently halo, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{3-5}carbocycyl, or C_{0-6}alkylene-C_{6-10}aryl, and C_{6-10}aryl is optionally substituted with 1-2 halo, or two R^7 with the carbon or carbons to which they are attached combine to form a spiro or fused C_{3-6}carbocyclyl ring; R^A and R^B are each independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{0-6}alkylene-C_{6-10}aryl, C_{0-6}alkylene-5-8 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S; n is 0-3; m is 0-5; and o is 0-5. In some ~~embodiment~~example**s**, Z is O or NR^1; each R^N is independently H or C_{1-6}alkyl; R^1 is C_{5-8}carbocyclyl optionally

What is claimed is:

1. A compound having a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

Z is O, NR^1, or a bond;

each R^N is independently H or C_{1-6}alkyl;

R^1 is C_{5-8}carbocyclyl optionally substituted with C_{1-6}alkylene-C_{6-10}aryl, or 5- to 8-membered N-heterocycle, wherein the ring nitrogen is optionally substituted with COO-C_{1-6}alkyl;

R^2 is C_{1-6}alkyl, C_{1-6}alkylene-C_{5-8}carbocycyl, 4-10 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O, and S, C_{1-6}alkylene-C_{6-10}aryl, or C_{0-6}alkylene-5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, wherein C_{1-6}alkylene is optionally substituted with 1-3 R^7, and the carbocyclyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-C_{6-10}aryl, O-C_{1-6}alkylene-C_{6-10}aryl, and CO_2C_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{5-8}carbocyclyl, C_{0-6}alkylene-C_{6-10}aryl optionally substituted with 1-2 halo, or an amino acid side chain;

each R^4 is independently halo, OH, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyl-OH, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}alkyloxyalkyl, oxo (=O), $NR^ASO_2R^B$, $SO_2NR^AR^B$, $COOR^A$, C_{0-4}alkylene-C_{6-10}aryl, C_{0-4}alkylene-(5-12 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S), or C_{0-4}alkylene-(4-12 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S); and the aryl, heteroaryl, and heterocycle is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl, or

two R^4 with the carbon or carbons to which they are attached combine to form a spiro or fused 3-12 membered carbocyclic or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkylene-O-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, SO_2-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl;

R^5 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, -$[C(O)]_{1-2}$-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S), -$[C(O)]_{1-2}$-NR^NR^N, C(O)-Y-H, or -$[C(O)]_{1-2}$-NR^N-Y-X-A, wherein A is H, C_{3-8}carbocyclyl, 4-12-membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, C_{6-10}aryl, or 5-8-membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl;

Y is a bond, C_{1-6}alkylene, C_{1-6}alkylene-O-C_{1-6}alkylene, or C_{1-6}alkenylene, wherein C_{1-6}alkylene and C_{1-}

$_{6}$alkenylene are optionally substituted with 1-3 substituents independently selected from halo, OH, NR^NR^N, and C_{1-6}alkoxy;

X is a bond, NR^NR^N, C(O), SO_2, or OC(O);

each R^6 is independently H, C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, CHO, or C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S);

each R^7 is independently halo, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{3-5}carbocycyl, or C_{0-6}alkylene-C_{6-10}aryl, and C_{6-10}aryl is optionally substituted with 1-2 halo, or

two R^7 with the carbon or carbons to which they are attached combine to form a spiro or fused C_{3-6}carbocyclyl ring;

R^A and R^B are each independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{0-6}alkylene-C_{6-10}aryl, C_{0-6}alkylene-5-8 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S;

n is 0-3;

m is 0-5; and

o is 0-5.

2. The compound or salt according to claim 1, wherein each R^N is H.

3. The compound or salt according to claim 1 or 2, wherein Z is NR^1.

4. The compound or salt according to claim 3, wherein R^1 is C_{5-8}carbocyclyl optionally substituted with C_{1-6}alkylene-C_{6-10}aryl.

5. The compound or salt according to claim 4, wherein R^1 is unsubstituted C_{5-8}carbocyclyl.

6. The compound or salt according to claim 5, wherein R^1 is unsubstituted C_{5-6}carbocyclyl.

7. The compound or salt according to claim 3, wherein R^1 is C_{5-8}carbocyclyl substituted with C_{1-6}alkylene-C_{6-10}aryl.

8. The compound or salt according to claim 7, wherein R^1 is C_{5-6}carbocyclyl substituted with C_{1-6}alkylene-C_{6-10}aryl.

9. The compound or salt according to claim 7 or 8, wherein R^1 is C_{5-6}carbocyclyl substituted with benzyl.

10. The compound or salt according to claim 3, wherein R^1 is 5- to 8-membered N-heterocycle, wherein the ring nitrogen is substituted with COO-C_{1-6}alkyl.

11. The compound or salt according to claim 10, wherein R^1 is 6-membered N-heterocycle, wherein the ring nitrogen is substituted with COO-C_{1-6}alkyl.

12. The compound or salt according to claim 10 or 11, wherein the heterocycle ring nitrogen is substituted with COO-*t*-butyl.

13. The compound or salt according to claim 1 or 2, wherein Z is O.

14. The compound or salt according to any one of claims 1 to 13, wherein R^2 is C_{1-6}alkyl.

15. The compound or salt according to claim 12, wherein R^2 is methyl.

16. The compound or salt according to any one of claims 1 to 13, wherein R^2 is C_{1-6}alkylene-C_{6-10}aryl.

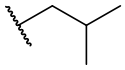
17. The compound or salt according to claim 16, wherein R^2 is benzyl.

18. The compound or salt according to any one of claims 1 to 13, wherein R^2 is C_{1-6}alkylene-C_{5-8}carbocycyl.

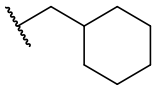
19. The compound or salt according to any one of claims 1 to 13, wherein R^2 is C_{1-6}alkylene-5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S.

20. The compound or salt according to any one of claims 16 to 19, wherein R^2 is substituted with 1-2 substituents independently selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}haloalkyl, and CO_2C_{1-6}alkyl.

21. The compound or salt according to any one of claims 1 to 20, wherein R^3 is C_{1-6}alkyl.

22. The compound or salt according to claim 21, wherein R^3 is .

23. The compound or salt according to any one of claims 1 to 20, wherein R^3 is C_{1-6}alkylene-C_{5-8}carbocyclyl.

24. The compound or salt according to claim 23, wherein R^3 is .

25. The compound or salt according to any one of claims 1 to 20, wherein R^3 is C_{2-6}alkenyl or C_{2-6}alkynyl.

26. The compound or salt according to any one of claims 1 to 20, wherein R^3 is C_{0-6}alkylene-C_{6-10}aryl.

27. The compound or salt according to any one of claims 1 to 20, wherein R^3 is an amino acid side chain.

28. The compound or salt according to claim 27, wherein R^3 is methyl, isopropyl, isobutyl, sec-butyl, $CH_2CH_2SCH_3$, CH_2-indolyl, benzyl, CH_2OH, $CH(OH)CH_3$, CH_2SH, CH_2-(4-OH-phenyl), $CH_2C(O)NH_2$, $CH_2CH_2C(O)NH_2$, CH_2COOH, CH_2CH_2COOH, $CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHC(NH)NH_2$, or imidazolyl.

29. The compound or salt according to any one of claims 1 to 28, wherein n is 0.

30. The compound or salt according to any one of claims 1 to 28, wherein n is 1, 2, or 3.

31. The compound or salt according to claim 30, wherein n is 1 or 2.

32. The compound or salt according to claim 30 or 31, wherein each R^4 is independently C_{1-6}alkyl, oxo (=O), C_{0-4}alkylene-C_{6-10}aryl, C_{0-4}alkylene-(5-12 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S), or C_{0-4}alkylene-(4-12 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S); and the aryl, heteroaryl, and heterocycle is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl.

33. The compound or salt according to claim 30 or 31, wherein at least one R^4 is halo, OH, CN, C_{1-6}haloalkyl, C_{1-6}alkyl-OH, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-6}alkyloxyalkyl, $NR^ASO_2R^B$, $SO_2NR^AR^B$, or $COOR^A$.

34. The compound or salt according to claim 31, wherein n is 2 and two R^4 with the carbon or carbons to which they are attached combine to form a spiro or fused 5-12 membered carbocycle or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl.

35. The compound or salt according to claim 34, wherein the two R^4 with the carbon to which they are attached combine to form a spiro 5-12 membered carbocycle or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl.

36. The compound or salt according to claim 34, wherein the two R^4 with the carbons to which they are attached combine to form a fused 5-12 membered carbocycle or heterocylic ring having 1-3 ring heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, C(O)-C_{1-6}alkyl, and COO-C_{1-6}alkyl.

37. The compound or salt according to any one of claims 1 to 36, wherein R^5 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S), $CONR^NR^N$, C(O)-C(O)N$(R^N)_2$, CHO, or C(O)-C(O)NR^N-Y-X-A, wherein A is C_{3-8}carbocyclyl, 4-12-membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, C_{6-10}aryl, or 5-8-membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl.

38. The compound or salt according to any one of claims 1 to 37, wherein Y is C_{1-6}alkylene optionally substituted with 1-3 substituents independently selected from halo, OH, NR^NR^N, and C_{1-6}alkoxy.

39. The compound or salt according to any one of claims 1 to 38, wherein R^2 is C_{1-6}alkyl, C_{1-6}alkylene-C_{5-8}carbocycyl, 4-10 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O, and S, C_{1-6}alkylene-C_{6-10}aryl, 5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, or C_{1-6}alkylene-5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O, and S, wherein C_{1-6}alkylene is substituted with 1-3 R^7.

40. The compound or salt according to claim 39, wherein C_{1-6}alkylene is substituted with 1 R^7.

41. The compound or salt according to claim 39, wherein C_{1-6}alkylene is substituted with 2 R^7.

42. The compound or salt according to claim 39, wherein C_{1-6}alkylene is substituted with 3 R^7.

43. The compound or salt according to any one of claims 39 to 42, wherein at least one R^7 is C_{0-6}alkylene-C_{6-10}aryl optionally substituted with 1-2 halo.

44. The compound or salt according to claim 43, wherein at least one R^7 is phenyl optionally substituted with 1-2 halo.

45. The compound or salt according to claim 43 or 44, wherein at least one R^7 is phenyl optionally substituted with 1 halo.

46. The compound or salt according to any one of claims 1 to 39, 41, and 42, wherein two R^7 with the carbon or carbons to which they are attached combine to form a spiro or fused C_{3-6}carbocyclyl ring.

47. The compound or salt according to claim 46, wherein two R^7 with the carbon to which they are attached combine to form a spiro C_{3-6}carbocyclyl ring.

48. The compound or salt according to claim 46, wherein two R^7 with the carbons to which they are attached combine to form a fused C_{3-6}carbocyclyl ring.

49. The compound or salt according to any one of claims 1 to 48, wherein o is 0.

50. The compound or salt according to any one of claims 1 to 48, wherein o is 1-5.

51. The compound or salt according to claim 50, wherein o is 1 or 2.

52. The compound or salt according to claim 50 or 51, wherein each R^6 is H.

53. The compound or salt according to claim 50 or 51, wherein at least one R^6 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, CHO, or C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S).

54. The compound or salt according to any one of claims 1 to 53, wherein m is 0.

55. The compound or salt according to any one of claims 1 to 53, wherein m is 1.

56. The compound or salt according to any one of claims 1 to 53, wherein m is 2.

57. The compound or salt according to any one of claims 1 to 56, wherein R^5 is C_{1-6}alkylene-OH, C_{1-6}alkylene-OH substituted with $PO(OCH_2CH_2)_2$, C_{1-6}alkylene-OH substituted with SO_3H, CHO, C(O)-(4-8 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S), or $CONR^NR^N$.

58. The compound or salt according to any one of claims 1 to 56, wherein R^5 is C(O)-C(O)NR^N-Y-X-A.

59. The compound or salt according to claim 58, wherein Y is C_{1-6}alkylene.

60. The compound or salt according to claim 58 or 59, wherein X is a bond.

61. The compound or salt according to claim 58 or 59, wherein X is NR^NR^N, C(O), SO_2, or OC(O).

62. The compound or salt according to any one of claims 58 to 61, wherein A is C_{5-8}carbocyclyl or C_{6-10}aryl, and optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl.

63. The compound or salt according to any one of claims 58 to 61, wherein A is 4-12-membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, or 5-8-membered heteroaryl having 1-3 ring

heteroatoms selected from N, O, and S, optionally substituted with 1-2 substituents independently selected from halo, C_{1-6}alkyl, and COO-C_{1-6}alkyl.

64. The compound or salt according to claim 63, wherein A comprises pyridyl.

65. A compound as recited in Table A, or a pharmaceutically acceptable salt thereof.

66. A compound as recited in Table B, or a pharmaceutically acceptable salt thereof.

67. A pharmaceutical formulation comprising the compound or salt according to any one of claims 1 to 66 and a pharmaceutically acceptable excipient.

68. Use of the compound or salt according to any one of claims 1 to 66 in the manufacture of a medicament ~~A method~~ for treating or preventing a viral infection in a host~~, comprising administering to the host a therapeutic amount of the compound or salt according to any one of claims 1 to 66~~.

69. The use~~method~~ according to claim 68, wherein the viral infection is coronavirus infection, calicivirus infection, or picornavirus infection.

70. The use~~method~~ according to claim 69, wherein the viral infection is a calicivirus infection.

71. The use~~method~~ according to claim 70, wherein the calicivirus infection is a norovirus infection.

72. The use~~method~~ according to claim 69, wherein the viral infection is a coronavirus infection.

73. The ~~method~~use according to claim 72, wherein the coronavirus infection is severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), or Coronavirus disease 2019 (COVID-19).

74. The ~~method~~use according to claim 69, wherein the viral infection is a picornavirus infection.

75. The ~~method~~use according to claim 74, wherein the picornavirus infection is rhinovirus infection.

76. The ~~method~~use according to claim 75, wherein the rhinovirus infection is a rhinovirus A, rhinovirus B, or rhinovirus C infection.

77. The ~~method~~use according to claim 72, wherein the coronavirus is an alpha coronavirus.

78. The ~~method~~use according to claim 72, wherein the coronavirus is a beta coronavirus.

79. The compound or salt according to any one of claims 1 to 66, for use in therapy.