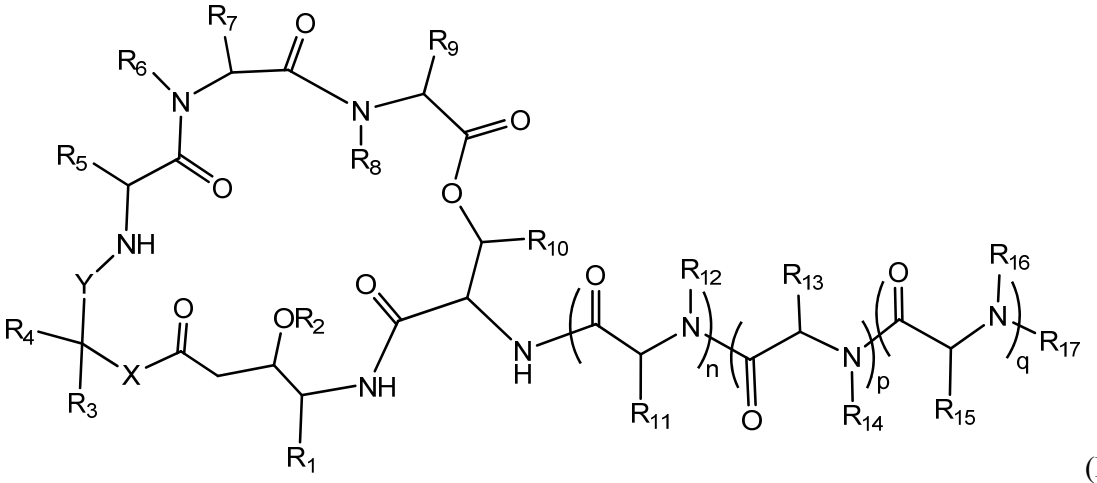
CLAIMS:

1. ~~A~~ Use of a compound of general formula **I**



(**I**)

wherein X is selected from O and NH;

Y is selected from CO and –COCH(CH_3)CO-;

each n and p is independently selected from 0 and 1, and q is selected from 0, 1 and 2;

each R_1, R_3, R_5, R_9, R_{11}, and R_{15} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, and substituted or unsubstituted C_2-C_6 alkynyl;

R_2 is selected from hydrogen, COR_a, $COOR_a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, and substituted or unsubstituted C_2-C_6 alkynyl;

each R_4, R_8, R_{10}, R_{12}, and R_{16} is independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl;

each R_7 and R_{13} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, and substituted or unsubstituted C_2-C_6 alkynyl; each R_6 and R_{14} is independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; or R_6 and R_7 and/or R_{13} and R_{14} together with the corresponding N atom and C atom to which they are attached may form a substituted or unsubstituted heterocyclic group;

R_{17} is selected from hydrogen, COR_a, $COOR_a$, $CONHR_b$, $COSR_c$, $(C{=}NR_b)OR_a$, $(C{=}NR_b)NHR_b$, $(C{=}NR_b)SR_c$, $(C{=}S)OR_a$, $(C{=}S)NHR_b$, $(C{=}S)SR_c$, SO_2R_c, SO_3R_c, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, with the proviso that when n, p, and q are 0 then R_{17} is not hydrogen; and

each R_a, R_b, and R_c is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

or a pharmaceutically acceptable salt or stereoisomer thereof, ~~for use in~~ in the manufacture of a medicament for the treatment of coronavirus (CoV) infection.

2. A compound according to claim 1, wherein R_3 and R_4 are independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_3 is isopropyl and R_4 is hydrogen.

3. A compound according to claim 1 or claim 2 of general formula **II**, wherein R_3 and R_4 are methyl.

4. A compound according to any preceding claim, wherein R_{11} is selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_{11} is methyl or isobutyl.

5. A compound according to any preceding claim, of general formula **III** wherein R_{11} is methyl and n=1.

6. A compound according to any preceding claim, wherein R_1, R_5, R_9, and R_{15} are independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_1 is selected from sec-butyl and isopropyl, R_5 is isobutyl, R_9 is p-methoxybenzyl, and R_{15} is selected from methyl and benzyl.

7. A compound according to any preceding claim, wherein R_8, R_{10}, R_{12}, and R_{16} are independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_8, R_{10} and R_{12} are methyl, and R_{16} is hydrogen.

8. A compound according to any preceding claim, wherein R_6 and R_{14} are independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_6 is selected from hydrogen and methyl, and R_{14} is hydrogen.

9. A compound according to any preceding claim, wherein R_7 and R_{13} are independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_7 is methyl and R_{13} is selected from hydrogen, methyl, isopropyl, isobutyl, and 3-amino-3-oxopropyl.

10. A compound according to any of claims 1 to 7, wherein R_6 and R_7 and/or R_{13} and R_{14} together with the corresponding N atom and C atom to which they are attached form a substituted or unsubstituted pyrrolidine group.

11. A compound according to any preceding claim, wherein R_2 is selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, and COR_a, and wherein R_a is a substituted or unsubstituted C_1-C_6 alkyl; preferably wherein R_2 is hydrogen.

12. A compound according to any preceding claim, wherein R_{17} is selected from hydrogen, COR_a, $COOR_a$, $CONHR_b$, $(C=S)NHR_b$, and SO_2R_c, and wherein each R_a, R_b, and R_c is independently selected from substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group; preferably wherein R_{17} is selected from hydrogen, COObenzyl, CObenzo[b]thiophen-2-yl, SO_2(p-methylphenyl), $COCOCH_3$ and $COOC(CH_3)_3$.

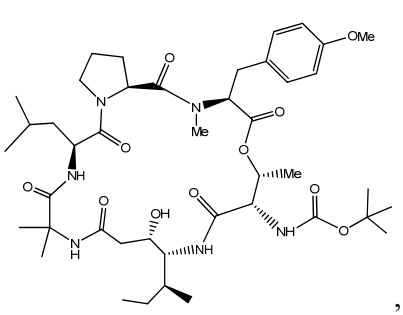
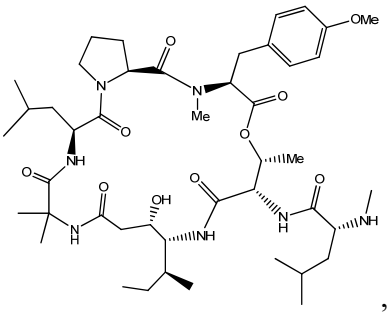
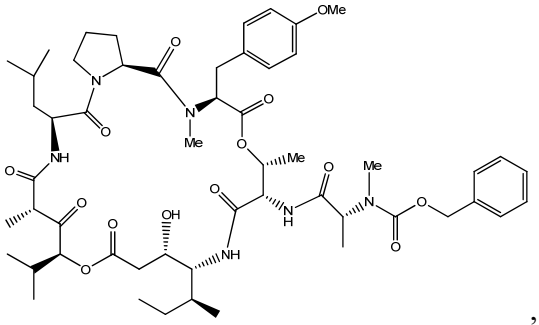
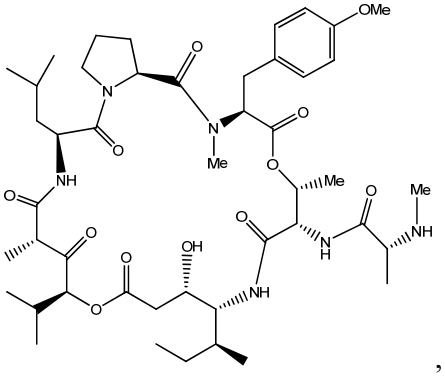
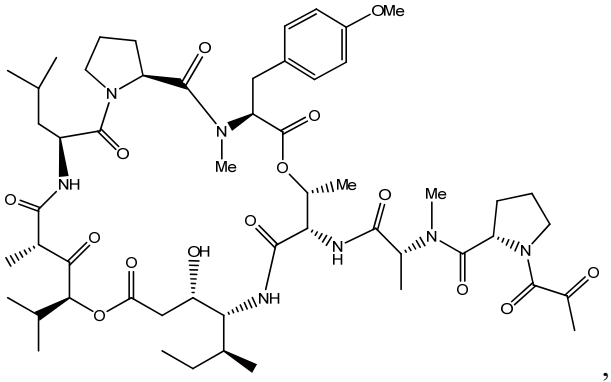
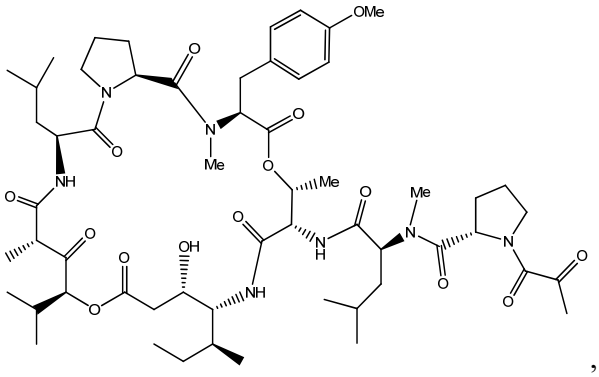
13. A compound according to any preceding claim, wherein X is NH.

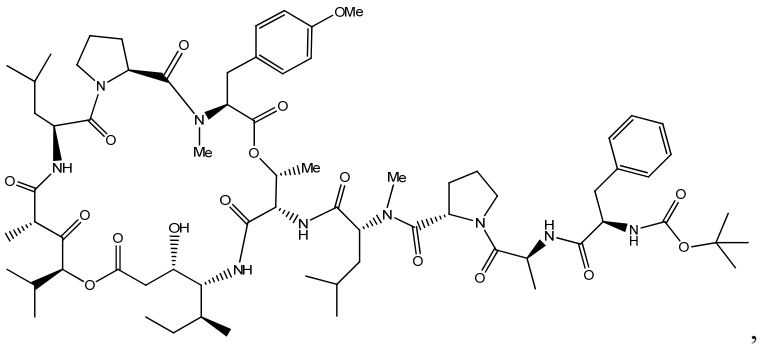
14. A compound according to any of claims 1 to 12, wherein X is O.

15. A compound according to any preceding claim wherein Y is CO.

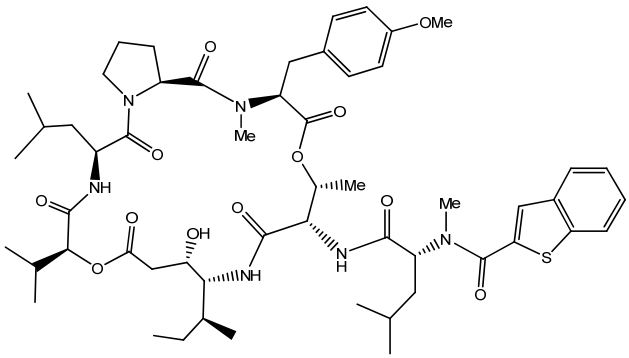
16. A compound according to any of claims 1 to 14, wherein Y is $COCH(CH_3)CO$.

~~172~~. ~~A compound~~The use according to claim 1, the compound having the following structure:

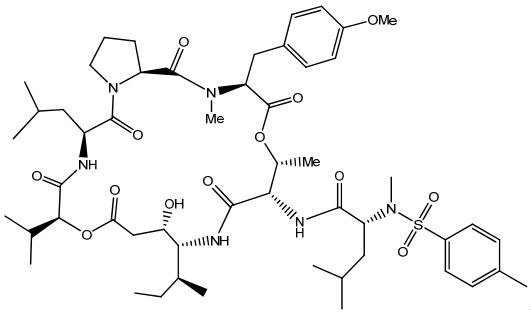

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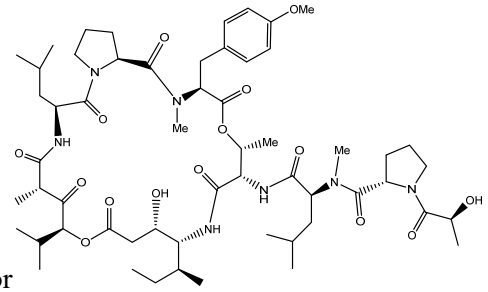
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, or



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or pharmaceutically acceptable salts or stereoisomers thereof.

~~183~~. ~~A compound~~The use according to claim 1, wherein the compound is PLD, or pharmaceutically acceptable salts or stereoisomers thereof.

~~194~~. The use ~~A compound~~ according to claim 1, wherein the compound is didemninB, or pharmaceutically acceptable salts or stereoisomers thereof.

~~205~~. ~~A compound~~The use according to any of the preceding claims, for ~~use in~~ the treatment of CoV infection, wherein the CoV is SARS-CoV-2; preferably~~.~~

~~21. A compound according to any one of claims 1 to 20, for use in~~ the treatment of COVID-19 and/or for use in the treatment of pneumonia caused by COVID-19.

~~226~~. A compound according to any preceding claim, wherein the CoV infection is mild

infection; and/or wherein the CoV infection is moderate infection; and/or wherein the CoV infection is severe infection.

~~23~~7. A compound according to any preceding claim, wherein the CoV infection is acute CoV infection, preferably wherein the CoV infection is acute COVID-19 infection; and/or wherein the CoV infection is ongoing symptomatic CoV infection, preferably wherein the CoV infection is ongoing symptomatic COVID-19 infection; and/or wherein the CoV infection is post-CoV syndrome, CoV persistent or long CoV; preferably wherein the CoV infection is post-COVID-19 syndrome, COVID persistent or long COVID.

~~24~~8. A compound according to claim ~~23~~7, wherein the post-CoV syndrome, CoV persistent or long CoV include one or more symptoms arising from the cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, metabolic, renal, dermatological, otolaryngological, haematological and autonomic systems; psychiatric problems, generalised pain, fatigue and/or persisting fever.

~~25~~9. A compound according to any preceding claim, for use in the treatment of a patient with signs and symptoms of CoV infection (preferably COVID-19) for up to 4 weeks; and/or for use in the treatment of a patient with signs and symptoms of CoV infection (preferably COVID-19) from 4 weeks to 12 weeks; and/or for use in the treatment of a patient with signs and symptoms of CoV infection, preferably COVID-19, for more than 12 weeks.

~~26~~10. A compound according to any preceding claim, for use in the prophylaxis, reduction or treatment of COVID persistent, long COVID or post-COVID syndrome; preferably wherein the prophylaxis, reduction or treatment minimises the likelihood that a patient suffers from COVID persistent, long COVID or post-COVID syndrome symptoms; and/or reduces the severity of such symptoms; further preferably wherein the treatment minimising the symptoms of CoV infection.

~~27~~11. A compound according to any preceding claim, wherein the treatment reduces the infectivity of CoV patients; including wherein the patient is asymptomatic or not very symptomatic patients yet has a high viral load.

~~28~~12. ~~A compound for~~The use according to any preceding claim, wherein the compound is administered in combination with a corticosteroid, preferably dexamethasone.

~~29~~13. A compound for use according to claim ~~28~~12, wherein the compound and corticosteroid are administered concurrently, separately or sequentially.

~~30~~14. ~~A compound for~~The use according to any one of claims 1 to ~~29~~13, wherein the compound is administered according to a regimen of a daily dose for 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days or 1 day; preferably 2-5 days, 3-5 days, or 3, 4 or 5 days; most preferably 3 days or 5 days; most preferably 3 days.

~~31~~15. A compound for use according to any one of claims 1 to ~~30~~14, wherein the compound is administered at a dose of 5mg a day or less, 4.5mg a day or less, 4mg a day or less, 3.5mg a day or less, 3mg a day or less, 2.5mg a day or less or 2mg a day or less; 0.5 mg/day, 1 mg/day, 1.5 mg/day, 2 mg/day, 2.5 mg/day, 3 mg/day, 3.5 mg/day, 4 mg/day, 4.5 mg/day, or 5mg/day; preferably 1 mg/day, 1.5 mg/day, 2 mg/day or 2.5 mg/day; more preferably 1.5-2.5 mg/day; most preferably 1.5 mg/day, 2.0 mg/day or 2.5 mg/day.

~~32~~16. A compound for use according to any one of claims 1 to ~~31~~15, wherein the compound is administered at a total dose of 1-50 mg, 1-40 mg, 1-30 mg, 1-20 mg, 1-15 mg, 3-15 mg, 3-12 mg, 4-12 mg, 4-10 mg, or 4.5-10 mg; 4mg, 4.5mg, 5mg, 5.5mg, 6mg, 6.5mg, 7mg, 7.5mg, 8mg,

8.5mg, 9mg, 9.5mg or 10mg; preferably 4.5mg, 5mg, 6mg, 7.5mg, 8mg, 9mg or 10mg; more preferably 4.5-7.5 mg/day.

~~33~~17. ~~A compound for~~The use according to any one of claims 1 to ~~32~~16, wherein the compound is administered by infusion~~.~~; preferably

~~34. A compound for use according to claim 33,~~ wherein the infusion is a 1 hour infusion, a 1.5 hour infusion, a 2 hour infusion or a 3 hour infusion, preferably a 1.5 hour infusion.

~~35~~18. A compound for use according to any one of claims 1 to ~~34~~17, wherein 1.5 mg of plitidepsin is administered as a 1.5-hour infusion, once a day for 3 consecutive days; or wherein 2 mg of plitidepsin is administered as a 1.5-hour infusion, once a day for 3 consecutive days; or wherein 2.5 mg of plitidepsin is administered as a 1.5-hour infusion, once a day for 3 consecutive days; or wherein 1 mg of plitidepsin is administered as a 1.5-hour infusion, once a day for 5 consecutive days; or wherein 2 mg of plitidepsin is administered as a 1.5-hour infusion, once a day for 5 consecutive days.

~~36~~19. ~~A compound for~~The use according to any one of claims 1 to 1~~35~~8, wherein the compound is administered using a loading dose and a maintenance dose~~.~~; including

~~37. A compound for use according to claim 36,~~ wherein the dosage regimen is:

a loading dose of 2.5 mg for day 1, and followed by a maintenance dose of 2 mg/day for subsequent days;

a loading dose of 2.5 mg for day 1, and followed by a maintenance dose of 1.5 mg/day for subsequent days;

a loading dose of 2.5 mg for day 1, and followed by a maintenance dose of 1 mg/day for subsequent days;

a loading dose of 2.5 mg for day 1, and followed by a maintenance dose of 0.5 mg/day for subsequent days;

a loading dose of 2 mg for day 1, and followed by a maintenance dose of 1.5 mg/day for subsequent days;

a loading dose of 2 mg for day 1, and followed by a maintenance dose of 1 mg/day for subsequent days;

a loading dose of 2 mg for day 1, and followed by a maintenance dose of 0.5 mg/day for subsequent days;

a loading dose of 1.5 mg for day 1, and followed by a maintenance dose of 1 mg/day for subsequent days;

a loading dose of 1.5 mg for day 1, and followed by a maintenance dose of 0.5 mg/day for subsequent days; or

a loading dose of 1 mg for day 1, and followed by a maintenance dose of 0.5 mg/day for subsequent days.

~~38~~20. ~~A compound for~~The use according to any one of claims 1 to ~~37~~19, wherein the compound

is administered in combination with a corticosteroid, and wherein the corticosteroid is administered on the same days as administration of the compound according to any one of claims 1 to ~~19~~19.

~~39~~21. A compound for use according to claim ~~38~~20, wherein the corticosteroid may also be administered on one or more subsequent days; preferably wherein the corticosteroid is administered with the compound on days 1-3 and the corticosteroid is further administered on one or more of days 4-10.

~~40~~22. A compound for use according to claim ~~39~~21, wherein the corticosteroid is administered intravenously on days when the compound is administered but is administered by oral administration or IV on subsequent days.

~~41~~23. A compound for use according to any one of claims ~~38–~~20 to ~~40~~22, wherein the corticosteroid is dexamethasone; preferably wherein dexamethasone is administered at a dose of 6.6 mg/day IV on days when the compound according to the present invention is administered; preferably.

~~42. A compound for use according to claim 41,~~ wherein dexamethasone is administered at a dose of 6 mg/day oral administration or IV on subsequent days, preferably one or more of days 4, 5, 6, 7, 8, 9 and 10.

~~43~~24. A compound for use according to any one of claims 1 to ~~42~~23, wherein PLD is administered 1.5 mg/day intravenous (IV) combined with dexamethasone 6.6 mg/day IV on Days 1 to 3, followed by dexamethasone 6 mg/day oral administration (PO)/IV from Day 4 and up to Day 10 (as per physician judgement according to patient clinical condition and evolution); or

wherein PLD is administered 2.0 mg/day intravenous (IV) combined with dexamethasone 6.6 mg/day IV on Days 1 to 3, followed by dexamethasone 6 mg/day oral administration (PO)/IV from Day 4 and up to Day 10 (as per physician judgement according to patient clinical condition and evolution); or

wherein PLD is administered 2.5 mg/day intravenous (IV) combined with dexamethasone 6.6 mg/day IV on Days 1 to 3, followed by dexamethasone 6 mg/day oral administration (PO)/IV from Day 4 and up to Day 10 (as per physician judgement according to patient clinical condition and evolution).

~~44~~25. A compound for use according to any one of claims ~~38–~~20 to ~~43~~24, wherein the corticosteroid is administered 20 to 30 minutes prior to starting treatment with the compound according to any one of claims 1 to ~~19~~4.

~~45. A compound for use according to any one of claims 1 to 44, wherein the patient additionally receives the following medications, preferably 20 to 30 minutes prior to starting treatment with the compound according to any one of claims 1 to 19:~~

~~Ondansetron 8 mg IV (or equivalent);~~

~~Diphenhydramine hydrochloride 25 mg IV (or equivalent); and~~

~~Ranitidine 50 mg IV (or equivalent).~~

~~46~~26. A compound for use according to any one of claims 1 to ~~45~~25, wherein on Days 4 and 5, patients receive ondansetron (or equivalent) 4 mg twice a day PO.

~~47~~27. The ~~A compound for~~ use according to any one of claims 1 to ~~34~~26, wherein the compound is administered as a single dose (on day 1).

~~48~~28. A compound for use according to claim ~~47~~27, wherein the single dose is 1-10 mg, 4-10 mg, 4.5-10 mg, 4mg, 4.5mg, 5mg, 5.5mg, 6mg, 6.5mg, 7mg, 7.5mg, 8mg, 8.5mg, 9mg, 9.5mg or 10mg, preferably 4.5mg, 5mg, 6mg, 7.5mg, 8mg, 9mg or 10mg, more preferably 5-9 mg, 6.5-8.5 mg, 7-8 mg or most preferably 7.5 mg.

~~49~~29. A compound for use according to any one of claims ~~47~~ 27 to ~~48~~28, wherein the compound is administered as a 1.5-hour infusion.

~~50~~30. A compound for use according to any one of claims ~~47~~ 27 to ~~49~~29, wherein a corticosteroid is administered according to the regimen according to any one of claims ~~38~~ 20 to ~~44~~25.

~~51~~31. A compound for use according to any one of claims ~~47~~ 1 to ~~50~~30, wherein the following prophylactic medications are administered 20-30 minutes prior to administration with a compound of the present invention:

Ondansetron 8 mg IV (or equivalent), particularly in slow infusion of 15 minutes;

Diphenhydramine hydrochloride 25 mg IV (or equivalent);

Ranitidine 50 mg IV (or equivalent).

~~52. A compound for use according to any one of claims 47 to 51, wherein ondansetron 4 mg orally is given every 12 hours for 3 days after administration of a compound of the present invention.~~

~~53. A compound for use according to any preceding claim, wherein dexamethasone is dexamethasone phosphate and is administered at a dose of 8 mg if administered on days when a compound of the invention is administered (equating to a dose of 6.6 mg base) and is administered at a dose of 7.2 mg if administered thereafter (equating to a dose of 6 mg base).~~

~~54. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 53, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier, for use in the treatment of coronavirus (CoV) infection; preferably wherein the CoV is SARS-CoV-2.~~

~~55. Use of a compound as defined in any of claims 1 to 53, or a pharmaceutically acceptable salt or stereoisomer thereof, in the manufacture of a medicament for the treatment of CoV infection; preferably wherein the CoV is SARS-CoV-2.~~

~~56. A method of treating a CoV infection, wherein the method comprises administering to an individual in need thereof, a therapeutically effective amount of a compound as defined in any of claims 1 to 53, or a pharmaceutically acceptable salt or stereoisomer thereof; preferably wherein the CoV is SARS-CoV-2.~~

~~57~~32. The use according to any preceding claim, in the manufacture of a medicament for the ~~A method of~~ prophylaxis, reduction or treatment of CoV persistent, long CoV or post-CoV syndrome, wherein the method comprises administering to an individual in need thereof, a therapeutically effective amount of a compound as defined in any of claims 1 to ~~53~~31, or a pharmaceutically acceptable salt or stereoisomer thereof; preferably wherein the CoV is SARS-

CoV-2; optionally wherein the treatment minimises the likelihood that a patient suffers from COVID persistent, long COVID or post-COVID syndrome symptoms; and/or reduces the severity of such symptoms.

~~58~~33. The use according to any preceding claim, in the manufacture of a medicament for ~~A method of~~ reducing the infectivity of CoV patients, wherein the method comprises administering to an individual in need thereof, a therapeutically effective amount of a compound as defined in any of claims 1 to ~~53~~31, or a pharmaceutically acceptable salt or stereoisomer thereof; preferably wherein the CoV is SARS-CoV-2; optionally wherein the patient is asymptomatic or not very symptomatic yet has a high viral load.

~~59~~34. The use according to any preceding claim, in the manufacture of a medicament for ~~A method of~~ minimising the symptoms of CoV infection, wherein the method comprises administering to an individual in need thereof, a therapeutically effective amount of a compound as defined in any of claims 1 to ~~53~~31, or a pharmaceutically acceptable salt or stereoisomer thereof; preferably wherein the CoV is SARS-CoV-2.

~~60. A corticosteroid for use in the treatment of CoV infection, wherein the corticosteroid is administered in combination with a compound according to any one of claims 1 to 53.~~

~~61. A compound according to any one of claims 1 to 19 and a corticosteroid for use in the treatment of CoV infection; wherein the use is according to any one of claims 1 to 53.~~

~~62. A method of treatment of CoV infection, the method comprising administering a combination therapy of compound according to any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof and a corticosteroid to a patient in need thereof, thereby treating the CoV infection; wherein said method is as defined in any one of claims 1 to 53.~~

~~63. Use of a compound as defined in any of claims 1 to 53 or a pharmaceutically acceptable salt or stereoisomer thereof, in the manufacture of a medicament for the treatment of CoV infection; wherein said treatment includes administration of a corticosteroid.~~

~~64~~35. Use of a corticosteroid in the manufacture of a medicament for the treatment of CoV infection; wherein said treatment includes administration of a compound as defined in any of claims 1 to ~~53~~ 34 or a pharmaceutically acceptable salt or stereoisomer thereof.

~~65~~36. Use of a compound as defined in any of claims 1 to ~~53~~ 34 or a pharmaceutically acceptable salt or stereoisomer thereof and a corticosteroid in the manufacture of a medicament for the treatment of CoV infection.

~~66~~37. A pharmaceutical package comprising a compound as defined in any of claims 1 to ~~53~~ 34 and a corticosteroid, optionally further comprising instructions according to any one of claims 1 to ~~53~~34.

~~67~~38. A kit comprising the compound as defined in any of claims 1 to ~~53~~ 34, optionally and a corticosteroid, together with instructions for treating CoV infections, said instructions according to any one of claims 1 to 34.

~~68. A kit comprising a compound as defined in any of claims 1 to 53 and a corticosteroid together with instructions for treating CoV infections.~~