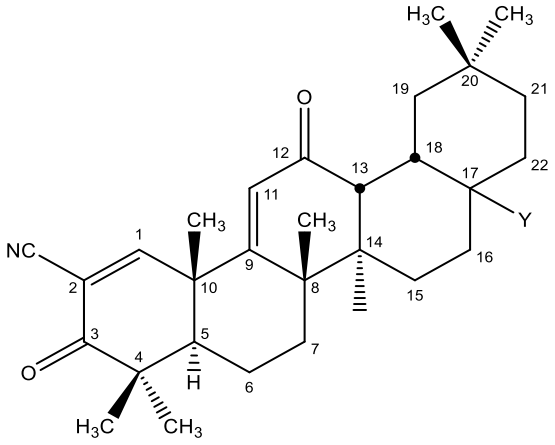
no specific drugs or vaccines for coronaviruses. As such, new therapies to treat COVID-19 are needed.

SUMMARY

[0006] The present disclosure provides methods of treating or preventing symptoms or complications of a coronavirus infection in a patient in need thereof. Such methods are described in the sections below, including for example the claims section, which is incorporated herein by reference.

[0006a] In an aspect of the present disclosure, there is provided use of a compound of the formula:



(V),

wherein:

Y is:

$-(CH_2)_mC(O)R_c$, wherein m is 0 and R_c is:

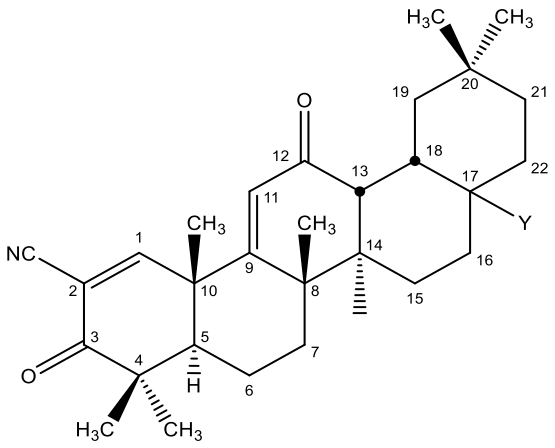
hydroxy, heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, or a substituted version of any of these groups; or

$-NHC(O)R_e$, wherein R_e is:

alkyl$_{(C\leq 8)}$, or a substituted alkyl$_{(C\leq 8)}$;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient infected with SARS-CoV-2, wherein the medicament comprises a pharmaceutically effective amount of the compound.

[0006b] In another aspect of the present disclosure, there is provided use of a compound of the formula:



(V),

wherein:

Y is:

$-(CH_2)_mC(O)R_c$, wherein m is 0 and R_c is:

hydroxy, $heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, or a substituted version of any of these groups; or

$-NHC(O)R_e$, wherein R_e is:

$alkyl_{(C\leq 8)}$, or a substituted $alkyl_{(C\leq 8)}$;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient infected with SARS-CoV-2, wherein the medicament comprises a pharmaceutically effective amount of the compound, and

wherein the patient has been identified as not having a history of left-sided heart failure or wherein the patient does not show evidence of left ventricular dysfunction.

[0007] In some examples, the compound is bardoxolone methyl (BARD, CDDO-Me or RTA 402). In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. In non-limiting examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

[0008] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 6.2, 12.4, 15.4, 18.6 and 24.9 °2θ. In some examples, the crystalline form is further characterized by one, two, three, four or five additional diffraction peaks selected from the group consisting of 8.6, 13.3, 13.7, 17.1 and 21.7 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα)

is substantially as shown in FIG. 1 of WO 2019/014412, which is incorporated herein by reference in its entirety.

[0009] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 3.6, 7.1, 10.8, 12.4 and 16.5 °2θ. In some examples, the crystalline form is further characterized by one, two, three, four or five additional diffraction peaks selected from the group consisting of 12.9, 13.9, 14.8, 18.6 and 20.6°2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 2 of WO 2019/014412, which is incorporated herein by reference in its entirety. In some examples, the crystalline form is further characterized by a Raman spectrum having peaks at 2949, 1671, 1618 and 1464 ± 4 cm^{-1}. In non-limited

examples, the Raman spectrum is substantially as shown in FIGS. 4 and 5 of WO 2019/014412, which is incorporated herein by reference in its entirety.

[0010] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a toluene solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 9.65, 7.58, 7.18, 6.29, 6.06, 5.47, 5.21, 4.77 and 3.07 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1 of CN102887936, which is incorporated herein by reference in its entirety.

[0011] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a semi-dioxane solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 10.01, 7.09, 6.84, 6.23, 5.29, 5.20, 5.10, 4.84, and 4.61 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 4 of CN102887936, which is incorporated herein by reference in its entirety.

[0012] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a semi-tetrahydrofuran solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 10.00, 7.14, 6.80, 6.65, 6.10, 5.62, 5.29, 4.88, and 4.50 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 8 of CN102887936, which is incorporated herein by reference in its entirety.

[0013] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a methanol solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 8.86, 8.45, 8.17, 7.90, 7.26, 4.67, 6.63, 6.46, and 3.64 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1 of CN102875634, which is incorporated herein by reference in its entirety.

[0014] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is an anhydrous crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 12.05, 8.90, 8.49, 8.13, 7.92, 7.29, 6.64, 4.67 and 3.65 °2θ. In non-limited examples, the X-ray

diffraction pattern (CuKα) is substantially as shown in FIG. 2 of CN102875634, which is incorporated herein by reference in its entirety.

[0015] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a dihydrate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 8.81, 8.48, 7.91, 7.32, 5.09, 4.24, 3.58, 3.36 and 3.17 °2θ. In non-limited examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 3 of CN102875634, which is incorporated herein by reference in its entirety.

[0016] In some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a T_g. In some variations, the compound is an amorphous form. In some variations, the compound is a glassy solid form of CDDO-Me, having an X-ray powder diffraction pattern with a halo peak at about 13.5 °2θ, as shown in FIG. 1C, and a T_g. In some variations, the T_g value falls within a range of about 120 °C to about 135 °C. In some variations, the T_g value is from about 125 °C to about 130 °C.

[0017] In some examples, the compound is administered locally. In some examples, the compound is administered systemically. In some examples, the compound is administered orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctivally, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof. For example, in some variations, the compound is administered intravenously, intra-arterially or orally. For example, in some variations, the compound is administered orally.

In some examples, the compound is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a solid dispersion, a wafer, or an elixir. In some variations, the

soft capsule is a gelatin capsule. In variations, the compound is formulated as a solid dispersion. In some variations the hard capsule, soft capsule, tablet or wafer further comprises a protective coating. In some variations, the formulated compound comprises an agent that delays absorption. In some variations, the formulated compound further comprises an agent that enhances solubility or dispersibility. In some variations, the compound is dispersed in a liposome, an oil-in-water emulsion or a water-in-oil emulsion.

[0018] In some examples, the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 500 mg of the compound. In some variations, the daily dose is from about 1 mg to about 300 mg of the compound. In some variations, the daily dose is from about 10 mg to about 200 mg of the compound. In some variations, the daily dose is about 25 mg of the compound. In other variations, the daily dose is about 75 mg of the compound. In still other variations, the daily dose is about 150 mg of the compound. In further variations, the daily dose is from about 0.1 mg to about 30 mg of the compound. In some variations, the daily dose is from about 0.5 mg to about 20 mg of the compound. In some variations, the daily dose is from about 1 mg to about 15 mg of the compound. In some variations, the daily dose is from about 1 mg to about 10 mg of the compound. In some variations, the daily dose is from about 1 mg to about 5 mg of the compound. In some variations, the daily dose is from about 2.5 mg to about 30 mg of the compound. In some variations, the daily dose is about 2.5 mg of the compound. In other variations, the daily dose is about 5 mg of the compound. In other variations, the daily dose is about 10 mg of the compound. In other variations, the daily dose is about 15 mg of the compound. In other variations, the daily dose is about 20 mg of the compound. In still other variations, the daily dose is about 30 mg of the compound.

[0019] In some examples, the pharmaceutically effective amount is a daily dose of 0.01 – 25 mg of compound per kg of body weight. In some variations, the daily dose is 0.05 – 20 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 10 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 5 mg of compound per kg of body weight. In some variations, the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.

[0020] In some examples, the pharmaceutically effective amount is administered in a single dose per day. In some examples, the pharmaceutically effective amount is administered in two or more doses per day.

[0021] In some examples, the patient is a mammal such as primate. In some variations, the primate is a human. In other variations, the patient is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

[0022] In some variations of the above methods, the compound is substantially free from optical isomers thereof. In some variations of the above methods, the compound is in the form of a pharmaceutically acceptable salt. In other variations of the above methods, the compound is not a salt.

[0023] In some examples, the compound is formulated as a pharmaceutical composition comprising (i) a therapeutically effective amount of the compound and (ii) an excipient selected from the group consisting of (A) a carbohydrate, carbohydrate derivative, or carbohydrate polymer, (B) a synthetic organic polymer, (C) an organic acid salt, (D) a protein, polypeptide, or peptide, and (E) a high molecular weight polysaccharide. In some variations, the excipient is a synthetic organic polymer. In some variations, the excipient is selected from the group consisting of a hydroxypropyl methyl cellulose, a poly[1-(2-oxo-1-pyrrolidinyl)ethylene] or copolymer thereof, and a methacrylic acid – methylmethacrylate copolymer. In some variations, the excipient is hydroxypropyl methyl cellulose phthalate ester. In some variations, the excipient is PVP/VA. In some variations, the excipient is a methacrylic acid – ethyl acrylate copolymer. In some variations, the methacrylic acid and ethyl acrylate may be present at a ratio of about 1:1. In some variations, the excipient is copovidone.

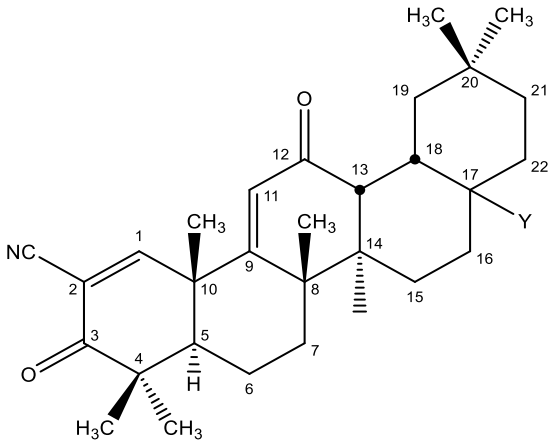
[0024] Any embodiment discussed herein with respect to one aspect of the invention applies to other aspects of the invention as well, unless specifically noted.

[0025] Further aspects and embodiments of this invention are elaborated in greater detail, for example, in the claims section and in the examples section, which are incorporated herein by reference.

[0026] Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to

CLAIMS

1. Use of a compound of the formula:



(V),

wherein:

Y is:

$-(CH_2)_mC(O)R_c$, wherein m is 0 and R_c is:

hydroxy, $heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, or a substituted version of any of these groups; or

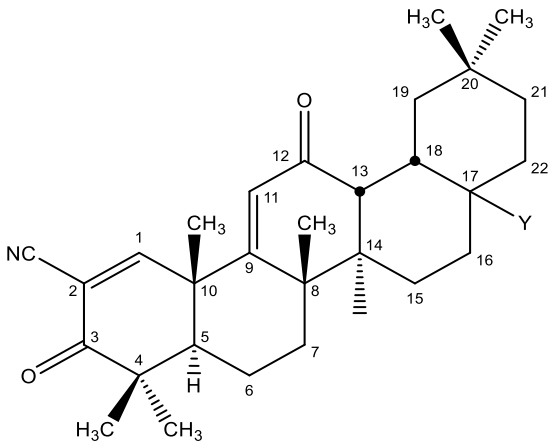
$-NHC(O)R_e$, wherein R_e is:

$alkyl_{(C\leq 8)}$, or a substituted $alkyl_{(C\leq 8)}$;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient infected with SARS-CoV-2, wherein the medicament comprises a pharmaceutically effective amount of the compound.

2. The use of claim 1, wherein the patient has been identified as not having a history of left-sided heart failure or wherein the patient does not show evidence of left ventricular dysfunction.

3. Use of a compound of the formula:



(V),

wherein:

Y is:

$-(CH_2)_mC(O)R_c$, wherein m is 0 and R_c is:

hydroxy, $heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, or a substituted version of any of these groups; or

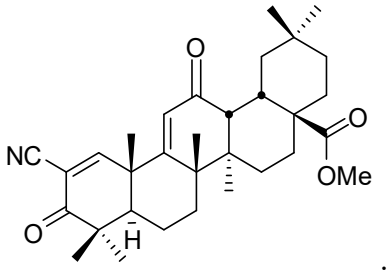
$-NHC(O)R_e$, wherein R_e is:

$alkyl_{(C\leq 8)}$, or a substituted $alkyl_{(C\leq 8)}$;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a patient infected with SARS-CoV-2, wherein the medicament comprises a pharmaceutically effective amount of the compound, and

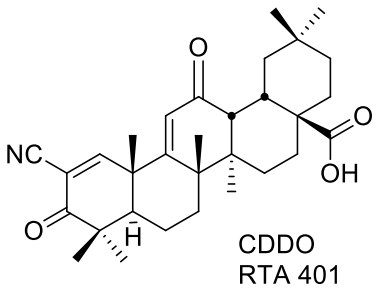
wherein the patient has been identified as not having a history of left-sided heart failure or wherein the patient does not show evidence of left ventricular dysfunction.

4. The use of any one of claims 1-3, wherein the compound is further defined as:



.

5. The use of any one of claims 1-3, wherein the compound is not



CDDO
RTA 401

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6. The use according to any one of claims 1-5, wherein the patient has radiographic infiltrates by imaging prior to treatment.

7. The use of claim 6, wherein the imaging is a chest X-ray or CT scan.

8. The use according to any one of claims 1-7, wherein the patient's blood oxygen saturation, at rest, is at most 94% prior to treatment.

9. The use according to any one of claims 1-8, wherein the patient requires supplemental oxygen prior to treatment.

10. The use according to any one of claims 1-9, wherein the patient requires non-invasive ventilation prior to treatment.

11. The use according to any one of claims 1-10, wherein the patient requires mechanical ventilation for up to 2 days prior to treatment.

12. The use according to any one of claims 1-11, wherein the use is for the manufacture of a medicament for treating or preventing COVID-19 in a patient in need thereof.

13. The use according to any one of claims 1-12, wherein the medicament is for treating or preventing inflammation-induced liver damage in the patient.

14. The use according to any one of claims 1-13, wherein the medicament is for treating or preventing acute lung injury in the patient.

15. The use according to any one of claims 1-14, wherein the medicament is for treating or preventing kidney damage in the patient.

16. The use according to any one of claims 1-15, wherein the medicament is for treating or preventing acute kidney injury in the patient.

17. The use according to any one of claims 1-16, wherein the medicament is for treating or preventing acute respiratory distress syndrome in the patient.

18. The use according to any one of claims 1-17, wherein the medicament is for treating or preventing brain inflammation in the patient.

19. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

20. The use of claim 19, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

21. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a transition glass temperature (T_g).

22. The use of claim 21, wherein the T_g value is in the range of 120 °C ± 10 °C to 135 °C ± 10 °C.

23. The use of claim 22, wherein the T_g value is in the range of 125 °C ± 10 °C to 130 °C ± 10 °C.

24. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 6.2, 12.4, 15.4, 18.6 and 24.9 °2θ.

25. The use of claim 24, wherein the crystalline form is further characterized by one, two, three, four or five additional diffraction peaks selected from the group consisting of 8.6, 13.3, 13.7, 17.1 and 21.7 °2θ.

26. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 3.6, 7.1, 10.8, 12.4 and 16.5 °2θ.

27. The use of claim 26, wherein the crystalline form is further characterized by one, two, three, four or five additional diffraction peaks selected from the group consisting of 12.9, 13.9, 14.8, 18.6 and 20.6°2θ.

28. The use of either claim 26 or 27, wherein the crystalline form is further characterized by a Raman spectrum having peaks at 2949, 1671, 1618 and 1464 ± 4 cm^{-1}.

29. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a toluene solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 9.65, 7.58, 7.18, 6.29, 6.06, 5.47, 5.21, 4.77 and 3.07 °2θ.

30. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a semi-dioxane solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 10.01, 7.09, 6.84, 6.23, 5.29, 5.20, 5.10, 4.84, and 4.61 °2θ.

31. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a semi-tetrahydrofuran solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 10.00, 7.14, 6.80, 6.65, 6.10, 5.62, 5.29, 4.88, and 4.50 °2θ.

32. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as a methanol solvate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 8.86, 8.45, 8.17, 7.90, 7.26, 4.67, 6.63, 6.46, and 3.64 °2θ.

33. The use according to any one of claims 4-18, wherein at least a portion of the compound is present as an anhydrous crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 12.05, 8.90, 8.49, 8.13, 7.92, 7.29, 6.64, 4.67 and 3.65 °2θ.

34. The use according to any one of claims 4-18, wherein at least a portion of the compound is present a dihydrate crystalline form having an X-ray diffraction pattern (CuKα) comprising diffraction peaks at about 8.81, 8.48, 7.91, 7.32, 5.09, 4.24, 3.58, 3.36 and 3.17 °2θ.

35. The use according to any one of claims 1-34, wherein the therapeutically effective amount is a daily dose from 0.1 mg to 300 mg of the compound.

36. The use of claim 35, wherein the daily dose is from 0.5 mg to 200 mg of the compound.

37. The use of claim 36, wherein the daily dose is from 1 mg to 150 mg of the compound.

38. The use of claim 37, wherein the daily dose is from 1 mg to 75 mg of the compound.

39. The use of claim 38, wherein the daily dose is from 1 mg to 20 mg of the compound.

40. The use of claim 35, wherein the daily dose is from 2.5 mg to 30 mg of the compound.

41. The use of claim 40, wherein the daily dose is about 2.5 mg of the compound.

42. The use of claim 40, wherein the daily dose is about 5 mg of the compound.

43. The use of claim 40, wherein the daily dose is about 10 mg of the compound.

44. The use of claim 40, wherein the daily dose is about 15 mg of the compound.

45. The use of claim 40, wherein the daily dose is about 20 mg of the compound.

46. The use of claim 40, wherein the daily dose is about 30 mg of the compound.

47. The use according to any one of claims 1-34, wherein the medicament is formulated for administration orally, intraarterially or intravenously.

48. The use according to any one of claims 1-34, wherein the medicament is formulated as a hard or soft capsule or a tablet.

49. The use according to any one of claims 1-34, wherein the medicament is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

50. The use of claim 49, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer.

51. The use of claim 50, wherein the copolymer comprises methacrylic acid and ethyl acrylate at a 1:1 ratio.