Claims

1. A (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt.

2. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1, where the salt is in a crystalline form exhibiting at least one of

a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm;

a differential scanning calorimetry thermogram having an endotherm with a maximum at between about 320 °C and about 335 °C;

a thermogravimetric analysis thermogram indicative of an unsolvated material;

a dynamic vapor sorption isotherm plot which does not exhibit a significant weight change from 0 to 95% relative humidity;

an X-ray powder diffraction pattern comprising characteristic peaks expressed in d-values (Å) of about 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7; and

an X-ray powder diffraction pattern comprising peaks at 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

3. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting at least one of

a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm;

an X-ray powder diffraction pattern comprising characteristic peaks expressed in d-values (Å) of 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7; and

an X-ray powder diffraction pattern comprising peaks at 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

4. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in d-values (Å) of 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7.

5. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

6. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm.

7. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of any of claims 1-6, where the crystalline form has a purity of at least 99.5%.

8. The tosylate salt of any of claims 1-7, where the crystalline form is free of an amorphous form of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one or a salt thereof.

9. A method of preparing a crystalline form of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt comprising

step (1): in the presence of one or more step 1 solvent(s) independently selected from tetrahydrofuran, acetone, methanol, acetonitrile, and dichloromethane, contacting (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one with p-toluenesulfonic acid at an elevated temperature, where the elevated temperature is 30 °C to 70 °C;

step (2): allowing to stand under conditions sufficient to precipitate the crystalline form, where the conditions sufficient to precipitate the crystalline form include cooling; and

step (3): isolating the crystalline form.

10. The method of claim 9 where the one or more step 1 solvent(s) are independently selected from methanol and acetonitrile.

11. The method of claim 9 where the one or more step 1 solvent(s) are independently selected from dichloromethane and acetonitrile.

12. The method of claim 9 where the one or more step 1 solvent(s) are independently selected from acetone and tetrahydrofuran.

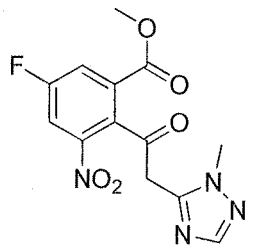
13. The method of claim 9 or 12 where the step 1 solvent is acetone.

14. The method of claim 9 or 12 where the step 1 solvent is tetrahydrofuran.

15. The method of any one of claims 9-13 where the conditions sufficient to precipitate the crystalline form include cooling to 25 °C or cooler.

16. The method of any of claims 9-15 further comprising

step (a): contacting



with 4-fluorobenzaldehyde in a mixture comprising one or more step (a) solvent(s) and titanium(III) chloride to make a first intermediate;

step (b): isolating by chiral separation an enantiomer of the first intermediate; and

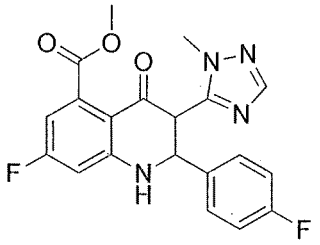
step (c): contacting the isolated enantiomer of the first intermediate with hydrazine monohydrate in one or more step (c) solvent(s) to make (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one.

17. The method of claim 16 where the isolated enantiomer of the first intermediate is contacted with hydrazine monohydrate in one or more step (c) solvent(s) independently selected from methanol, ethanol, and acetonitrile.

18. The method of claim 16 or 17 where the one or more step (a) solvent(s) are independently selected from tetrahydrofuran and methanol.

19. The method of any of claims 9-15 further comprising

step (x): contacting



with hydrazine monohydrate in one or more step x solvents to yield 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one; and

step (y): isolating (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one by chiral separation.

20. The method of claim 19 where the one or more step (x) solvent(s) is independently selected from methanol, ethanol, and acetonitrile.

21. A (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt prepared according to the method of any of claims 9-20.

22. The tosylate salt of claim 21, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in d-values (Å) of 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7.

23. The tosylate salt of claim 21 or 22, where the salt exhibits a single endothermal peak on differential scanning calorimetry between room temperature and 350 °C, where the single endothermal peak maximum occurs between 320 °C to 335 °C.

24. The tosylate salt of any of claims 21-23, where the salt exhibits less than 2% thermal weight loss at or below a temperature of 280 °C by thermogravimetric analysis.

25. The tosylate salt of any of claims 21-24, where the salt exhibits a value of hysteressis less than 1% in dynamic vapor sorption at 25 °C from RH 0% to RH 95%.

26. A pharmaceutical composition comprising a tosylate salt according to any of claims 1-7 and 21-25 and a pharmaceutically acceptable excipient.

27. The pharmaceutical composition according to claim 26, where the composition is formulated for oral administration to a subject.

28. Use of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt in the manufacture of a medicament for treating cancer in a subject.

29. The use of claim 28, where the cancer is bladder cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, Burkitt's lymphoma, nasopharyngeal carcinoma, EBV+ gastric cancer, endometrial cancers, gastrointestinal stromal tumor, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, lung cancer, lymphoma, medulloblastoma, melanoma, meningioma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, small cell lung carcinoma, thyroid cancer or uterine cancer.

30. The use of claim 28 or 29, where 0.3 μg/kg body weight to 3.0 μg/kg body weight of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt are to be administered per day to the subject.

31. The method of any of claims 28-30 where the (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt is a crystalline form according to any of claims 2-8.

32. Use of a crystalline (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt in the manufacture of a medicament for treating of a disease or condition in a subject.

33. The use of claim 32, where the disease or condition is a cancer.

WHAT IS CLAIMED:

1. A (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt.

2. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1, where the salt is in a substantially pure crystalline form.

3. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting at least one of

a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm;

a differential scanning calorimetry thermogram having an endotherm with a maximum at between about 320 °C and about 335 °C;

a thermogravimetric analysis thermogram indicative of an unsolvated material;

a dynamic vapor sorption isotherm plot which does not exhibit a significant weight change from 0 to 95% relative humidity;

an X-ray powder diffraction pattern comprising characteristic peaks expressed in d-values (Å) of about 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7; and

an X-ray powder diffraction pattern comprising peaks at 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

4. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting at least one of

a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm;

an X-ray powder diffraction pattern comprising characteristic peaks expressed in d-values (Å) of about 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7; and

an X-ray powder diffraction pattern comprising peaks at 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

5. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in d-values (Å) of about 11.9, 5.9, 4.9, 4.4, 4.3, 3.9, and 3.7.

6. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in 2θ angle degrees ± 0.2 2θ angle degrees of 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

7. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of claim 1 or 2, where the salt is a crystalline form exhibiting a solid state ^{13}C NMR spectrum with peaks at 143.2, 136.0, 131.8, 123.9, 112.2, 105.2, and 100.3 ppm ± 0.2 ppm.

8. The (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt of any of claims 1-7, where the crystalline form has a purity of at least about 99.5%.

9. The tosylate salt of any of claims 1-8, where the crystalline form is substantially free of an amorphous form of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one or a salt or solvate thereof.

10. A method of preparing a crystalline form of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt comprising

step (1): in the presence of one or more step 1 solvent(s) independently selected from THF, acetone, methanol, acetonitrile, and DCM, contacting (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one with p-toluenesulfonic acid at an elevated temperature;

step (2): allowing to stand under conditions sufficient to precipitate the crystalline form; and

step (3): isolating the crystalline form.

11. The method of claim 10 where the elevated temperature is about 30 °C to about 70 °C.

12. The method of claim 10 or 11 where the one or more step 1 solvent(s) are independently selected from methanol and acetonitrile.

13. The method of claim 10 or 11 where the one or more step 1 solvent(s) are independently selected from DCM and acetonitrile.

14. The method of claim 10 or 11 where the one or more step 1 solvent(s) are independently selected from acetone and THF.

15. The method of claim 10, 11, or 14 where the step 1 solvent is acetone.

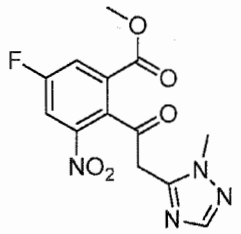
16. The method of claim 10, 11, or 14 where the step 1 solvent is THF.

17. The method of any of claims 10-15 where the conditions sufficient to precipitate the crystalline form include cooling.

18. The method of claim 17 where the conditions sufficient to precipitate the crystalline form include cooling to 25 °C or cooler.

19. The method of any of claims 10-18 further comprising

step (a): contacting



with 4-fluorobenzaldehyde in a mixture comprising one or more step (a) solvent(s) and titanium(III) chloride to make a first intermediate;

step (b): isolating by chiral separation an enantiomer of the first intermediate; and

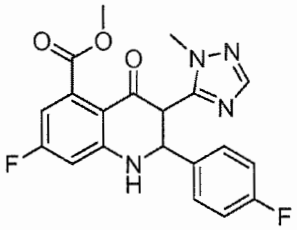
step (c): contacting the isolated enantiomer of the first intermediate with hydrazine monohydrate in one or more step (c) solvent(s) to make (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one.

20. The method of claim 19 where the isolated enantiomer of the first intermediate is contacted with hydrazine monohydrate in one or more step (c) solvent(s) independently selected from methanol, ethanol, and acetonitrile.

21. The method of claim 19 or 20 where the one or more step (a) solvent(s) are independently selected from THF and methanol.

22. The method of any of claims 10-18 further comprising

step (x): contacting



with hydrazine monohydrate in one or more step x solvents to yield 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one; and

step (y): isolating (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one by chiral separation.

23. The method of claim 22 where the one or more step (x) solvent(s) is independently selected from methanol, ethanol, and acetonitrile.

24. A (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt prepared according to the method of any of claims 10-23.

25. The tosylate salt of claim 24, where the salt is a crystalline form exhibiting an X-Ray Powder Diffraction pattern comprising characteristic peaks expressed in d-values (Å) of about 7.4, 15.1, 18.1, 20.1, 20.4, 22.6, and 24.0.

26. The tosylate salt of claim 24 or 25, where the salt exhibits a single endothermal peak on differential scanning calorimetry between room temperature and about 350 °C, where the single endothermal peak maximum occurs between about 320 °C to about 335 °C.

27. The tosylate salt of any of claims 24-26, where the salt exhibits less than 2% thermal weight loss at or below a temperature of about 280 °C by thermogravimetric analysis.

28. The tosylate salt of any of claims 24-27, where the salt exhibits a value of hysteressis less than about 1% in dynamic vapor sorption at about 25 °C from RH 0% to RH 95%.

29. A pharmaceutical composition comprising a tosylate salt according to any of claims 1-8 and 24-28 and a pharmaceutically acceptable excipient.

30. The pharmaceutical composition according to claim 29, where the composition is formulated for oral administration to a subject.

31. Use of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt in the manufacture of a medicament for treating cancer in a subject.

32. The use of claim 31, where the cancer is bladder cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, Burkitt's lymphoma, nasopharyngeal carcinoma, EBV+ gastric cancer, endometrial cancers, gastrointestinal stromal tumor, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, lung cancer, lymphoma, medulloblastoma, melanoma, meningioma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, small cell lung carcinoma, thyroid cancer or uterine cancer.

33. The use of claim 31 or 32, where about 0.3 μg/kg body weight to about 3.0 μg/kg body weight of (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt are to be administered per day to the subject.

34. The method of any of claims 31-33 where the (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt is a crystalline form according to any of claims 3-9.

35. Use of a crystalline (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one tosylate salt in the manufacture of a medicament for treating of a disease or condition in a subject.

36. The use of claim 35, where the disease or condition is a cancer.