# CRYSTALLINE (8*S*,9*R*)-5-FLUORO-8-(4-FLUOROPHENYL)-9-(1-METHYL-1H-1,2,4-TRIAZOL-5-YL)-8,9-DIHYDRO-2H-PYRIDO[4,3,2-DE]PHTHALAZIN-3(7H)-ONE TOSYLATE SALT

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** The present application claims the benefit of priority of U.S. Provisional Application No. 61/405,476, filed October 21, 2010~~, the content of which is hereby incorporated by reference in its entirety~~.

## TECHNICAL FIELD

**[0002]** This application relates to (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 forms, including crystalline forms; methods of preparing (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 and tosylate salt forms thereof; and pharmaceutical compositions comprising 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 form.

## BACKGROUND

**[0003]** Enzymes in the poly(ADP-ribose)polymerase (PARP) protein family participate in a number of cellular functions including assisting in the repair of DNA damage. Inhibiting PARP activity is a promising therapeutic approach to treatment of certain cancers. A number of PARP inhibitors are in clinical and preclinical stages as candidate drugs for treatments of ovarian, breast, colorectal, prostate and other cancers. A class of PARP inhibitors disclosed in U.S. Pub. No. 2010/0035883 includes (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. Preclinical studies indicate that this compound may be a useful therapy for some cancer patients.

**[0004]** U.S. Pub. No. 2010/0035883 provides a synthesis of 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 chiral resolution of its (8*S*,9*R*) enantiomer. *See, e.g.,* U.S. 2010/0035883, Examples 94 and 155, incorporated herein by reference in its entirety for all purposes. Additional methods of preparing

the compound are described in WO 2011/097602. To move a drug candidate such as (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 to a viable pharmaceutical product, it can be important to understand whether the drug candidate has polymorph forms, as well as the relative stability and interconversions of these forms under conditions likely to be encountered upon large-scale production, transportation, storage and pre-usage preparation. The ability to control and produce a stable polymorph with a robust manufacturing process can be key for regulatory approval and marketing. Large scale production processes for high purity 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 are sought, which is hampered by the fact that parameters affecting the stability of this compound are not known and polymorphic forms of the compound have not been available.

## BRIEF SUMMARY

**[0005]** In one aspect the present invention refers to 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, wherein the salt is in crystalline form. In another aspect, the present invention refers to 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. In another aspect, the present invention refers to a pharmaceutical composition comprising a tosylate salt according to the present invention and a pharmaceutically acceptable excipient. In still another aspect, the present invention refers to the 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. In still another aspect, the present invention refers to the 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. ~~In one aspect, provided~~ Also disclosed herein is a tosylate salt 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. In some ~~embodiments~~ examples the tosylate salt is in a crystalline form. In some ~~embodiments~~examples, ~~provided~~ disclosed herein are solid forms of a tosylate salt 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, including crystalline forms, amorphous forms, or mixtures thereof.

**[0006]** ~~In another aspect, provided~~Further disclosed herein are methods of synthesizing (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 in a free base form ("free base").

**[0007]** ~~In another aspect,~~Also disclosed herein is a method of preparing a tosylate salt 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 is provided. In certain ~~embodiments~~examples, the tosylate salt is prepared from a suspension in tetrahydrofuran (THF).

**[0008]** ~~In another aspect, the present application provides~~Further disclosed herein is a pharmaceutical composition comprising a tosylate salt 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 solid form thereof, as described herein.

**[0009]** ~~In another aspect, the present application provides~~Also disclosed herein is a method of treating cancer with a tosylate salt 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, in another example a crystalline form thereof, or a composition thereof.

## DESCRIPTION OF THE DRAWINGS

**[0010]** **Fig.1** provides an overlay of five examples of powder X-ray powder diffraction (XRPD) patterns of 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.

**[0011]** **FIG. 2a** provides a differential scanning calorimetric (DSC) graph 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 polymorph, 8, from acetone-THF preparation.

**[0012]** **Fig. 2b** provides a thermogravimetric analysis (TGA) graph 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 polymorph, 8, from acetone-THF preparation.

**[0013]** **FIG. 3a** provides a DSC graph 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 polymorph, 5, from DCM-ACN preparation.

**[0014]** **Fig. 3b** provides a TGA graph 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 polymorph, 5, from DCM-ACN preparation.

**[0015]** **FIG. 4a** provides a DSC graph 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 polymorph, 6, from acetone preparation.

**[0016]** **Fig. 4b** provides a TGA graph 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 polymorph, 6, from acetone preparation.

**[0017]** **FIG. 5a** provides a DSC graph 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 polymorph, 7, from THF preparation.

## 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, wherein the salt is in crystalline form.

**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.

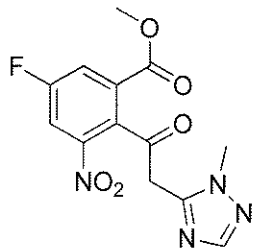
**13.** The method of claim 9 or 12 where the step 1 solvent is acetone.

**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

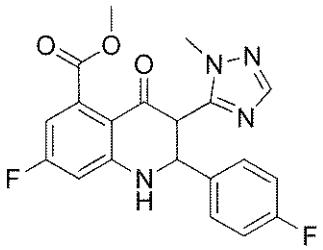
step (c): contacting the isolated enantiomer of the first intermediate with hydrazine monohydrate in one or more step (c) solvent(s) to make (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one.

**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.** 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 exhibits 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.

**22.** 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 21, 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.

**23.** 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 and 21-22, where the salt exhibits less than 2% thermal weight loss at or below a temperature of 280 °C by thermogravimetric analysis.

**24.** 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 and 21-23, where the salt exhibits a value of hysteresis less than 1% in dynamic vapor sorption at 25 °C from RH 0% to RH 95%.

**25.** A pharmaceutical composition comprising a tosylate salt according to any of claims 1-7 and 21-24 and a pharmaceutically acceptable excipient.

**26.** The pharmaceutical composition according to claim 25, where the composition is formulated for oral administration to a subject.

**27.** 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.

**28.** The use of claim 27, 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.

**29.** The use of claim 27 or 28, 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.

**30.** The method of any of claims 27-29 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.

**31.** 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.

**32.** The use of claim 31, where the disease or condition is a cancer.

## 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.

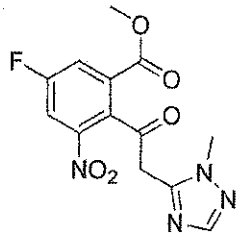
**13.** The method of claim 9 or 12 where the step 1 solvent is acetone.

**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

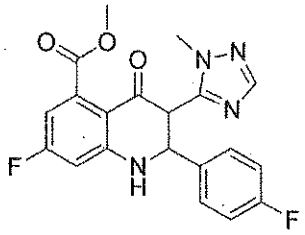
step (c): contacting the isolated enantiomer of the first intermediate with hydrazine monohydrate in one or more step (c) solvent(s) to make (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-de]phthalazin-3(7*H*)-one.

**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.