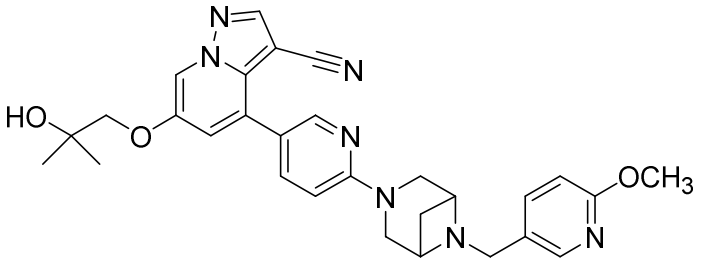
CRYSTALLINE RET INHIBITOR

BACKGROUND

[0001] Selpercatinib (LOXO-292 or RETEVMO™) is a RET inhibitor approved in the United States for use in the treatment of patients with metastatic RET fusion-positive NSCLC, RET-mutant medullary thyroid cancer, and RET fusion-positive thyroid cancer. Selpercatinib, or 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile, has the following chemical structure:



(Formula I).

[0002] While U.S. Patent No. 10,584,124 describes several crystal forms for selpercatinib, including a crystalline form referred to as “Form A,” disclosed herein is a new, thermodynamically more stable crystal form, and methods of making this crystal form. This new crystal form can be incorporated into formulations, such as tablets, capsules, and suspensions, which would benefit patients.

SUMMARY

[0002a] In one aspect of the present disclosure, there is provided a crystalline form of selpercatinib, which is characterized by an x-ray powder diffraction (XRPD) pattern comprising peaks occurring at 7.5°, 10.9°, 12.0°, 13.2°, 17.1°, 17.7°, 18.2°, 19.8°, 21.1°, and 24.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a crystalline form of selpercatinib disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0002c] In a further aspect of the present disclosure, there is provided a use of selpercatinib disclosed herein in the manufacture of a medicament for treating cancer.

[0002d] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment of cancer.

[0002e] In a further aspect of the present disclosure, there is provided a process for making the crystalline form of selpercatinib disclosed herein, comprising the steps of:

(a) suspending selpercatinib in a solvent; wherein the solvent comprises methanol;

(b) heating the suspension to between 50 ^{o}C and 60 ^{o}C while stirring for 30 to 90 minutes;

(c) removing the heat and allowing the suspension to cool to room temperature to form solid crystals; and

(d) collecting the solid crystals.

[0002f] In another aspect of the present disclosure, there is provided a method of converting selpercatinib Form A to selpercatinib Form B, the method comprising: combining selpercatinib Form A with a C_1-C_5 alcohol to generate a slurry; and isolating selpercatinib Form B from the slurry, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

[0002g] In a further aspect of the present disclosure, there is provided a method of converting selpercatinib Form A to selpercatinib Form B, the method comprising:

a. dissolving the selpercatinib Form A in a solvent comprising DMSO to form a solution, wherein the concentration of Form A dissolved in DMSO is 12-13 mL/g;

b. adding water to the solution and thereby forming a slurry;

c. isolating the selpercatinib Form B,

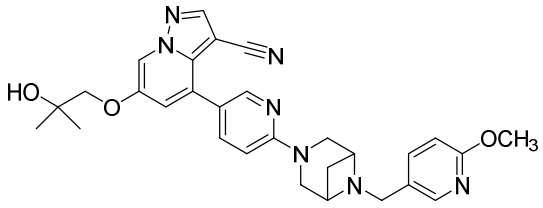
wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

[0002h] In another aspect of the present disclosure, there is provided a method of converting selpercatinib Form A to selpercatinib Form B, the method comprising:

combining selpercatinib Form A and methanol to form a slurry, and stirring the slurry until >99 wt% of the Form A is converted to Form B, wherein the concentration of the selpercatinib Form A in the methanol is 8 mL/g, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

[0002i] In a further aspect of the present disclosure, there is provided a method of converting selpercatinib Form A to selpercatinib Form B, the method comprising dissolving selpercatinib Form A in DMSO at 60-80 °C to form a solution having a concentration of 10-15 mL/g of DMSO per gram of Form A; cooling the solution to 40-60 °C, adding water; optionally seeding the resulting mixture with Form B seed crystals; stirring the mixture; adding more water; heating the mixture to 60-80 °C; cooling the mixture and isolating the Form B, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

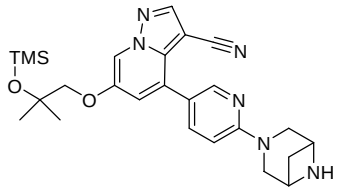
[0002j] In another aspect of the present disclosure, there is provided a process for preparing selpercatinib as polymorph Form B, of Formula I:



(Formula I)

or a pharmaceutically acceptable salt thereof,

wherein the process comprises reacting a compound of the structure:



[3]

or a salt thereof, in a solvent with 6-methoxynicotinaldehyde in the presence of an acid and a reducing agent to prepare selpercatinib Form B or a pharmaceutically acceptable salt thereof, wherein the solvent comprises anisole and wherein Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

[0002k] In a further aspect of the present disclosure, there is provided a compound that is 4-[6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-3-pyridyl]-6-(2-methyl-2-

What is claimed is:

1. A crystalline form of selpercatinib, which is characterized by an x-ray powder diffraction (XRPD) pattern comprising peaks occurring at 7.5°, 10.9°, 12.0°, 13.2°, 17.1°, 17.7°, 18.2°, 19.8°, 21.1°, and 24.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

2. A pharmaceutical composition comprising a crystalline form of selpercatinib according to claim 1, and a pharmaceutically acceptable carrier, diluent, or excipient.

3. The pharmaceutical composition according to claim 2, wherein the composition contains less than 20% by wt. of other crystal forms of selpercatinib.

4. The pharmaceutical composition according to claim 2, wherein the composition contains less than 10% by wt. of other crystal forms of selpercatinib.

5. The pharmaceutical composition according to claim 2, wherein the composition contains less than 5% by wt. of other crystal forms of selpercatinib.

6. Use of selpercatinib according to claim 1 in the manufacture of a medicament for treating cancer.

7. Use of a pharmaceutical composition according to any of claims 2-5 in the manufacture of a medicament for the treatment of cancer.

8. The use according to claim 6 or 7, wherein the cancer is selected from the group consisting of: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

9. The use according to claim 8, wherein the cancer is medullary thyroid cancer.

10. The use according to claim 8, wherein the cancer is lung cancer and the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, RET fusion lung cancer, or lung adenocarcinoma.

11. The use according to claim 8 wherein the cancer is RET fusion lung cancer.

12. A process for making the crystalline form of selpercatinib of claim 1, comprising the steps of:

(a) suspending selpercatinib in a solvent; wherein the solvent comprises methanol;

(b) heating the suspension to between 50 ^{o}C and 60 ^{o}C while stirring for 30 to 90 minutes;

(c) removing the heat and allowing the suspension to cool to room temperature to form solid crystals; and

(d) collecting the solid crystals.

13. A method of converting selpercatinib Form A to selpercatinib Form B, the method comprising: combining selpercatinib Form A with a C_1-C_5 alcohol to generate a slurry; and isolating selpercatinib Form B from the slurry, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

14. The method according to claim 13, wherein the C_1-C_5 alcohol is 10 °C to 30 °C, and the C_1-C_5 alcohol comprises methanol.

15. The method according to claim 13 or 14, wherein C_1-C_5 alcohol comprises at least 90 wt% methanol.

16. A method of converting selpercatinib Form A to selpercatinib Form B, the method comprising:

a. dissolving the selpercatinib Form A in a solvent comprising DMSO to form a solution, wherein the concentration of Form A dissolved in DMSO is 12-13 mL/g;

b. adding water to the solution and thereby forming a slurry;

c. isolating the selpercatinib Form B,

wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5

± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

17. The method according to claim 16, wherein forming the solution of step a comprises heating the selpercatinib Form A and the solvent comprising DMSO to 50 °C to 70 °C.

18. The method according to claim 16 or 17, wherein the solution is cooled to a temperature less than 70 °C and greater than 20 °C.

19. The method according to any one of claims 16-18, wherein step b comprises adding 0.1 to 1 mL of water per gram of Form A to the solution.

20. The method according to any one of claims 16-19, wherein step b comprises adding 0.3 mL of water per gram of Form A to the solution.

21. The method according to any one of claims 16-20, wherein step b further comprises adding 1 to 15 wt% of Form B seed crystals.

22. The method according to any one of claims 16-21, wherein the slurry is stirred for 6 to 72 hours, after the water is added in step b.

23. The method according to any one of claims 16-22, wherein step b further comprises adding a second tranche of water to the slurry.

24. The method according to claim 23, wherein 0.5 to 3 mL of water per gram of Form A is added to the slurry.

25. The method according to any one of claims 16-24, wherein the slurry of step b is cooled to 20-30 °C.

26. The method according to any one of claims 16-25, wherein the isolated selpercatinib Form B from step c is washed with a solvent comprising methanol, ACN, MTBE, or water.

27. The method according to claim 26, wherein the isolated selpercatinib Form B is washed with methanol until the isolated selpercatinib Form B contains less than 0.5 wt % DMSO.

28. A method of converting selpercatinib Form A to selpercatinib Form B, the method comprising: combining selpercatinib Form A and methanol to form a slurry,

and stirring the slurry until >99 wt% of the Form A is converted to Form B, wherein the concentration of the selpercatinib Form A in the methanol is 8 mL/g, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

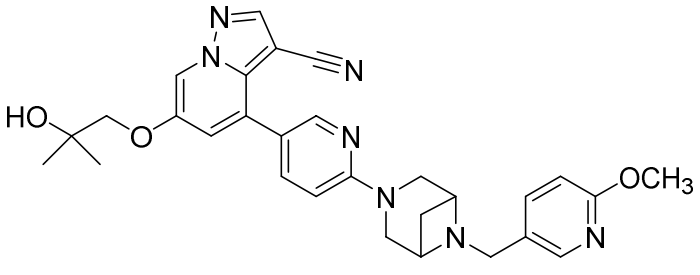
29. A method of converting selpercatinib Form A to selpercatinib Form B, the method comprising dissolving selpercatinib Form A in DMSO at 60-80 °C to form a solution having a concentration of 10-15 mL/g of DMSO per gram of Form A; cooling the solution to 40-60 °C, adding water; optionally seeding the resulting mixture with Form B seed crystals; stirring the mixture; adding more water; heating the mixture to 60-80 °C; cooling the mixture and isolating the Form B, wherein Form A is characterized by an XRPD pattern comprising peaks at 4.9 ± 0.2°, 9.7 ± 0.2°, and 15.5° ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å and Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

30. The method according to claim 29, wherein 5 wt% of Form B seed crystals are added to the mixture.

31. The method according to claim 29 or 30, wherein the first addition of water is 0.1 mL/g of Form A to 0.5 mL/g of Form A.

32. The method according to any one of claims 29-31, wherein the second addition of water is 1.0-1.5 mL/g of Form A.

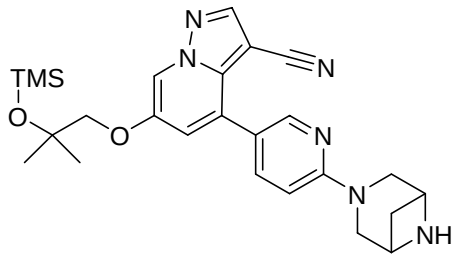
33. A process for preparing selpercatinib as polymorph Form B, of Formula I:



(Formula I)

or a pharmaceutically acceptable salt thereof,

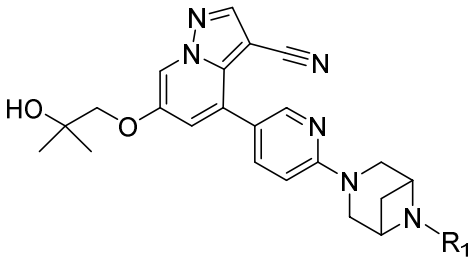
wherein the process comprises reacting a compound of the structure:



[3]

or a salt thereof, in a solvent with 6-methoxynicotinaldehyde in the presence of an acid and a reducing agent to prepare selpercatinib Form B or a pharmaceutically acceptable salt thereof, wherein the solvent comprises anisole and wherein Form B is characterized by an XRPD pattern comprising peaks at 7.5 ± 0.2°, 10.9 ± 0.2°, and 12.0 ± 0.2° 2θ as measured using an x-ray wavelength of 1.5418 Å.

34. The process of claim 33, further comprising preparing compound of structure **[3]**, or a salt thereof, the process comprising reacting a compound of the structure



[12]

or a salt thereof, wherein R_1 is an amine protecting group, with a deprotecting agent to form the compound of structure **[3]** or a salt thereof.

35. The process of claim 33 or 34, wherein the deprotecting agent is selected from the group consisting of trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydriodic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, p-toluene sulfonic acid, acetyl chloride, aluminum trichloride, and boron trifluoride.

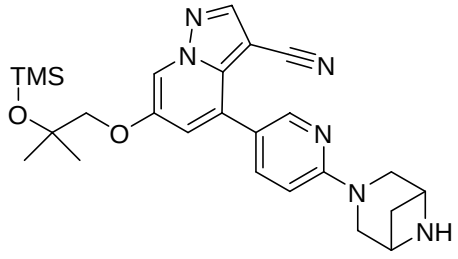
36. The process of any one of claims 33-35, wherein the reducing agent is selected from the group consisting of an alkali metal borohydride, a hydrazine compound, citric acid, a citric acid salt, succinic acid, a succinic acid salt, ascorbic acid, and an ascorbic acid salt.

37. The process of any one of claims 33-36, wherein the reducing agent is selected from the group consisting of sodium triacetoxyborohydride (STAB), sodium borohydride, and sodium cyanoborohydride.

38. The process of any one of claims 33-37, wherein R_1 is selected from the group consisting of formyl, acetyl, trifluoroacetyl, benzyl, benzoyl, carbamate, benzyloxycarbonyl, p-methoxybenzyl carbonyl, tert-butyloxycarbonyl (Boc), trimethylsilyl, 2-trimethylsilyl-ethanesulfonyl, trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, nitroveratryloxycarbonyl, p-methoxybenzyl, and tosyl.

39. The process of any one of claims 33-38, wherein the acid is selected from the group consisting of pivalic acid and acetic acid.

40. A compound that is 4-[6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-3-pyridyl]-6-(2-methyl-2-trimethylsilyloxy-propoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile, which has the structure **[3]**



[3]

or a pharmaceutically acceptable salt thereof.

41. The selpercatinib according to claim 1, or the pharmaceutical composition according to any of claims 2-5, for use in therapy.