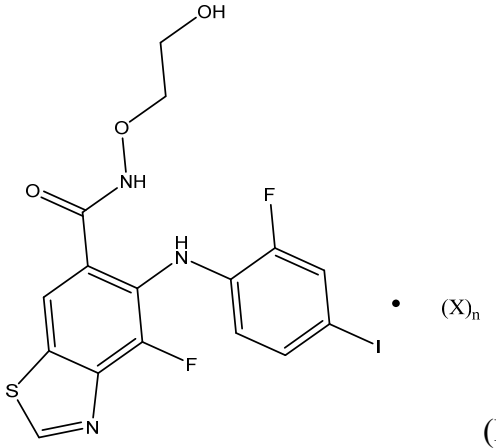
CLAIMS

1. A polymorph of formula (I)



(I)

wherein n is 0, and the polymorph is crystalline form I, characterized in that the X-ray powder diffraction pattern of the form I comprises characteristic diffraction peaks at the following 2θ positions: 16.71°±0.2°, 21.82°±0.2°, and 23.75°±0.2°, using Cu-Kα radiation.

2. The polymorph according to claim 1, wherein the X-ray powder diffraction pattern of the crystalline form I further comprises characteristic diffraction peaks at the following 2θ positions: 7.48°±0.2° and 22.36°±0.2°.

3. The polymorph according to claim 2, wherein the X-ray powder diffraction pattern of the crystalline form I further comprises characteristic diffraction peaks at the following 2θ positions: 5.3°±0.2°, 24.57°±0.2° and 27.08°±0.2°.

4. The polymorph according to claim 3, wherein the X-ray powder diffraction pattern of the crystalline form I further comprises characteristic diffraction peaks at the following 2θ positions: 11.81°±0.2°, 15.83°±0.2°, 17.92°±0.2°, 18.95°±0.2° and 19.17°±0.2°.

5. The polymorph according to claim 1, wherein the X-ray powder diffraction pattern of the crystalline form I comprises characteristic diffraction peaks at the following 2θ positions: 5.30 ° ± 0.2 °, 7.48 ° ± 0.2 °, 11.81 ° ± 0.2 °, 14.85 ° ± 0.2 °, 15.83 ° ± 0.2 °, 16.71 ° ± 0.2 °, 17.92 ° ± 0.2 °, 18.95 ° ± 0.2 °, 19.17 ° ± 0.2 °, 19.43 ° ± 0.2 °, 21.14 ° ± 0.2 °, 21.82 ° ± 0.2 °, 22.36 ° ± 0.2 °, 23.75 ° ± 0.2 °, 24.57 ° ± 0.2 °, 27.08 ° ± 0.2 °, 27.83 ° ± 0.2 °, 28.88 ° ± 0.2 °, 31.20 ° ± 0.2 °, 31.92 ° ± 0.2 °, 32.40 ° ± 0.2 °, 33.91 ° ± 0.2 °, 35.83 ° ± 0.2 ° 37.51 ° ± 0.2 ° and 39.04 ° ± 0.2 °.

6. The polymorph according to claim 1, wherein the X-ray powder diffraction pattern of the crystalline form I substantially as shown in Figure 3.

7. The polymorph according to claim 1, wherein the crystalline form I has a TGA thermogram and / or DSC thermogram as shown in Fig. 4.

8. The polymorph according to claim 1, wherein the crystalline form I contains less than 0.15% by weight of impurities (A) relative to the crystalline form I.

9. A pharmaceutical composition comprising a polymorph of any one of claims 1-8, as well as a pharmaceutically acceptable carrier and/or excipient.

10. Use of the polymorph according to any one of claims 1-8 in the manufacture of a medicament for treating mammalian tumors, chronic inflammatory diseases, inflammatory intestinal diseases, skin diseases, diabetes, eye diseases, diseases associated with mammalian angiogenesis or angiogenesis, diseases associated with chronic pain, and other diseases modulated by Mek cascade.

11. A method for preparing crystalline form I of claim 1, comprising any one of the following:

a) the amorphous sample of compound 1 is added to the solvent, and then heated at a temperature above about 70 ℃, the resulting clear liquid is cooled to room temperature, which is kept at room temperature to continue stirring, solid precipitation, filtration, drying; or

b) The amorphous sample of compound 1 is dissolved in a good solvent, filtered to obtain a clear solution, stir the clear solution while adding an anti-solvent until solid precipitated; or

c) the amorphous sample of compound 1 is dissolved in a solvent, stirred at about 50 ºC, then filter out the filtrate, cool the resulting filtrate to about 5 ºC, and collect the precipitated solid.

12. The method according to claim 11, wherein the heating temperature in method a) ranges from approximately 75 ℃ to approximately 100 ℃; About 80 ℃ to about 90 ℃; Or about 75 ℃ or about 85 ℃, wherein the room temperature in method a) is approximately 20-25 ℃.

13. The method according to claim 11, wherein the solvent in method a) is water, methanol, ethanol, isopropanol, acetone, methyl isobutyl ketone, 2-butanone, ethyl acetate, isopropyl acetate, methyl tert-butyl ether, tetrahydrofuran, benzyl ether, 2-methyltetrahydrofuran, cyclopentyl methyl ether, 1,4-dioxane, acetonitrile, dichloromethane, toluene, m-xylene, n-hexane, n-pentane, dimethyl sulfoxide, dimethylacetamide N-methylpyrrolidone or its mixture; wherein the good solvent in method b) is MEK, 1-dioxane or DMSO, and the antisolvent in method b) is MTBE, EtOAc, $CHCl_3$, n-heptane, Anisole, EtOAc, H_2O, IPAc, CPME, DCM or toluene.

14. The method according to claim 11, wherein the cooling rate of method c) is 0.1 ℃ / min, and solvent of method c) is MIBK, Methyl acetate, 2-MeTHF, or acetone/EtOH (1:1).

15. Use of the polymorph according to any one of claims 1-8 in the manufacture of a medicament for treating mammalian RAS or RAF mutant cancers, wherein the RAS or RAF mutant cancer is, such as, KRAS mutant cancer, NRAS mutant cancer, HRAS mutant cancer or BRAF mutant cancer.

16. The use according to claim 15, wherein the RAS mutant cancer is pancreatic cancer, colorectal cancer, lung cancer, melanoma, acute myeloid leukemia, bladder cancer or head and neck cancer, etc.

17. The use according to claim 15, wherein KRAS comprises mutations at one or more positions selected from codons 12, 13, 59, and 61.

18. The use according to claim 15 or 16, wherein NRAS comprises mutations at one or more

positions selected from codons 12, 13, 59, 61, and 146, and wherein the NRAS mutation form has mutations at one or more amino acid positions selected from G12, G13, A59, Q61, K117, and A146.

19. The use according to claim 18, wherein the NRAS mutant form has one or more amino acid substitutions selected from: G12C, G12R, G12S, G12A, G12D, G12V, G13C, G13R, G13S, G13A, G13D, G13V, A59D, A59T, Q61K, Q61L, Q61R, Q61H, K117N, K117R, K117E, A146P, A146T, and A146V.

20. The use according to claim 15 or 16, wherein the cancer is an early, middle or advanced stage cancer. Cancer can be locally advanced or metastatic.

21. The use according to claim 15 or 16, wherein the mammal has previously received immunotherapy.

22. The use according to claim 21, wherein the mammal has previously received immunotherapy and suffers from advanced melanoma with NRAS mutation.

23. The use according to claim 15 or 16, wherein the melanoma is selected from: advanced melanoma, unresectable melanoma, metastatic melanoma, melanoma with BRAF mutation, melanoma with NRAS mutation, skin melanoma, or intraocular melanoma.

24. The use according to any one of claims 15 to 23, wherein the polymorph is in the form of a capsule.

25. The use according to claim 24, wherein the polymorph is to be administered in a dose of 5-50mg once or twice a day.