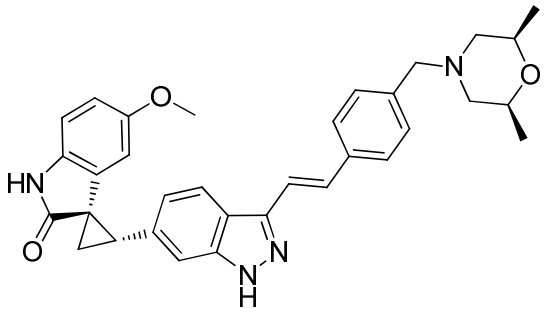
CLAIMS

1. A fumarate salt of compound (I) represented by the following structural formula:




Compound (I)

,

wherein the molar ratio between compound (I) and fumaric acid is 1:1, and the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern which comprises peaks at 6.6°, 9.8°, 16.3°, 21.1°, 28.7°, and 30.2° ± 0.2 in 2θ.

2. The fumarate salt of Claim 1, wherein the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern which comprises peaks at 6.6°, 9.8°, 16.3°, 21.1°, 28.7°, 29.4°, and 30.2° ± 0.2 in 2θ.

3. The fumarate salt of Claim 1, wherein the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern which comprises peaks at 6.6°, 9.8°, 13.0°, 16.3°, 19.5°, 21.1°, 22.5°, 28.7°, 29.4°, and 30.2° ± 0.2 in 2θ.

4. The fumarate salt of Claim 1, wherein the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern which comprises peaks at 6.6°, 9.8°, 13.0°, 16.3°, 19.5°, 21.1°, 22.5°, 22.9°, 23.9°, 28.7°, 29.4°, and 30.2° ± 0.2 in 2θ.

5. The fumarate salt of Claim 1, wherein the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern which comprises peaks at 6.6°, 9.8°, 11.6°, 13.0°, 16.3°, 17.1°, 19.5°, 21.1°, 21.5°, 22.0°, 22.5°, 22.9°, 23.9°, 24.3°, 28.7°, 29.4°, and 30.2° ± 0.2 in 2θ.

6. The fumarate salt of Claim 1, wherein the fumarate salt comprises crystal form S4, characterized by an X-ray powder diffraction pattern substantially similar to Figure 1.

7. The fumarate salt of any one of Claims 1 to 6, wherein at least 90% by weight of the salt is in a single crystal form, form S4.

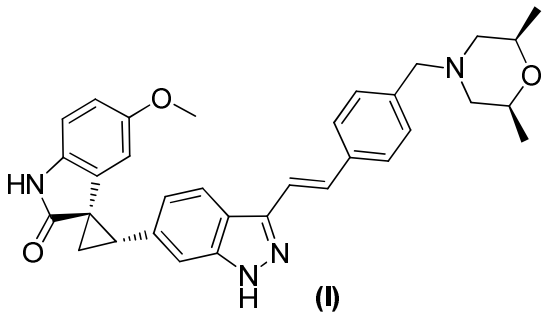
8. The fumarate salt of any one of Claims 1 to 6, wherein at least 99% by weight of the salt is in a single crystal form, form S4.

9. The fumarate salt of any one of Claims 1 to 8, wherein the fumarate salt contains less than 30% by weight crystal form D, characterized by an X-ray powder diffraction pattern which comprises peaks at 9.6°, 12.8°, 16.0°, 16.9°, 21.2°, and 22.0° ± 0.2 in 2θ.

10. The fumarate salt of any one of Claims 1 to 8, wherein the fumarate salt contains less than 10% by weight crystal form D, characterized by an X-ray powder diffraction pattern which comprises peaks at 9.6°, 12.8°, 16.0°, 16.9°, 21.2°, and 22.0° ± 0.2 in 2θ.

11. A pharmaceutical composition comprising the fumarate salt of any one of Claims 1 to 10, and a pharmaceutically acceptable carrier or diluent.

12. A method of preparing crystal form S4 of a fumarate salt of compound (I) according to claim 1:




(I)

comprising dissolving fumaric acid and compound (I) in a dissolution solvent comprising 2-butanone, water, and ethanol to form a crystallization solution, and then precipitating the crystal form S4 from the crystallization solution, wherein:

the molar ratio between compound (I) and fumaric acid in the dissolution solvent is ~~about~~ 1:1 to ~~about~~ 1:1.3; and the molar ratio between compound (I) and fumaric acid in the fumarate salt is 1:1.

13. The method of Claim 12, comprising dissolving fumaric acid and compound (I) in the dissolution solvent at an elevated temperature, and precipitating the crystal form S4 from the crystallization solution by way of cooling and/or adding methylcyclohexane with cooling.

14. The method of Claim 12 or 13, comprising the following steps:

(i) dissolving compound (I) in a mixture of 2-butanone and water at an elevated temperature to form a compound (I) solution;

(ii) dissolving fumaric acid in ethanol at an elevated temperature to form a fumaric acid solution;

(iii) adding the fumaric acid solution to the compound (I) solution at an elevated temperature to form the crystallization solution;

(iv) optionally adding seed crystals at an elevated temperature to the crystallization solution; and

(v) reducing the temperature of the crystallization solution to precipitate the S4 crystal form.

15. The method of Claim 14, wherein the volume ratio between 2-butanone and water is between 80:20 and 98:2, ~~and the volume ratios of 2-butanone/water to ethanol to methylcyclohexane are 6-7 to 4-5 to 11-22;~~ the elevated temperature is between 45 $^{o}$C and 55 $^{o}$C; and the reduced temperature is between 20 $^{o}$C and 30 $^{o}$C.

16. The method of Claim 14, wherein the volume ratio between 2-butanone and water is between 90:10 and 98:2, ~~and the volume ratios of 2-butanone/water to ethanol to methylcyclohexane are 6-7 to 4-5 to 11-22;~~ the elevated temperature is between 45 $^{o}$C and 55 $^{o}$C; and the reduced temperature is between 20 $^{o}$C and 30 $^{o}$C.

17. The method of Claim 14, further comprising adding methylcyclohexane at a reduced temperature to the crystallization solution to precipitate the S4 crystal form.

18. The method of Claim 17, wherein the volume ratio between 2-butanone and water is between 80:20 and 98:2, the elevated temperature is between 45 $^{o}$C and 55 $^{o}$C; and the

volume ratios of 2-butanone/water to ethanol to methylcyclohexane are 6-7 to 4-5 to 11-22.

~~18~~19. The method of Claim 17, wherein the temperature of the crystallization solution is further reduced to precipitate the S4 crystal form.

~~19~~20. The method of Claim 17, wherein the reduced temperature is between 20 $^{o}$C and 30 $^{o}$C.

~~20~~21. The method of Claim ~~18~~19, wherein the further reduced temperature is between 0 $^{o}$C and 10 $^{o}$C.

~~21~~22. Use of the fumarate salt of any one of Claims 1 to 10, or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of cancer in a subject, wherein an effective amount of the fumarate salt or the pharmaceutical composition thereof is to be administered to the subject.

~~22~~23. The use of Claim ~~21~~22, wherein the cancer is selected from the group consisting of lung cancer, breast cancer, colon cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiforme, ovarian cancer, lymphoma, leukemia, osteosarcoma, germinoma, glioma, fibrosarcoma, gastrointestinal sarcoma, fibrous histiocytoma, round cell sarcoma, synovial sarcoma, cervical cancer, anogenital cancer, head and neck cancer, and oropharyngeal cancer.

~~23~~24. The use of Claim ~~21~~22, wherein the cancer is selected from the group consisting of lung cancer, breast cancer and colon cancer.

~~24~~25. The use of Claim ~~21~~22, wherein the cancer is breast cancer.

~~25~~26. The use of Claim ~~21~~22, wherein the cancer is triple negative breast cancer.

~~26~~27. The use of Claim ~~25~~26, wherein the triple negative breast cancer is unresectable or metastatic.

~~27~~28. Use of the fumarate salt of any one of Claims 1 to 10, or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of pancreatic cancer in a subject, wherein an effective amount of the fumarate salt or the pharmaceutical composition thereof is to be administered to the subject.