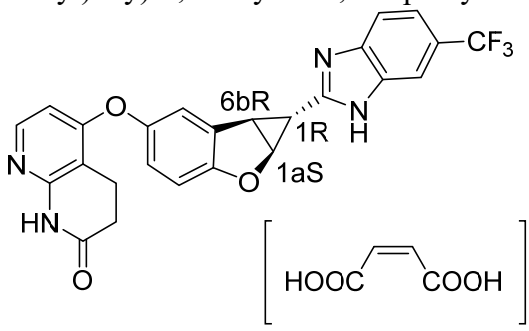
CLAIMS

1. A compound of Formula (***I***) in a crystalline form, which is a maleate salt of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one:



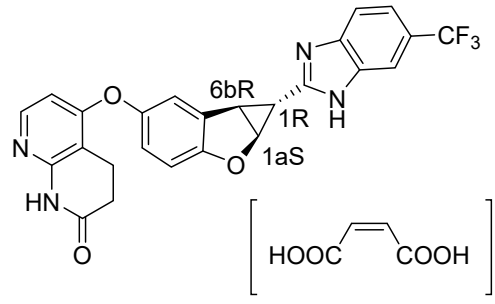
(***I***),

wherein n is a number from 0.3 to 1.5.

2. The compound of Claim 1, wherein n is a number selected from the group consisting of 0.5±0.05, 1.0±0.1, and 1.5±0.2.

3. The compound of Claim 1, wherein n is 0.5, 1.0, or 1.5.

4. The compound of any one of Claims 1 to 3, wherein n is 1.5, and the compound is a crystalline sesqui-maleate salt of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one of Formula:



(***II***).

5. The compound of claim 4, which is in Crystalline Form A* and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 6.3±0.2, 8.9±0.2, 9.4±0.2, 11.2±0.2, 12.6±0.2, 13.4±0.2, 17.9±0.2, 18.6±0.2, 18.8±0.2, 19.3±0.2, 20.1±0.2, 20.7±0.2, 21.2±0.2, 21.8±0.2, 22.4±0.2, 22.6±0.2, 23.3±0.2, 23.8±0.2, 24.7±0.2, 25.6±0.2, 26.1±0.2, 27.4±0.2, 28.3±0.2, 28.6±0.2, 29.0±0.2, 29.4±0.2, and 30.4±0.2 degrees.

6. The compound of Claim 4, which is in Crystalline Form A and is characterized by a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 8.3±0.2, 11.2±0.2, 17.9±0.2, 18.4±0.2, 18.6±0.2, 19.3±0.2, 20.8±0.2, and 22.5±0.2 degrees.

7. The compound of Claim 4, which is in Crystalline Form A** and is a single crystal characterized as follows:

Crystal system: monoclinic;

Space group: C2;

Unit cell dimensions:

a = 19.7026(5) Å;

b = 5.1350(2) Å;

c = 28.4299(8) Å;

alpha = 90.00 deg.;

beta = 93.692(2) deg.; and

gamma = 90.00 deg.

8. The compound of Claim 1, which is in Crystalline Form B and is characterized by a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 11.1±0.2, 15.8±0.2, 17.7±0.2, 18.4±0.2, 19.6±0.2, 22.3±0.2, 23.1±0.2, and 28.8±0.2 degrees.

9. The compound of Claim 1, which is in Crystalline Form C and is characterized by a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 3.1±0.2, 8.8±0.2, 11.2±0.2, 17.8±0.2, 18.5±0.2, 19.3±0.2, 20.1±0.2, 20.7±0.2, 21.9±0.2, and 22.4±0.2 degrees.

10. The compound of Claim 1, which is in Crystalline Form D and is characterized by a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 8.9±0.2, 14.9±0.2, 16.7±0.2, 17.8±0.2, 19.9±0.2, 20.4±0.2, 20.9±0.2, and 26.9±0.2 degrees.

11. The compound of Claim 1, which is in Crystalline Form F and is characterized by a powder X-ray diffraction pattern comprising three or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 12.9±0.2, 17.0±0.2, 18.5±0.2, 19.4±0.2, 20.5±0.2, 22.5±0.2, and 24.1±0.2 degrees.

12. The compound of Claim 1, which is in Crystalline Form G and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 3.4±0.2, 5.6±0.2, 7.0±0.2, 10.3±0.2, 10.9±0.2, 11.7±0.2, 12.4±0.2, 13.1±0.2, 14.0±0.2, 14.9±0.2, 16.4±0.2, 17.4±0.2, 18.6±0.2, 19.3±0.2, 20.1±0.2, 21.0±0.2, 21.9±0.2, 23.6±0.2, 24.2±0.2, 25.6±0.2, and 26.4±0.2 degrees.

13. The compound of Claim 1, which is in Crystalline Form H and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle

values independently selected from the group consisting of: 6.3±0.2, 9.0±0.2, 10.1±0.2, 11.2±0.2, 12.7±0.2, 14.5±0.2, 16.1±0.2, 16.6±0.2, 17.9±0.2, 18.1±0.2, 18.5±0.2, 19.0±0.2, 20.1±0.2, 21.9±0.2, 22.4±0.2, 23.9±0.2, 25.1±0.2, 26.2±0.2, and 28.7±0.2 degrees.

14. The compound of Claim 1, which is in Crystalline Form I and is characterized by a powder X-ray diffraction pattern comprising five or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 3.1±0.2, 5.5±0.2, 6.8±0.2, 10.8±0.2, 11.5±0.2, 13.7±0.2, 16.1±0.2, 16.3±0.2, 17.8±0.2, 19.8±0.2, 21.5±0.2, 23.8±0.2, 24.4±0.2, and 28.3±0.2 degrees.

15. The compound of Claim 1, which is in Crystalline Form J and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 5.5±0.2, 8.2±0.2, 10.9±0.2, 11.3±0.2, 13.6±0.2, 14.8±0.2, 15.8±0.2, 17.4±0.2, 18.0±0.2, 19.1±0.2, 19.8±0.2, 20.0±0.2, 20.4±0.2, 21.1±0.2, 21.9±0.2, 22.6±0.2, 23.4±0.2, 24.1±0.2, 25.0±0.2, 26.1±0.2, 26.9±0.2, 27.3±0.2, 28.4±0.2, 29.1±0.2, 33.1±0.2, and 35.9±0.2 degrees.

16. The compound of Claim 1, which is in Crystalline Form K and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 3.1±0.2, 8.9±0.2, 9.3±0.2, 11.2±0.2, 16.7±0.2, 17.9±0.2, 18.6±0.2, 18.8±0.2, 19.4±0.2, 20.2±0.2, 21.9±0.2, 22.4±0.2, 23.4±0.2, 23.9±0.2, 24.6±0.2, 26.2±0.2, 27.4±0.2, 28.5±0.2, 29.4±0.2, and 30.4±0.2 degrees.

17. The compound of Claim 1, which is in Crystalline Form M and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 5.0±0.2, 9.3±0.2, 11.3±0.2, 14.9±0.2, 15.9±0.2, 17.4±0.2, 18.0±0.2, 18.7±0.2, 19.4±0.2, 20.2±0.2, 22.1±0.2, 23.4±0.2, 24.3±0.2, 25.4±0.2, 26.5±0.2, 27.5±0.2, 28.5±0.2, and 29.3±0.2 degrees.

18. The compound of Claim 1, substantially characterized by a powder X-ray diffraction pattern selected from the group consisting of **Fig. 2, Fig. 16**, **Fig. 17**, **Fig. 18, Fig. 19, Fig. 20, Fig. 21, Fig. 22, Fig. 23, Fig. 24, Fig. 25, Fig. 26, Fig. 28** and **Fig. 33**.

19. A compound of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one Maleate (1:1), which is in crystalline form N and is characterized by a powder X-ray diffraction pattern comprising seven or more diffraction peaks having 2θ angle values independently selected from the group consisting of: 3.30±0.2, 6.61±0.2, 9.88±0.2, 11.73±0.2, 13.14±0.2, 15.23±0.2, 16.56±0.2, 17.94±0.2, 18.72±0.2, 19.34±0.2, 19.93±0.2, 20.76±0.2, 22.04±0.2, 22.95±0.2, 23.86±0.2, 25.19±0.2, 26.61±0.2, 28.36±0.2, 30.13±0.2, 31.36±0.2, 33.49±0.2, and 37.22±0.2.

20. The compound according to Claim 19, which substantially characterized by a powder X-ray diffraction pattern as shown in **Fig. 33**.

21. A method for preparing a crystalline form selected from Crystalline Form A*, A**, A, B, C, D, F, G, H, I, J, K, or M as defined by claims 1-20, comprising any one of the following procedures:

(a) dissolving free base or a salt other than maleate of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one in a solvent or solvent mixture to form a solution or suspension; mixing the resultant solution or suspension with maleic acid to form a mixture; and precipitating out 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate salt in a target crystalline form;

(b) dissolving or suspending 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one sesqui-maleate salt in a solvent or solvent mixture; and precipitating out 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate salt in a target crystalline form;

(c) storing a crystalline 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate salt for an extended period to obtain a target crystalline form;

(d) heating a crystalline or amorphous 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate salt to an elevated temperature, and cooling the salt to obtain a target crystalline form; and

(e) exposing a crystalline or amorphous 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate salt to a vapor of a solvent to obtain a target crystalline form.

22. The method of Claim 21, wherein said procedure (a) or (b) further comprises one or more procedures independently selected from heating, filtering to remove undissolved impurities, distilling solvent, adding a counter solvent or solvent mixture, adding crystal seeds, adding precipitaion inducing agent(s), cooling, precipitating, and filtering to collect the crystalline product.

23. The method of Claim 21 or 22, comprising said procedure (a) or (b), wherein the solvent or solvent mixture is selected from the group consisting of water, lower alkyl alcohols, ketones, ethers, esters, lower aliphatic carboxylic acids, lower aliphatic nitriles, optionally halogenated aromatic solvents, and combinations thereof.

24. The method of Claim 21 or 22, wherein the solvent is isopropanol, ethanol, methanol, acetone, THF, 1,4-dioxane, acetic acid, acetonitrile, water, or a combination thereof.

25. The method of Claim 21, comprising said procedure (a), wherein said free base is an isolated and purified free base, an isolated but unpurified free base, or a crude reaction product containing the free base.

26. The method of Claim 21, comprising said procedure (c), wherein said extended period is at least three days, at least one week, or at least two weeks.

27. The method of Claim 21, comprising said procedure (d), wherein said elevated temperature is at least 40 °C, at least 60 °C, at least 80 °C, or at least 100 °C, but lower than decomposition temperature of the sesqui-maleate salt.

28. The method of Claim 21, comprising said procedure (e), wherein said vapor is a vapor of acetic acid.

29. The method of Claim 21, wherein:

1) said procedure (a) or (b) comprises using isopropanol-water (v/v > 60/40) as the solvent to produce Crystalline Form A*;

2) said procedure (a) or (b) comprises using acetone as the solvent to produce Crystalline Form A**;

3) said procedure (a) or (b) comprises using an IPA-water (v:v=4:1) mixture as the solvent to produce Crystalline Form A;

4) said procedure (a) or (b) comprises using 1,4-dioxane as the solvent to produce Crystalline Form B;

5) said procedure (a) or (b) comprises using ethanol as the solvent to produce Crystalline Form C;

6) said procedure (a) or (b) comprises using methanol as the solvent to produce Crystalline Form D;

7) said procedure (a) or (b) comprises using an acetonitrile-water (v:v=1:1) mixture as the solvent to produce Crystalline Form F;

8) said procedure (a) or (b) comprises using an acetic acid-water mixture as the solvent to produce Crystalline Form G;

9) said procedure (a) or (b) comprises using tetrahydrofuran (THF) as the solvent to produce Crystalline Form H;

10) said procedure (a) or (b) comprises using an IPA-water (v:v=3:1) mixture as the solvent to produce Crystalline Form I;

11) said procedure (c) comprises storing Crystalline Form D at ambient temperature for two weeks to produce Crystalline Form K;

12) said procedure (c) comprises storing Crystalline Form J at ambient temperature for two weeks to produce Crystalline Form M; and

13) said procedure (e) comprises interaction of Crystalline Form A with acetic acid vapor to produce Crystalline Form J.

30. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to any one of Claims 1 to 20 and a pharmaceutically acceptable carrier.

31. The pharmaceutic composition of Claim 30, wherein the pharmaceutical composition is suitable for oral administration.

32. The pharmaceutical composition of Claim 30, wherein the pharmaceutical composition is in the form of tablet or capsule.

33. The pharmaceutical composition of Claim 30, wherein the unit dosage of the tablet or capsule is 5-80 mg.

34. The pharmaceutical composition of Claim 30, wherein the weight percentage of the compound in the pharmaceutical composition is 1-99%.

35. A compound according to any one of Claims 1 to 20 or a pharmaceutical composition according to any one of claims 30 to 34 for use in a method of treating or preventing a disease or disorder in a subject, wherein a therapeutically effective amount of the compound according to any one of Claims 1 to 20 or the pharmaceutical composition according to any one of claims 30 to 34 is to be administered to said subject.

36. Use of a compound according to any one of Claims 1 to 20 in the manufacture of a composition for treating or preventing a cancer in a subject, wherein a therapeutically effective amount of the compound is to be administered to the subject.

37. The use of Claim 36, wherein the disease or disorder is a cancer selected from the group consisting of brain cancer, lung cancer, kidney cancer, bone cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, colorectal cancer, lymphoma, or thyroid tumors and their complications.

38. The use of Claim 36, wherein the disease is selected from the group consisting of BRAF, NRAS and KRAS mutant brain cancer, lung cancer, kidney cancer, bone cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, colorectal cancer, lymphoma, or thyroid tumors and their complications.

39. The use of Claim 38, wherein the dosage of the compound according to any one of claims 1 to 20 to be administered is 1-100 mg/day, and the administration frequency is to be one to three times a day.

40. The use of Claim 38, wherein the dosage of the compound according to any one of Claims 1 to 20 to be administered is 5-50 mg/day, and the administration frequency is to be one to three times a day.

41. The use of Claim 38, wherein the dosage of the compound according to any one of Claims 1 to 20 to be administered is 10-40 mg/day, and the administration frequency is to be one time a day.

42. The use of any one of Claims 36 to 40, wherein said compound is 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate in a crystalline form selected from the group consisting of Crystalline Forms A*, A**, A, B, C, D, F, G, H, I, J, K, M and N.

43. A process for preparing a crystalline 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one sesqui-maleate comprising:

a) mixing at about 50°C a mixture of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one and maleic acid in a mixed solvent of i-PrOH and H_2O, or

b) mixing at about 50°C 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one with a mixture or a suspension or a solution of maleic acid in a mixed solvent of i-PrOH and H_2O, or

c) mixing at about 50°C a mixture or a suspension or a solution of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one in a mixed solvent of i-PrOH and H_2O with maleic acid,

wherein in each of (a), (b) and (c), the amount of i-PrOH is greater than 40 vol% in terms of the total volume of i-PrOH and water.

44. The process according to Claim 43, wherein in each of (a), (b) and (c), the amount of i-PrOH is greater than 60vol%, and preferably 90vol% in terms of the total volume of i-PrOH and water.

45. The process according to Claim 43, wherein the mixed solvent is replaced with i-PrOH.

46. The process according to any one of Claims 43 to 45, further comprising adding some crystal seeds into the resultant mixture after cooling to room temperature, and then letting the mixture stand for a certain duration.

47. A process for preparing a crystalline form of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate (1:1) comprising mixing a crystalline form of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one sesqui-maleate with methanol.

48. The process according to Claim 47, wherein the mixing is performed with stirring.

49. The process according to Claim 47 or 48, wherein the crystalline form of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one maleate (1:1) is Form N.

50. The process according to any one of Claims 47, and 48, wherein the crystalline form of 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyridin-2(1H)-one sesqui-maleate is any one selected from the group consisting of Crystalline Form A* according to claim 6, Crystalline Form A** according to claim 8, and Crystalline Form A according to claim 7.