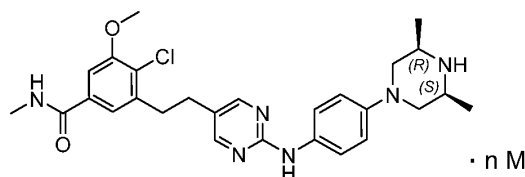


What is claimed:

1. A salt of Formula A:



Formula A

wherein n is 0.5 or 1; and M is a pharmaceutically acceptable acid.

2. The salt of Formula A according to claim 1, wherein M is hydrochloric acid, tartaric acid, or p-toluenesulfonic acid.

3. The salt of Formula A according to claim 2, wherein n is 1 and M is hydrochloric acid; n is 0.5 and M is tartaric acid; or n is 1 and M is p-toluenesulfonic acid.

4. The salt of Formula A according to claim 3, wherein n is 1 and M is hydrochloric acid, and the salt is Form A-III having the X-ray powder diffraction characteristic diffraction angles (2θ) of 5.8±0.2°, 6.2±0.2°, 12.3±0.2°, 13.3±0.2°, 23.1±0.2°, and 24.1±0.2°;

preferably, said Form A-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of 5.8±0.2°, 6.2±0.2°, 10.3±0.2°, 12.3±0.2°, 13.3±0.2°, 15.0±0.2°, 16.2±0.2°, 22.2±0.2°, 23.1±0.2°, 24.1±0.2°, and 26.4±0.2°;

more preferably, said Form A-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of 5.8±0.2°, 6.2±0.2°, 10.3±0.2°, 12.3±0.2°, 13.3±0.2°, 15.0±0.2°, 15.8±0.2°, 16.2±0.2°, 18.3±0.2°, 18.5±0.2°, 20.2±0.2°, 22.2±0.2°, 23.1±0.2°, 24.1±0.2°, 26.4±0.2°, 27.1±0.2°, and 27.8±0.2°;

further preferably, said Form A-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of 5.8±0.2°, 6.2±0.2°, 7.9±0.2°, 10.3±0.2°, 12.3±0.2°, 13.3±0.2°, 15.0±0.2°, 15.8±0.2°, 16.2±0.2°, 16.8±0.2°, 17.4±0.2°, 18.3±0.2°, 18.5±0.2°, 19.6±0.2°, 20.2±0.2°, 21.0±0.2°, 22.2±0.2°, 23.1±0.2°, 24.1±0.2°, 24.8±0.2°, 26.4±0.2°, 27.1±0.2°, and 27.8±0.2°;

most preferably, said Form A-III has the X-ray powder diffraction pattern as shown in Figure 1.

5. The salt of Formula A according to claim 4, wherein said Form A-III has the differential scanning calorimetry (DSC) curve having an endothermic peak at about 290.2-295.4°C.

6. The salt of Formula A according to claim 3, wherein n is 0.5 and M is tartaric acid, and the salt is Form B-II having the X-ray powder diffraction characteristic diffraction angles (2θ) of 7.5±0.2°, 11.3±0.2°, 13.9±0.2°, 15.1±0.2°, 18.0±0.2°, and 20.6±0.2°;

preferably, said Form B-II has the X-ray powder diffraction characteristic diffraction angles (2θ) of 3.8±0.2°, 7.5±0.2°, 11.3±0.2°, 13.9±0.2°, 15.1±0.2°, 15.7±0.2°, 18.0±0.2°, 19.8±0.2°, 20.6±0.2°, 21.7±0.2°, and 23.0±0.2°;

more preferably, said Form B-II has the X-ray powder diffraction characteristic diffraction angles (2θ) of $3.8\pm0.2^\circ$, $7.5\pm0.2^\circ$, $10.1\pm0.2^\circ$, $11.3\pm0.2^\circ$, $13.4\pm0.2^\circ$, $13.9\pm0.2^\circ$, $15.1\pm0.2^\circ$, $15.7\pm0.2^\circ$, $18.0\pm0.2^\circ$, $19.8\pm0.2^\circ$, $20.6\pm0.2^\circ$, $21.7\pm0.2^\circ$, $23.0\pm0.2^\circ$, $25.1\pm0.2^\circ$, and $27.8\pm0.2^\circ$;

further preferably, said Form B-II has the X-ray powder diffraction characteristic diffraction angles (2θ) of $3.8\pm0.2^\circ$, $7.5\pm0.2^\circ$, $10.1\pm0.2^\circ$, $11.3\pm0.2^\circ$, $11.8\pm0.2^\circ$, $13.1\pm0.2^\circ$, $13.4\pm0.2^\circ$, $13.9\pm0.2^\circ$, $15.1\pm0.2^\circ$, $15.7\pm0.2^\circ$, $18.0\pm0.2^\circ$, $19.8\pm0.2^\circ$, $20.6\pm0.2^\circ$, $21.1\pm0.2^\circ$, $21.7\pm0.2^\circ$, $23.0\pm0.2^\circ$, $25.1\pm0.2^\circ$, and $27.8\pm0.2^\circ$;

most preferably, said Form B-II has the X-ray powder diffraction pattern as shown in Figure 4.

7. The salt of Formula A according to claim 6, wherein said Form B-II has the differential scanning calorimetry (DSC) curve having endothermic peaks at about $54.8-92.2^\circ\text{C}$, $166.9-174.4^\circ\text{C}$, and $263.3-265.3^\circ\text{C}$, and an exothermic peak at about $194.2-202.7^\circ\text{C}$.

8. The salt of Formula A according to any one of claims 6-7, wherein said Form B-II has a thermogravimetric analysis (TGA) curve as shown in Figure 6, indicating a weight loss of about 4.3% in the range from 30°C to 100°C .

9. The salt of Formula A according to claim 3, wherein n is 0.5 and M is tartaric acid, and the salt is Form B-III having the X-ray powder diffraction characteristic diffraction angles (2θ) of $13.1\pm0.2^\circ$, $14.6\pm0.2^\circ$, $18.3\pm0.2^\circ$, $18.9\pm0.2^\circ$, $19.4\pm0.2^\circ$, and $26.3\pm0.2^\circ$;

preferably, said Form B-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of $12.4\pm0.2^\circ$, $13.1\pm0.2^\circ$, $13.7\pm0.2^\circ$, $14.6\pm0.2^\circ$, $16.5\pm0.2^\circ$, $18.3\pm0.2^\circ$, $18.9\pm0.2^\circ$, $19.4\pm0.2^\circ$, $21.4\pm0.2^\circ$, $22.6\pm0.2^\circ$, $23.7\pm0.2^\circ$, and $26.3\pm0.2^\circ$;

more preferably, said Form B-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of $7.6\pm0.2^\circ$, $8.9\pm0.2^\circ$, $10.0\pm0.2^\circ$, $11.0\pm0.2^\circ$, $12.4\pm0.2^\circ$, $13.1\pm0.2^\circ$, $13.4\pm0.2^\circ$, $13.7\pm0.2^\circ$, $14.6\pm0.2^\circ$, $15.9\pm0.2^\circ$, $16.5\pm0.2^\circ$, $18.3\pm0.2^\circ$, $18.9\pm0.2^\circ$, $19.4\pm0.2^\circ$, $21.4\pm0.2^\circ$, $22.6\pm0.2^\circ$, $23.7\pm0.2^\circ$, and $26.3\pm0.2^\circ$;

further preferably, said Form B-III has the X-ray powder diffraction characteristic diffraction angles (2θ) of $7.6\pm0.2^\circ$, $8.9\pm0.2^\circ$, $10.0\pm0.2^\circ$, $11.0\pm0.2^\circ$, $12.4\pm0.2^\circ$, $13.1\pm0.2^\circ$, $13.4\pm0.2^\circ$, $13.7\pm0.2^\circ$, $14.6\pm0.2^\circ$, $15.9\pm0.2^\circ$, $16.5\pm0.2^\circ$, $17.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $18.9\pm0.2^\circ$, $19.4\pm0.2^\circ$, $19.6\pm0.2^\circ$, $21.4\pm0.2^\circ$, $22.6\pm0.2^\circ$, $23.7\pm0.2^\circ$, $24.6\pm0.2^\circ$, $26.3\pm0.2^\circ$, $27.6\pm0.2^\circ$, and $29.2\pm0.2^\circ$;

most preferably, said Form B-III has the X-ray powder diffraction pattern as shown in Figure 7.

10. The salt of Formula A according to claim 9, wherein said Form B-III has the differential scanning calorimetry (DSC) curve having an endothermic peak at about $269.2-271.3^\circ\text{C}$.

11. The salt of Formula A according to any one of claims 9-10, wherein said Form B-III has a thermogravimetric analysis (TGA) curve as shown in Figure 9.

12. The salt of Formula A according to claim 3, wherein n is 1 and M is p-toluenesulfonic acid, and the salt is Form C-I having the X-ray powder diffraction characteristic diffraction angles (2θ) of $7.8\pm0.2^\circ$, $11.1\pm0.2^\circ$, $11.7\pm0.2^\circ$, $16.6\pm0.2^\circ$, $17.9\pm0.2^\circ$, $18.2\pm0.2^\circ$, $19.2\pm0.2^\circ$, and $24.0\pm0.2^\circ$;

preferably, said Form C-I has the X-ray powder diffraction characteristic diffraction angles (2θ) of $5.5\pm 0.2^\circ$, $7.8\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $11.1\pm 0.2^\circ$, $11.7\pm 0.2^\circ$, $13.8\pm 0.2^\circ$, $14.3\pm 0.2^\circ$, $16.6\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.2\pm 0.2^\circ$, $19.2\pm 0.2^\circ$, $22.2\pm 0.2^\circ$, $24.0\pm 0.2^\circ$, and $26.1\pm 0.2^\circ$;

more preferably, said Form C-I has the X-ray powder diffraction characteristic diffraction angles (2θ) of $5.5\pm 0.2^\circ$, $7.8\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $11.1\pm 0.2^\circ$, $11.7\pm 0.2^\circ$, $13.5\pm 0.2^\circ$, $13.8\pm 0.2^\circ$, $14.3\pm 0.2^\circ$, $14.7\pm 0.2^\circ$, $16.6\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.2\pm 0.2^\circ$, $19.2\pm 0.2^\circ$, $20.0\pm 0.2^\circ$, $20.6\pm 0.2^\circ$, $22.2\pm 0.2^\circ$, $24.0\pm 0.2^\circ$, $26.1\pm 0.2^\circ$, and $27.4\pm 0.2^\circ$;

further preferably, said Form C-I has the X-ray powder diffraction characteristic diffraction angles (2θ) of $5.5\pm 0.2^\circ$, $7.8\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $11.1\pm 0.2^\circ$, $11.7\pm 0.2^\circ$, $12.2\pm 0.2^\circ$, $12.9\pm 0.2^\circ$, $13.5\pm 0.2^\circ$, $13.8\pm 0.2^\circ$, $14.3\pm 0.2^\circ$, $14.7\pm 0.2^\circ$, $16.6\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.2\pm 0.2^\circ$, $19.2\pm 0.2^\circ$, $20.0\pm 0.2^\circ$, $20.6\pm 0.2^\circ$, $22.2\pm 0.2^\circ$, $23.5\pm 0.2^\circ$, $24.0\pm 0.2^\circ$, $25.0\pm 0.2^\circ$, $26.1\pm 0.2^\circ$, $27.4\pm 0.2^\circ$, and $32.8\pm 0.2^\circ$;

most preferably, said Form C-I has the X-ray powder diffraction pattern as shown in Figure 12.

13. The salt of Formula A according to claim 12, wherein said Form C-I has the differential scanning calorimetry (DSC) curve having an endothermic peak at about $289.77\text{--}291.04^\circ\text{C}$.

14. The salt of Formula A according to any one of claims 12-13, wherein said Form C-I has a thermogravimetric analysis (TGA) curve as shown in Figure 14.

15. A pharmaceutical composition, comprising an effective amount of the salt of Formula A according to any one of claims 1-14, and optionally a pharmaceutically acceptable carrier.

16. A method of preventing or treating a disease responsive to inhibition of FGFR activity, comprising administering to a subject in need thereof an effective amount of the salt of Formula A according to any one of claims 1-14.

17. Use of the salt of Formula A according to any one of claims 1-14 in the manufacture of a medicament for preventing or treating a disease responsive to inhibition of FGFR activity, such as cancer.

18. The use according to claim 17, wherein said cancer is selected from lung cancer (such as squamous non-small cell lung cancer and small cell lung cancer), gastric cancer, liver cancer, breast cancer, ovarian cancer, endometrial cancer, bladder cancer, urothelial cancer, esophageal cancer, biliary tract cancer, colon cancer, rectal cancer, head and neck cancer, cervical cancer, pancreatic cancer, adrenal cancer, glioma, mesothelioma, and hematologic malignancy (such as myeloproliferative neoplasm).

19. The salt of Formula A according to any one of claims 1-14 for use in therapy.

20. The salt of Formula A according to any one of claims 1-14 for use in the treatment of a disease responsive to inhibition of FGFR activity, such as cancer.

21. The salt of Formula A according to claim 20, wherein said cancer is selected from lung

cancer (such as squamous non-small cell lung cancer and small cell lung cancer), gastric cancer, liver cancer, breast cancer, ovarian cancer, endometrial cancer, bladder cancer, urothelial cancer, esophageal cancer, biliary tract cancer, colon cancer, rectal cancer, head and neck cancer, cervical cancer, pancreatic cancer, adrenal cancer, glioma, mesothelioma, and hematologic malignancy (such as myeloproliferative neoplasm).

22. A method for preparing the salt of Formula A according to any one of claims 4-5, comprising:

- (1) mixing the compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide with hydrochloric acid in a dissolution solvent or in a mixed solvent consisting of water miscible organic solvent and water under heating and stirring for reacting to form a salt;
- (2) cooling the reaction obtained in step (1) to precipitate the solid sufficiently;
- (3) isolating the precipitated solid as Form A-III;
- (4) optionally drying the solid obtained in step (3).

23. The method according to claim 22, wherein said hydrochloric acid is concentrated hydrochloric acid with the concentration of 36%-38% by weight.

24. The method according to any one of claims 22-23, wherein the molar ratio of said hydrochloric acid to said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 1:1, such as is about 1:1 or 1.2:1.

25. The method according to any one of claims 22-24, wherein the ratio of the volume of said dissolution solvent or said mixed solvent to the weight of said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 10 ml/g, such as is about 20 ml/g or about 60 ml/g.

26. The method according to any one of claims 22-25, wherein said dissolution solvent is selected from C₁₋₆ alkanol; preferably, said dissolution solvent is selected from methanol, ethanol, i-propanol, t-butanol, and the mixture thereof; more preferably, said dissolution solvent is ethanol.

27. The method according to any one of claims 22-26, wherein said water miscible organic solvent is selected from C₁₋₆ alkanol; preferably, said water miscible organic solvent is selected from methanol, ethanol, i-propanol, t-butanol, and the mixture thereof; more preferably, said water miscible organic solvent is selected from ethanol, i-propanol, and the mixture thereof.

28. The method according to any one of claims 22-27, wherein the volume percentage of said water miscible organic solvent in said mixed solvent is not more than about 95%; preferably, the volume percentage of said water miscible organic solvent in said mixed solvent is 95%, 90%, or 80%.

29. The method according to any one of claims 22-28, wherein in the optional step (4), the drying temperature is 50-80°C.

30. A method for preparing the salt of Formula A according to any one of claims 6-8,
5 comprising:

(1) mixing the compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide with L-tartaric acid in ethanol under heating and stirring for reacting to form a salt;

(2) cooling the reaction obtained in step (1) to precipitate the solid sufficiently;

10 (3) isolating the precipitated solid as Form B-II;

(4) optionally drying the solid obtained in step (3).

31. The method according to claim 30, wherein the molar ratio of said L-tartaric acid to said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 1:2, preferably, is about 4:5 or about 3.4:1.
15

32. The method according to any one of claims 30-31, wherein the ratio of the volume of said ethanol to the weight of said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 10 ml/g, such as is about 72 ml/g or about 75 ml/g.
20

33. The method according to any one of claims 30-32, wherein in the optional step (4), the drying temperature is 50-85°C.
25

34. A method for preparing the salt of Formula A according to any one of claims 9-11, comprising:

(1) mixing the compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide with L-tartaric acid in a dissolution solvent, in water, or in a mixed solvent consisting of water miscible organic solvent and water under heating and stirring for reacting to form a salt, thereby obtaining the first solution; provided that said dissolution solvent is not the single solvent ethanol;
30

(2) optionally adding an anti-dissolution solvent into said first solution to obtain the second solution;

35 (3) cooling said first solution or second solution to precipitate the solid sufficiently;

(4) isolating the precipitated solid as Form B-III;

(5) optionally drying the solid obtained in step (4).

35. The method according to claim 34, wherein the molar ratio of said L-tartaric acid to said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 1:1, preferably, the molar ratio is about 1:1 or about 1.5:1.
40

36. The method according to any one of claims 34-35, wherein the ratio of the volume of said dissolution solvent, said water, or said mixed solvent consisting of water miscible organic solvent and water to the weight of said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-N-methylbenzamide is not less than about 10 ml/g, such as is about 20 ml/g, about 30 ml/g, about 33 ml/g, about 50 ml/g, about 65 ml/g, about 98 ml/g, or about 286 ml/g.

37. The method according to any one of claims 34-36, wherein said dissolution solvent is selected from C₁₋₆ alkanol, acetone, toluene, organic acid ester with not more than eight carbon atoms, and the mixture thereof; preferably, said dissolution solvent is selected from methanol, ethanol, i-propanol, t-butanol, n-butanol, acetone, toluene, n-propyl acetate, ethyl acetate, and the mixture thereof; more preferably, said dissolution solvent is selected from methanol, ethanol, i-propanol, acetone, toluene, n-propyl acetate, ethyl acetate, and the mixture thereof.

38. The method according to claim 37, wherein said dissolution solvent is selected from a mixed solvent consisting of two solvents of methanol, ethanol, toluene, n-propyl acetate, and ethyl acetate, for example, n-propyl acetate/methanol (in the volume ratio of about 3:2), toluene/ethanol (in the volume ratio of about 1:1), or ethyl acetate/ethanol (in the volume ratio of about 11:15).

39. The method according to any one of claims 34-38, wherein said water miscible organic solvent is selected from C₁₋₆ alkanol, acetone, and the mixture thereof; preferably, said water miscible organic solvent is selected from methanol, ethanol, i-propanol, t-butanol, acetone, and the mixture thereof; more preferably, said water miscible organic solvent is selected from ethanol, i-propanol, acetone, and the mixture thereof.

40. The method according to any one of claims 34-39, wherein the volume percentage of said water miscible organic solvent in said mixed solvent is not more than about 95%, such as 95%, 90%, 80%.

41. The method according to any one of claims 34-40, wherein said anti-dissolution solvent is selected from toluene, organic acid ester with not more than eight carbon atoms, and the mixture thereof; preferably, said anti-dissolution solvent is selected from toluene, ethyl acetate, n-propyl acetate, and the mixture thereof; more preferably, said anti-dissolution solvent is selected from toluene, ethyl acetate, and the mixture thereof.

42. The method according to any one of claims 34-41, wherein in step (3), said cooling is cooling naturally or cooling at a controlled temperature.

43. The method according to any one of claims 34-42, wherein in step (5), the drying temperature is 50-85°C.

44. A method for preparing the salt of Formula A according to any one of claims 12-14, comprising:

(1) mixing the compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide with p-toluenesulfonic acid monohydrate in a mixed solvent consisting of water miscible organic solvent and water under heating and stirring for reacting to form a salt;

- 5 (2) cooling the reaction obtained in step (1) to precipitate the solid sufficiently;
(3) isolating the precipitated solid as Form C-I;
(4) optionally drying the solid obtained in step (3).

45. The method according to claim 44, wherein the molar ratio of said p-toluenesulfonic acid monohydrate to said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide is not less than about 1:1, such as is about 1.5:1.

46. The method according to any one of claims 44-45, wherein the ratio of the volume of said mixed solvent consisting of water miscible organic solvent and water to the weight of said compound 4-chloro-3-(2-(2-((4-((3S,5R)-3,5-dimethylpiperazin-1-yl)phenyl)amino)pyrimidin-5-yl)ethyl)-5-methoxy-*N*-methylbenzamide in step (1) is not less than about 10 ml/g, such as is about 36 ml/g or about 43 ml/g.

47. The method according to any one of claims 44-46, wherein said water miscible organic solvent is selected from C₁₋₆ alkanol, acetone, and the mixture thereof; preferably, said water miscible organic solvent is selected from i-propanol, acetone, and the mixture thereof.

48. The method according to any one of claims 44-47, wherein the volume percentage of said water miscible organic solvent in said mixed solvent is not more than about 95%, such as is 80%.

49. The method according to any one of claims 44-48, wherein after the completion of the reaction in step (1), an anti-dissolution solvent (such as i-propanol) is added prior to step (2).

50. The method according to any one of claims 44-49, wherein in step (2), said cooling is cooling naturally or cooling at a controlled temperature.

51. The method according to any one of claims 44-50, wherein in the optional step (4), the drying temperature is 50-60°C.