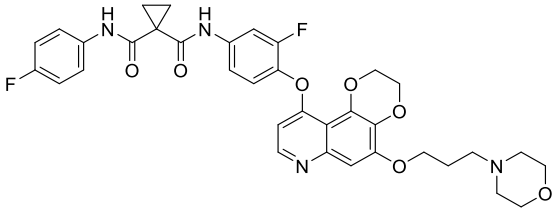
CLAIMS

1. A pharmaceutically acceptable salt of a compound represented by formula (I) N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide,



Formula (I),

wherein the pharmaceutically acceptable salt is selected from inorganic salts and organic salts, alternatively a p-toluenesulfonate salt, a mucate salt, and a phosphate salt.

2. The pharmaceutically acceptable salt according to claim 1, wherein the pharmaceutically acceptable salt is a salt of N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and p-toluenesulfonic acid in a chemical ratio of 1:1 or 1:2.

3. A method for preparing a pharmaceutically acceptable salt according to claim 1, comprising the step of subjecting N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide to a salt-forming reaction with an inorganic acid or an organic acid, alternatively with p-toluenesulfonic acid, mucic acid or phosphoric acid.

4. The preparation method according to claim 3, wherein the salt-forming reaction is carried out in a solvent selected from water, alcohol solvents, halogenated hydrocarbon solvents, ketone solvents, ether solvents, nitrile solvents, ester solvents, amide solvents, aliphatic hydrocarbon solvents, alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, a mixed solvent of alcohol solvents and water, a mixed solvent of ketone solvents and water, a mixed solvent of alcohol solvents and ether solvents, a mixed solvent of halogenated hydrocarbon solvents and nitrile solvents, a mixed solvent of amide solvents and water, or a mixed solvent of nitrile solvents and water; the ketone solvent is alternatively acetone, the alcohol solvent is alternatively methanol, ethanol or isopropanol, the ether solvent is alternatively diethyl ether, methyl tert-butyl ether, tetrahydrofuran, 2-methyltetrahydrofuran or dioxane, the halogenated hydrocarbon solvent is alternatively dichloromethane or chloroform, the nitrile solvent is alternatively acetonitrile, the ester solvent is alternatively ethyl acetate,

isopropyl acetate or butyl acetate, the amide solvent is alternatively N,N-dimethylformamide or N,N-dimethylacetamide, the aliphatic hydrocarbon solvent is alternatively n-heptane, the alicyclic hydrocarbon solvent is alternatively cyclohexane, the aromatic hydrocarbon solvent is alternatively toluene, xylene or isopropylbenzene, the mixed solvent of the alcohol solvent and the ether solvent is alternatively a mixed solvent of diethyl ether and methanol, the mixed solvent of the halogenated hydrocarbon solvent and the nitrile solvent is alternatively a mixed solvent of dichloromethane and acetonitrile, the mixed solvent of the alcohol solvent and water is alternatively a mixed solvent of methanol and water or ethanol and water, the mixed solvent of the ketone solvent and water is alternatively a mixed solvent of acetone and water, and the mixed solvent of the amide solvent and water is alternatively a mixed solvent of N,N-dimethylformamide and water.

5. The method for preparing a pharmaceutically acceptable salt according to claim 3, comprising the step of forming a salt from N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and p-toluenesulfonic acid in a chemical ratio of 1:1 or 1:2.

6. A crystal form A-I of a mucate salt of the compound of formula (I) N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, wherein in its X-ray powder diffraction pattern, there are characteristic peaks at 2θ angles of 3.95, 5.54, 7.46, 10.87, and 16.58, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, there are characteristic peaks at 2θ angles of 3.47, 3.95, 5.54, 7.46, 8.46, 10.48, 10.87, 14.90, 15.28, 16.16, and 16.58, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

yet alternatively, there are characteristic peaks at 2θ angles of 3.47, 3.95, 5.54, 7.46, 8.46, 10.48, 10.87, 11.72, 14.08, 14.90, 15.28, 16.16, 16.58, 17.90, 20.29, 21.65, 22.35, 23.37, 24.53, 25.45, 27.35, and 32.58, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, wherein the XRPD pattern is as shown in Fig. 1;

alternatively, further characterized by: having a weight loss of 1.1% of its weight upon heated to 150 °C in thermogravimetric analysis, alternatively, wherein the TGA curve is as shown in Fig. 2;

alternatively, further characterized by: having an endothermic peak at 207.3 °C in differential scanning calorimetry analysis, alternatively, wherein the DSC curve is as shown in Fig. 3.

7. A crystal form A-II of a p-toluenesulfonate salt of the compound of formula (I) N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-

fluorophenyl)cyclopropane-1,1-dicarboxamide, wherein in its X-ray powder diffraction pattern, there are characteristic peaks at 2θ angles of 5.30, 6.54, 7.97, 8.78, 13.01, 15.86, 19.70, 19.94, and 20.62, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, there are characteristic peaks at 2θ angles of 5.30, 6.54, 7.97, 8.78, 10.52, 11.63, 11.81, 13.01, 15.86, 17.54, 19.34, 19.70, 19.94, 20.62, 22.50, and 25.95, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

yet alternatively, there are characteristic peaks at 2θ angles of 5.30, 6.54, 7.97, 8.78, 10.52, 11.63, 11.81, 13.01, 13.54, 14.33, 14.52, 15.06, 15.86, 16.46, 17.54, 18.02, 18.25, 18.75, 19.34, 19.70, 19.94, 20.62, 21.06, 21.46, 22.50, 23.67, 24.02, 24.35, 25.12, 25.95, 26.45, 27.20, 27.87, 29.20, 30.15, 30.87, and 31.83, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, wherein the XRPD pattern is as shown in Fig. 4;

alternatively, further characterized by: having a weight loss of 1.0% of its weight upon heated to 150 °C in thermogravimetric analysis, alternatively, wherein the TGA curve is as shown in Fig. 5;

alternatively, further characterized by: having an endothermic peak at 156.2 °C in differential scanning calorimetry analysis, alternatively, wherein the DSC curve is as shown in Fig. 6.

8. A crystal form A-IV of a di-p-toluenesulfonate salt of the compound of formula (I) N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, wherein in its X-ray powder diffraction pattern, there are characteristic peaks at 2θ angles of 6.36, 13.60, and 19.20, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, there are characteristic peaks at 2θ angles of 6.36, 9.87, 11.50, 13.60, 16.00, 19.20, 20.26, 20.86, and 21.36, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

yet alternatively, there are characteristic peaks at 2θ angles of 6.36, 9.45, 9.87, 11.50, 12.88, 13.60, 14.40, 16.00, 19.20, 20.26, 20.86, 21.36, 22.59, 23.76, and 26.73, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, wherein the XRPD pattern is as shown in Fig. 10;

alternatively, further characterized by: having a weight loss of 1.3% of its weight upon heated to 150 °C in thermogravimetric analysis, alternatively, wherein the TGA curve is as shown in Fig. 11;

alternatively, further characterized by: having an endothermic peak at 228.8 °C in differential scanning calorimetry analysis, alternatively, wherein the DSC curve is as shown in Fig. 12.

9. A crystal form A-V of a phosphate salt of the compound of formula (I) N-(3-fluoro-4-((5-(3-morpholinopropoxy)-2,3-dihydro-[1,4]dioxano[2,3-f]quinolin-10-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, wherein in its X-ray powder diffraction pattern, there are characteristic peaks at 2θ angles of 5.68, 7.56, and 16.93, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, there are characteristic peaks at 2θ angles of 4.03, 5.68, 6.84, 7.56, 9.36, 11.30, 11.94, 16.93, 19.76, and 23.01, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

yet alternatively, there are characteristic peaks at 2θ angles of 4.03, 5.68, 6.84, 7.56, 9.36, 11.30, 11.94, 12.56, 13.69, 16.17, 16.93, 19.76, 22.02, 23.01, 23.98, and 25.19, wherein the error range of 2θ angle of each characteristic peak is ±0.2;

alternatively, wherein the XRPD pattern is as shown in Fig. 13;

alternatively, further characterized by: having a weight loss of 7.1% of its weight upon heated to 150 °C in thermogravimetric analysis, alternatively, wherein the TGA curve is as shown in Fig. 14;

alternatively, further characterized by: having two endothermic peaks at 90.5 °C and 148.2 °C in differential scanning calorimetry analysis, alternatively, wherein the DSC curve is as shown in Fig. 15.

10. A pharmaceutical composition comprising the pharmaceutically acceptable salt according to any one of claims 1 to 2 or the crystal form according to any one of claims 6 to 9, and one or more pharmaceutically acceptable carriers or excipients.

11. The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition further comprises one or more additional therapeutic agents.

12. The pharmaceutically acceptable salt according to any one of claims 1 to 2, the crystal form according to any one of claims 6 to 9, or the pharmaceutical composition according to claims 10 to 11, for use in treating diseases related to tyrosine kinases VEGFR-2, c-MET, c-KIT, PDGFRa, RET, AXL, or NTRK.

13. Use of the pharmaceutically acceptable salt according to any one of claims 1 to 2, the crystal form according to any one of claims 6 to 9, or the pharmaceutical composition according to claims 10 to 11 in the manufacture of a medicament for treating diseases related to tyrosine kinases VEGFR-2, c-MET, c-KIT, PDGFRa, RET, AXL, or NTRK.

14. The pharmaceutically acceptable salt according to claim 12 or the use according to claim 13, wherein the disease is cancer or an autoimmune disease, in particular ocular fundus disease, xerophthalmia, psoriasis, leucoderma, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus

erythematosus, Crohn's disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, myelofibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic granulocytic leukemia, acute myelocytic leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary tract carcinosarcoma, or cholangiocarcinoma.