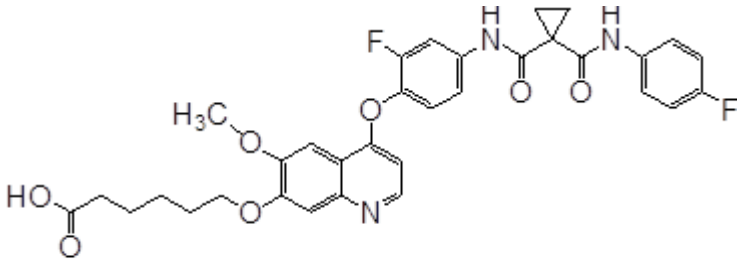
CLAIMS

What is claimed is:

1. A crystalline form AB of compound 1,



Compound 1

wherein an X-ray powder diffraction pattern of the crystalline form AB represented by an angle of 2θ has diffraction peaks at 4.6±0.1°, 6.7±0.1°, 10.7±0.1°, 16.2±0.1°, 17.0±0.1°, 17.4±0.1°, 19.5±0.1°, 20.7±0.1°, 21.9±0.1°, 22.5±0.1°, 23.8±0.1°, and 25.1±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form AB represented by an angle of 2θ has diffraction peaks at 4.6±0.1°, 6.7±0.1°, 9.3±0.1°, 9.7±0.1°, 10.7±0.1°, 11.6±0.1°, 13.4±0.1°, 13.8±0.1°, 15.3±0.1°, 16.2±0.1°, 17.0±0.1°, 17.4±0.1°, 18.6±0.1°, 19.5±0.1°, 20.7±0.1°, 21.9±0.1°, 22.3±0.1°, 22.5±0.1°, 23.4±0.1°, 23.8 ± 0.1°, 24.4±0.1°, 25.1±0.1°, 26.0±0.1°, 26.8±0.1°, 27.7±0.1°, 29.7±0.1°, 32.8±0.1°, and 33.1±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form AB represented by an angle of 2θ is shown in FIG. 3; and

further, TGA and DSC patterns of the crystalline form AB are shown in FIG. 4.

2. A method for preparing the crystalline form AB of compound 1 according to claim 1, the method comprising steps of:

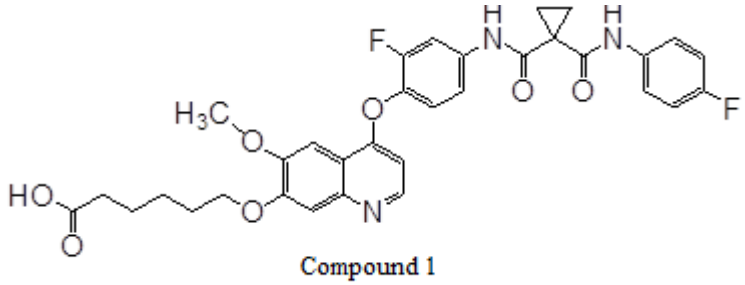
(1) adding the compound 1 to an alcohol solvent, heating at a temperature ranging from 75°C to 80°C to dissolve the compound 1;

(2) precipitating crystals at a temperature below -5°C, and stirring at a temperature ranging from -10°C to -15°C to further precipitate crystals; and

(3) filtering and drying the crystals to obtain the crystalline form AB,

preferably, the alcohol solvent being selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, n-pentanol, tert-pentanol or a mixed solvent containing ethanol; preferably, the mixed solvent containing ethanol being selected from tetrahydrofuran/water/ethanol, tetrahydrofuran/ethanol, or DMF/ethanol.

3. A crystalline form M of compound 1,



Compound 1

wherein an X-ray powder diffraction pattern of the crystalline form M represented by an angle of 2θ has diffraction peaks at 9.5±0.1°, 10.2±0.1°, 10.6±0.1°, 11.4±0.1°, 13.2±0.1°, 14.3±0.1°, 18.2±0.1°, 18.9±0.1°, 19.3±0.1°, 19.7±0.1°, 20.4±0.1°, 23.3±0.1°, 26.7±0.1°, and 29.6±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form M represented by an angle of 2θ has diffraction peaks at 9.5±0.1°, 10.2±0.1°, 10.6±0.1°, 11.4±0.1°, 13.2±0.1°, 14.3±0.1°, 15.2±0.1°, 15.7±0.1°, 16.4±0.1°, 17.4±0.1°, 18.2±0.1°, 18.9±0.1°, 19.3±0.1°, 19.7±0.1°, 20.4±0.1°, 22.1±0.1°, 23.3±0.1°, 24.2±0.1°, 25.3±0.1°, 25.7±0.1°, 26.7±0.1°, 27.2±0.1°, 27.7±0.1°, 28.8±0.1°, and 29.6±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form M represented by an angle of 2θ is shown in FIG. 5; and

further, TGA and DSC patterns of the crystalline form M are shown in FIG. 6.

4. A method for preparing a crystalline form M of compound 1 according to claim 3, the method comprising steps of:

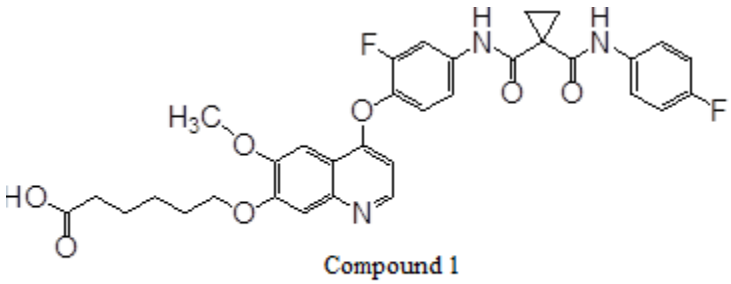
(1) adding the compound 1 to an alcohol solvent and heating to dissolve the compound 1;

(2) stirring at a temperature ranging from 10°C to 30°C to precipitate crystals; and

(3) filtering and drying the crystals to obtain the crystalline form M,

preferably, the alcohol solvent being selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, n-pentanol, tert-pentanol or a mixed solvent containing ethanol; preferably, the mixed solvent containing ethanol being selected from tetrahydrofuran/water/ethanol, tetrahydrofuran/ethanol, or DMF/ethanol.

5. A crystalline form F of compound 1,



Compound 1

wherein an X-ray powder diffraction pattern of the crystalline form F represented by an angle of 2θ has diffraction peaks at 7.1±0.1°, 8.0±0.1°, 10.0±0.1°, 10.9±0.1°, 14.0±0.1°, 15.4±0.1°, 16.0±0.1°, 16.5±0.1°, 17.1±0.1°, 19.5±0.1°, 22.0±0.1°, 25.0±0.1°, and 28.1±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form F represented by an angle of 2θ has diffraction peaks at 7.1±0.1°, 8.0±0.1°, 9.0±0.1°, 10.0±0.1°, 10.9±0.1°, 11.3±0.1°, 14.0±0.1°, 15.4±0.1°, 16.0±0.1°, 16.5±0.1°, 17.1±0.1°, 18.0±0.1°, 19.5±0.1°, 19.8±0.1°, 20.4±0.1°, 21.4±0.1°, 22.0±0.1°, 22.8±0.1°, 24.4±0.1°, 25.0±0.1°, 26.2±0.1°, 27.7±0.1°, 28.1±0.1°, 29.6±0.1°, and 33.5±0.1°;

further, the X-ray powder diffraction pattern of the crystalline form F represented by an angle of 2θ is shown in FIG. 7; and

further, TGA and DSC patterns of the crystalline form F are shown in FIG. 8.

6. A method for preparing a crystalline form F of compound 1 according to claim 5, the method comprising steps of:

(1) adding the crystalline form AB according to claim 1 to dimethylacetamide, dissolving for clarification, adding an anti-solvent of water while stirring, and performing stirring to precipitate crystals; and

(2) separating the crystals and performing vacuum drying at a temperature ranging from 22°C to 30°C followed by vacuum drying at a temperature ranging from 45°C to 60°C.

7. A method for preparing a crystalline form F of compound 1 according to claim 5, the method comprising steps of:

(1) adding the compound 1 to an organic solvent and stirring at a temperature ranging from 20°C to 60°C to dissolve the compound 1 or to prepare a suspension;

(2) stirring at a temperature ranging from 20°C to 60°C with the crystalline form F as a seed crystal to precipitate crystals;

(3) filtering and drying the crystals to obtain the crystalline form F,

the organic solvent being selected from DMSO, ethyl acetate, methanol, ethanol or a mixed solvent of DMSO/ethyl acetate, or a mixed solvent of DMSO/water.

8. A method for preparing a crystalline form F of compound 1 according to claim 5, the method comprising steps of:

(1) adding the crystalline form AB according to claim 1 to ethyl acetate, and heating to 50±3°C to prepare a solid-liquid suspension system; and

(2) stirring and reacting at 50±3°C for 1-2 days with the crystalline form F as a seed crystal to precipitate crystals, filtering the crystals, and drying a filter cake to obtain the crystalline form F.

9. A pharmaceutical composition, comprising: at least one of the compound 1 in the crystalline form AB according to claim 1, the compound 1 in the crystalline form M according to claim 3, or the compound 1 in the crystalline form F according to claim 5; and a pharmaceutically acceptable carrier,

preferably, the pharmaceutical composition being a tablet or a capsule.

10. Use of the crystalline form AB according to claim 1 or 2, the crystalline form M according to claim 3 or 4, the crystalline form F according to claim 5 or 6, and the pharmaceutical composition according to claim 9 in manufacture of a medicament for treatment of a ~~disease~~ cancer caused by abnormal activity of protein kinases AXL and/or VEGFR2,

further, the ~~disease~~ cancer caused by abnormal activity of protein kinases AXL and/or VEGFR2 comprising thyroid cancer, gastric cancer, esophageal cancer, kidney cancer, liver cancer, ovarian cancer, cervical cancer, cancer of large intestine, cancer of small intestine, brain cancer, leukemia, lung cancer, bone cancer, prostate cancer, pancreatic cancer, skin cancer, lymphoma, solid tumor, Hodgkin's disease, and non-Hodgkin's lymphoma,

wherein the thyroid cancer comprises medullary thyroid cancer;

the kidney cancer comprises renal carcinoma;

the liver cancer comprises hepatocellular carcinoma;

the brain cancer comprises astrocytic tumor, wherein the astrocytic tumor comprises glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglia components;

the lung cancer comprises non-small cell lung cancer; and

the prostate cancer comprises castration-resistant prostate cancer.