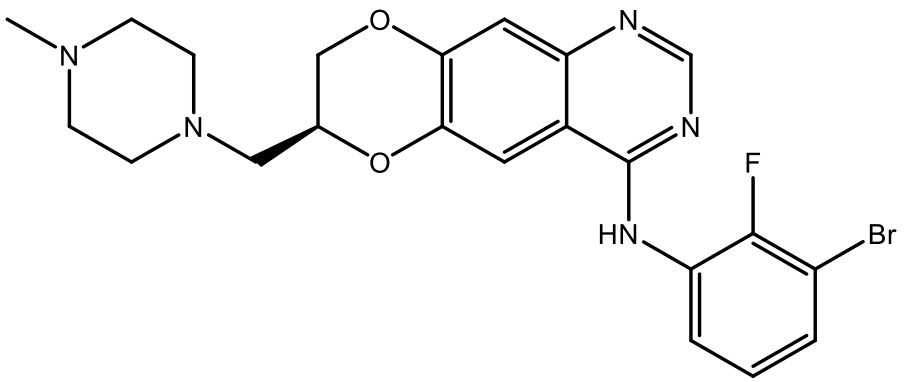
candidate in the formulation. Many active pharmaceutical ingredients can exist in more than one polymorphic form. Moreover, a preferred form may also exist as a free base, free acid, or pharmaceutically acceptable salt. Therefore, the identification of pharmaceutically acceptable salt forms, as well as free base or free acid forms, for manufacturing represents an important step in the development of a drug candidate.

**[0004]** In deciding or identifying the preferred solid form, the preferred solid form is often one that possesses an unpredictable physical property. A particular solid form (crystalline, semi- solid) may be preferable because of ease of preparation, stability, etc. On the other hand, a different crystalline solid may be preferred for greater solubility and/or superior pharmacokinetics. Thus, while pharmaceutically acceptable salts of the active ingredient may provide increased solubility or increased solubility, the development of a particular pharmaceutical form, such as a crystalline solid, may be necessary to achieve a clinical pharmaceutical formulation.

SUMMARY

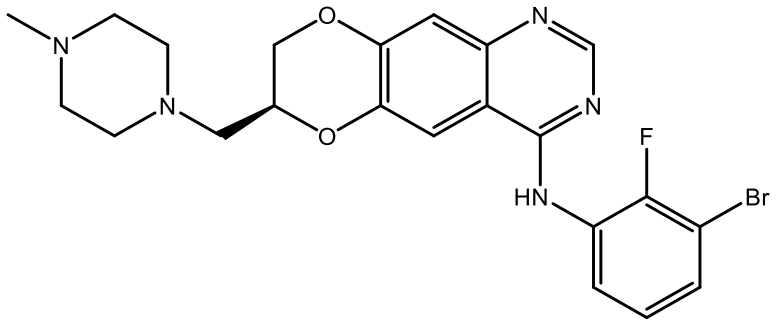
**[0005]** The present application is directed to polymorphs of (S)-N-(3-bromo-2-fluorophenyl)-7-((4-methylpiperazin-1-yl)methyl)-7,8-dihydro-[1,4]dioxino[2,3-g]quinazolin-4-amine.

**[0006]** In one example, the disclosure relates to a polymorph form of Compound (I):




Compound (I).

**[0006a]** In one aspect, the disclosure refers to a polymorph of Compound (I):




Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6±0.2°2θ, 16.9±0.2°2θ, 19.1±0.2°2θ, 19.5±0.2°2θ, 22.5±0.2°2θ and 26.0±0.2°2θ.

**[0007]** In an example, the polymorph form of Compound (I) is Form A and has an X-ray powder diffraction pattern with characteristic peaks expressed in values of degrees 2-theta at about 4.9±0.2, about 13.9±0.2, about 22.1±0.2, and about 25.1±0.2.

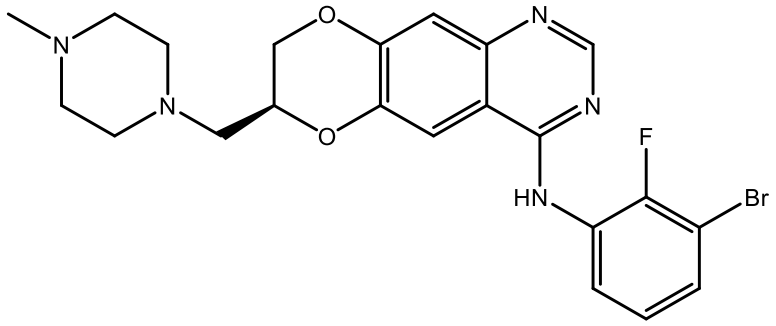
**[0008]** In an example, the polymorph form of Compound (I) is Form B and has an X-ray powder diffraction pattern with characteristic peaks expressed in values of degrees 2-

theta at about 4.8±0.2, about 9.8±0.2, about 13.8±0.2, about 14.7±0.2, about 17.7±0.2, about 20.2±0.2, about 24.1±0.2, about 24.6±0.2 and about 25.1±0.2.

**[0009]** In an example, the polymorph form of Compound (I) is Form C and has an X-ray powder diffraction pattern with characteristic peaks expressed in values of degrees 2-theta at about 4.9±0.2, about 22.9±0.2, about 23.2±0.2, about 23.7±0.2 and about 24.3±0.2.

**[0010]** In an example, the polymorph form of Compound (I) is Form D and has an X-ray powder diffraction pattern with characteristic peaks expressed in values of degrees 2-theta at about 15.6±0.2, about 16.9±0.2, about 19.1±0.2, about 19.5±0.2, about 22.5±0.2 and about 26.0±0.2.

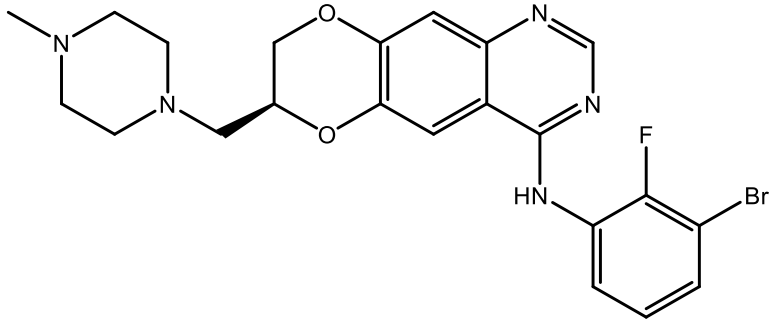
**[0011]** In one example, the disclosure relates to a method of purifying Compound (I):




Compound (I),

the method comprising preparing crystals of polymorph Form A and isolating the crystals of polymorph Form A.

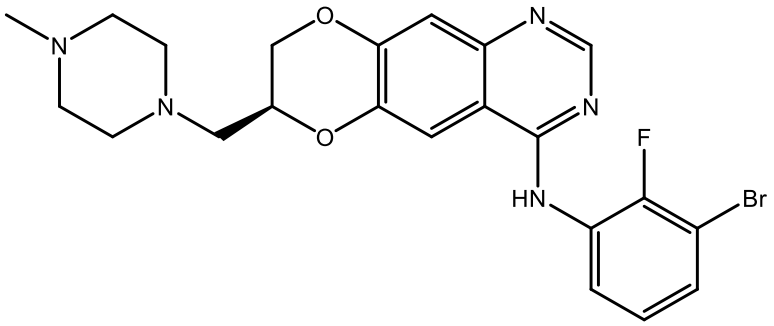
**[0012]** In one example, the disclosure relates to method of purifying Compound (I):




Compound (I),

the method comprising preparing crystals of polymorph Form B and isolating the crystals of polymorph Form B.

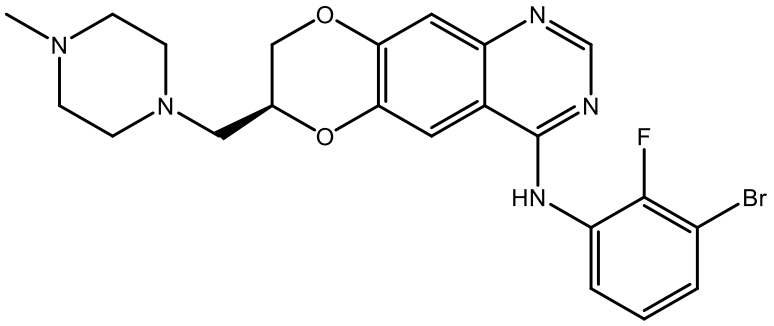
[0013] In one example, the disclosure relates to a method of purifying Compound (I):




Compound (I),

the method comprising preparing crystals of polymorph Form C and isolating the crystals of polymorph Form C.

**[0014]** In one example, the disclosure relates to a method of purifying Compound (I):




Compound (I),

the method comprising preparing crystals of polymorph Form D and isolating the crystals of polymorph Form D.

**[0014a]** In another aspect, the disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and the polymorph of Compound (I) as defined above.

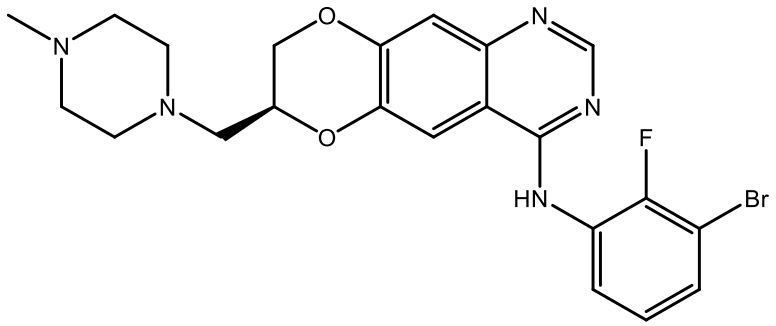
**[0015]** In one example, the disclosure relates to a pharmaceutical composition comprising a polymorph form of Compound (I), and a pharmaceutically acceptable excipient.

**[0016]** In one example, the disclosure relates to method of treating a subject having cancer, the method comprising administering to the subject one or more polymorph forms A, B, C, or D of Compound (I).

**[0017]** In one example, the disclosure relates to use of one or more polymorph forms A, B, C, or D of Compound (I) in the manufacture of a medicament for treating a subject having cancer.

**[0017a]** In another aspect, there is provided the use of the polymorph of Compound (I) as defined above in the manufacture of a medicament for treating cancer in a subject in need thereof.

**[0017b]** In another aspect, the disclosure refers a process for preparing the polymorph of Compound (I) as defined above:



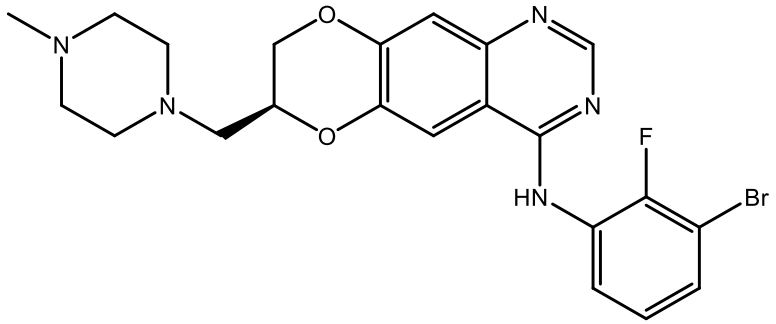

Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6 ± 0.2 °2θ, 16.9 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 22.5 ± 0.2 °2θ and 26.0 ± 0.2 °2θ;

wherein the process comprises:

evaporating a solution of an amorphous form of Compound (I):




Compound (I),

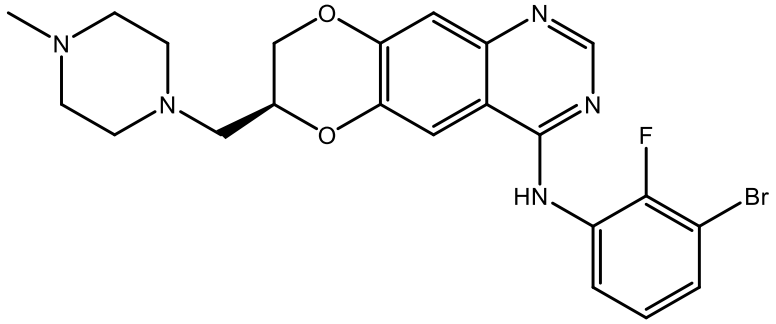
wherein a solvent of the solution is selected from the group consisting of (a), (b), and (c):

(a) acetone:heptane (1:3);

(b) n-butyl acetate; and

(c) methanol:diisopropyl ether (1:12).

**[0017c]** In another aspect, the disclosure refers to a process for preparing the polymorph of Compound (I) as defined above:



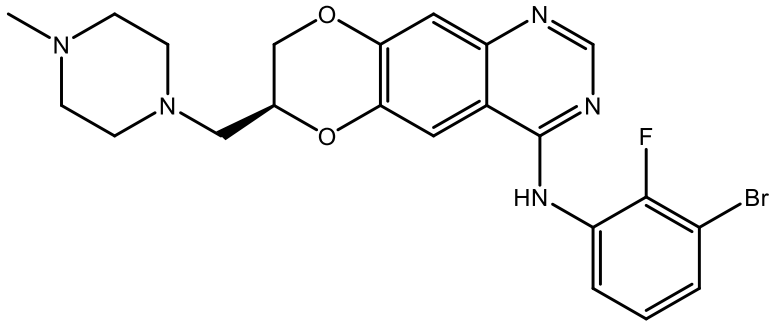

Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6 ± 0.2 °2θ, 16.9 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 22.5 ± 0.2 °2θ and 26.0 ± 0.2 °2θ;

wherein the process comprises:

crystallizing an amorphous form of Compound (I):




Compound (I),

in a non-aqueous solvent system via a technique selected from the group consisting of equilibrating, seeding, and slurrying, or a combination thereof, to convert the amorphous form of Compound (I) to polymorph Form D of Compound (I).

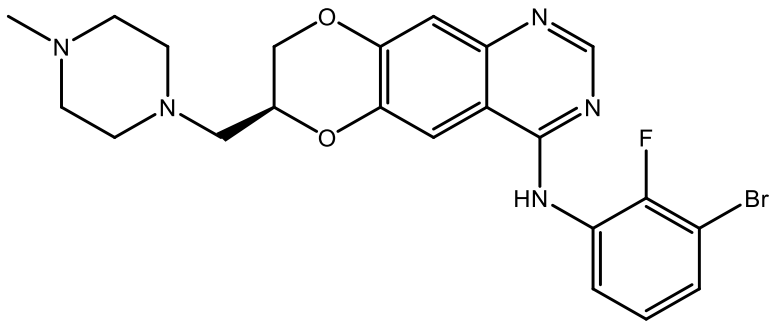
## BRIEF DESCRIPTION OF FIGURES

**[0018] Figure 1** shows a powder X-ray diffraction (PXRD) spectrum of crystalline Form A of Compound (I).

## CLAIMS

What is claimed is:

1. A polymorph of Compound (I):




Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6±0.2°2θ, 16.9±0.2°2θ, 19.1±0.2°2θ, 19.5±0.2°2θ, 22.5±0.2°2θ and 26.0±0.2°2θ.

2. The polymorph of claim 1, wherein the polymorph is further characterized by an X-ray powder diffraction pattern comprising a characteristic peak expressed in a value (°2θ) at 15.2±0.2°2θ.

3. The polymorph of claim 1, wherein the polymorph is further characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 10.2±0.2°2θ, 13.5±0.2°2θ, 15.9±0.2°2θ, 23.3±0.2°2θ, 24.3±0.2°2θ, 24.7±0.2°2θ, 24.9±0.2°2θ, 27.9±0.2°2θ and 29.6±0.2°2θ.

4. The polymorph of claim 1, wherein the polymorph is further characterized by a melting point of 153 °C.

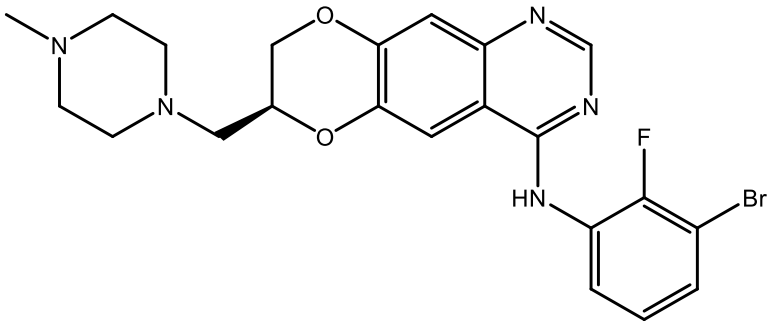
5. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the polymorph of Compound (I) of claim 1.

6. Use of the polymorph of Compound (I) of claim 1 in the manufacture of a medicament for treating cancer in a subject in need thereof.

7. The use of claim 6, wherein the cancer is characterized by aberrant epidermal growth factor receptor (EGFR) expression.

8. The use of claim 6, wherein the cancer is brain cancer.

9. A process for preparing the polymorph of Compound (I) of claim 1:



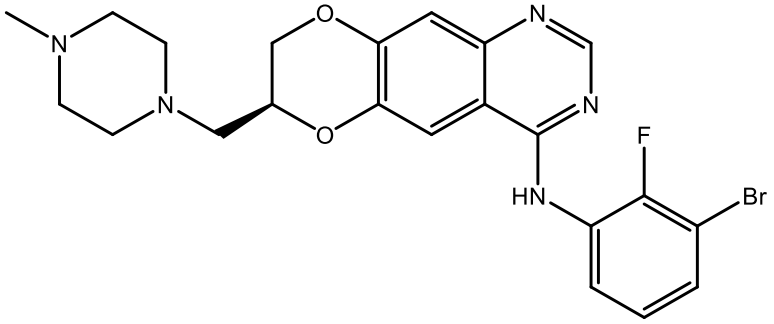
Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6 ± 0.2 °2θ, 16.9 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 22.5 ± 0.2 °2θ and 26.0 ± 0.2 °2θ;

wherein the process comprises:

evaporating a solution of an amorphous form of Compound (I):



Compound (I),

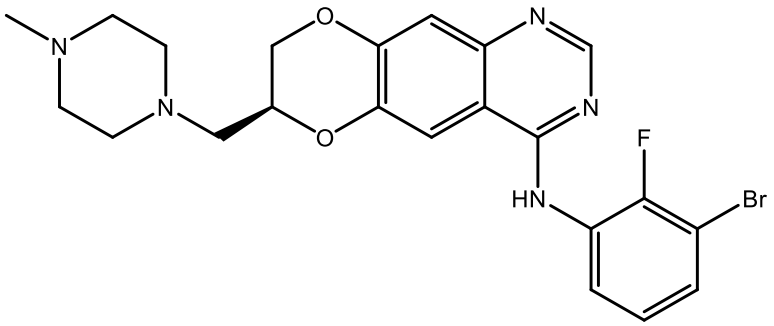
wherein a solvent of the solution is selected from the group consisting of (a), (b), and (c):

(a) acetone:heptane (1:3);

(b) n-butyl acetate; and

(c) methanol:diisopropyl ether (1:12).

10. A process for preparing the polymorph of Compound (I) of claim 1:



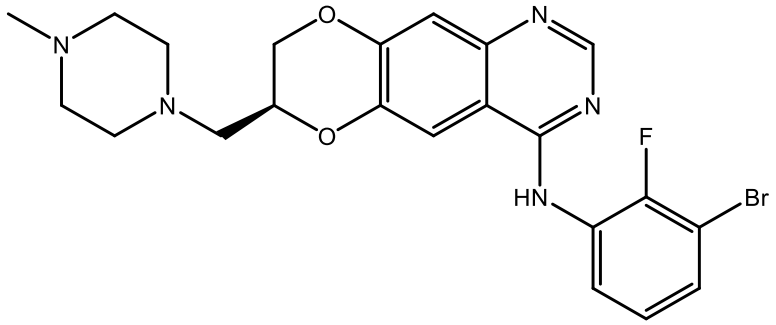
Compound (I),

wherein the polymorph is Form D; and

wherein the polymorph is characterized by an X-ray powder diffraction pattern comprising characteristic peaks expressed in values (°2θ) at 15.6 ± 0.2 °2θ, 16.9 ± 0.2 °2θ, 19.1 ± 0.2 °2θ, 19.5 ± 0.2 °2θ, 22.5 ± 0.2 °2θ and 26.0 ± 0.2 °2θ;

wherein the process comprises:

crystallizing an amorphous form of Compound (I):




Compound (I),

in a non-aqueous solvent system via a technique selected from the group consisting of equilibrating, seeding, and slurrying, or a combination thereof, to convert the amorphous form of Compound (I) to polymorph Form D of Compound (I).

11. The process of claim 10, wherein the crystallizing further comprises an equilibrating, a seeding, or a slurrying technique selected from the group consisting of (a), (b), (c), (d), (e), and (f):

(a) equilibrating in isopropyl acetate:heptane (1:1).

(b) equilibrating in isopropyl acetate:heptane (2:3);

(c) equilibrating in methyl tetrahydrofuran (THF):methylcyclohexane (1:2);

(d) seeding with Form D in ethyl acetate;

(e) slurrying in acetontirile; and

(f) slurrying in ethyl acetate.

12. The process of claim 11, wherein the equilibrating is suspension equilibrating.

13.The process of claim 12, wherein the suspension equilibrating further comprises a suspension equilibrating technique selected from the group consisting of (a), (b), (c), (d), (e), (f), (g), (h), and (i):

(a) suspension equilibrating in n-butyl acetate:heptane (5:2);

(b) suspension equilibrating in tert-butylmethylether (TBME) with seeding with Form D;

(c) suspension equilibrating in heptane:methyl isobutyl ketone (MIBK) (4:1);

(d) suspension equilibrating in isopropyl acetate:cyclohexane (1:2);

(e) suspension equilibrating in diisopropyl ether;

(f) suspension equilibrating in methanol:methylcyclohexane (1:4);

(g) suspension equilibrating in methyl ethyl ketone (MEK):diisopropyl ether;

(h) suspension equilibrating in methyl ethyl ketone (MEK):*p*-xylene (1:2) and partial evaporation of solvent; and

(i) suspension equilibrating in trimethylamine.