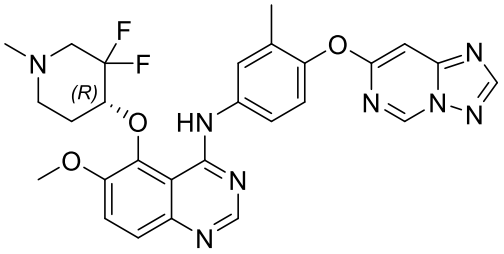
can be distinguished in a laboratory by X-ray diffraction spectroscopy, such as X-ray powder diffraction ("XRPD"), and by other methods, such as infrared spectrometry. Additionally, polymorphic forms of the same drug substance or active pharmaceutical ingredient can be administered by itself or formulated as a drug product pharmaceutical composition and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products. For more, see Hilfiker, Rolf (ed.), Polymorphism in the Pharmaceutical Industry, Weinheim, Germany: Wiley-VCH 2006.

Discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. Therefore, there is a continuous need to investigate polymorphic forms of aforementioned quinazoline compounds which exhibit type I receptor tyrosine kinases inhibitory activity. It has now been found that new polymorphic forms of compound (I) exist.

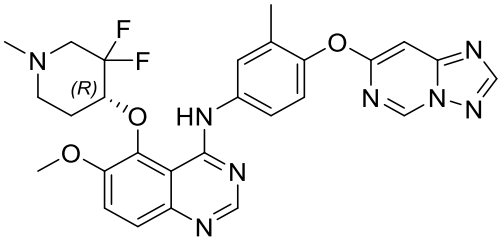
SUMMARY

The present disclosure is directed to crystalline forms of (*R*)-N-(4-([1,2,4]triazolo[1,5-c]pyrimidin-7-yloxy)-3-methylphenyl)-5-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-6-methoxyquinazolin-4-amine (compound (I)), which is a complex of free base with a pharmaceutically acceptable acid, or free base.



(I)

In one aspect, the present disclosure is directed to a crystalline form of compound (I) represented by the following structural formula:



(I),

wherein the crystalline form is a complex of free base with a pharmaceutically acceptable acid, or the crystalline form is free base.

In some examples, the complex of free base with a pharmaceutically acceptable acid or the free base is a solvate or non-solvate. In some examples, the complex of free base with a pharmaceutically acceptable acid is a salt or a cocrystal or a cocrystal of salt. In some examples, disclosed herein are crystalline forms of compound (I), designated as Fumarate Type A, Fumarate Type B, Fumarate Type C, Fumarate Type E, Freebase Type A, Freebase Type B, Freebase Type C, Freebase Type D, Freebase Type E, Freebase Type F, Freebase Type G, HCl Salt Type A, HCl Salt Type B, Mesylate Type A, Mesylate Type B, Phosphate Type A, L-tartrate Type A and Adipate Type A.

The present disclosure is directed to amorphous forms of compound (I), which is a pharmaceutically acceptable salt or free base. In some examples, disclosed herein are amorphous forms of compound (I), designated as Amorphous Fumarate and Amorphous Freebase.

The present disclosure is directed to methods for the preparation of the crystalline forms of compound (I).

In another aspect, the present disclosure is directed to a method for the preparation of the crystalline form as described herein, comprising:

where the crystalline form is a complex of free base with a pharmaceutically acceptable acid,

a) adding compound (I) and the acid in a solvent,

b) slurrying at a temperature for a time sufficient to initiate precipitation of the complex;

where the crystalline form is free base,

c) adding compound (I) in a solvent; and

d) slurrying at a temperature for a time sufficient to initiate precipitation of the free base; optionally:

(i) wherein the acid is chosen from a group consisting of hydrochloride, methane sulfonic acid, phosphoric acid, tartaric acid, fumaric acid and adipic acid; and/or

(ii) wherein in step a), where the crystalline form is a complex of free base with a pharmaceutically acceptable acid, the compound (I) and the acid are added in the solvent at an acid/base molar ratio in a range of 0.5:1 to 3:1; preferably, 0.5:1 to 2.5:1; more preferably, 1:1 to 1.5:1; and/or

(iii) wherein the solvent is selected from a group consisting of H_2O, EtOH, EtOAc, n-heptane, ethyl formate, acetone, cyclohexane, isopropyl alcohol, methyl isobutyl ketone, tetrahydrofuran, acetonitrile methyl tert-butyl ether and combination thereof; and/or

(iv) wherein the method further comprises seeding the solvent with a crystalline form as described herein; and/or

(v) wherein the temperature is about 5~50 °C; and/or

(vi) wherein the time is about 2~7.5 hours.

In another aspect, the present disclosure is directed to a method for the preparation of Fumarate Type A crystalline form of compound (I) as described herein, comprising:

a) dissolving free base of compound (I) in an ester or an alcohol to form a free base solution;

b) dissolving fumaric acid in EtOH to form an acid solution;

c) adding the acid solution into the free base solution dropwise while stirring;

d) adding an alkane dropwise; then optionally seeding the mixture with a Fumarate Type A crystalline form of compound (I);

e) stirring at 0-10 °C for 12-24 hours; and

f) isolating a solid via filtration and then vacuum drying the solid at 40-60 °C, optionally:

(i) wherein the ester is selected from a group consisting of ethyl acetate, ethyl formate, methyl acetate and isopropyl acetate, further optionally

wherein the ester is ethyl acetate; or

(ii) wherein the alcohol is selected from a group consisting of methanol, ethanol, n-propanol and isopropanol, further optionally

wherein the alcohol is ethanol; or

(iii) wherein the alkane is selected from a group consisting of n-hexane, n-heptane, n-octane and a mixture thereof, further optionally

wherein the alkane is n-heptane.

In another aspect, the present disclosure is directed to a method for the preparation of Fumarate Type B crystalline form of compound (I) as described herein, comprising:

a) suspending a Fumarate Type A crystalline form of compound (I) in H_2O;

b) magnetically stirring at a speed of about 1000 rpm at about room temperature for about 11 days; and

c) isolating a solid via centrifugation and storing the solid at ambient conditions openly for about 4 days.

In another aspect, the present disclosure is directed to a method for the preparation of Fumarate Type E crystalline form of compound (I) as described herein, comprising:

a) dissolving a Fumarate Type A crystalline form of compound (I) in ethyl formate;

b) evaporating the ethyl formate at about room temperature; and

c) isolating a solid.

In another aspect, the present disclosure is directed to a method for the preparation of Freebase Type B crystalline form of compound (I) as described herein, comprising:

a) suspending amorphous free base of compound (I) in a solvent of methyl isobutyl ketone/Cyclohexane with a volume ratio of about 1:4;

b) magnetically stirring at a speed of about 1000 rpm at about 5 ºC for about 7 days; and

c) isolating a solid via centrifugation.

In another aspect, the present disclosure is directed to a method for the preparation of Freebase Type F crystalline form of compound (I) as described herein, comprising:

a) suspending amorphous free base of compound (I) in a solvent of acetonitrile/n-heptane;

b) magnetically stirring at a speed of about 1000 rpm at about room temperature for about 2 days; and

c) isolating a solid.

Also, disclosed herein are methods for the preparation of the amorphous forms of compound (I).

The present disclosure is directed to pharmaceutical compositions comprising the crystalline form or amorphous form of compound (I), and a pharmaceutically acceptable carrier or excipient.

In another aspect, the present disclosure is directed to a pharmaceutical composition comprising the crystalline form as described herein, and a pharmaceutically acceptable carrier or excipient.

The present disclosure is directed to dosage forms comprising a therapeutically effective amount of the crystalline form, the amorphous form, or the pharmaceutical composition described herein.

The present disclosure is directed to methods of treating or ameliorating a hyperproliferative disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of the crystalline form or amorphous form of compound (I).

The present disclosure is directed to crystalline forms or amorphous forms of compound (I) for use in treating or ameliorating a hyperproliferative disease.

In another aspect, the present disclosure is directed to the crystalline form as described herein for use in treating or ameliorating a hyperproliferative disease, optionally wherein:

(a) the hyperproliferative disease is cancer; further optionally wherein:

(i) wherein the cancer is ErbB2 positive, and/or

(ii) wherein the cancer is selected from breast, gastric, biliary, colorectal, brain, lung, NSCLC, pancreatic, head and neck, ovarian and uterine cancer; and/or

(b) one or more additional compounds having anti-cancer properties are to be administered in combination.

The present disclosure is directed to use of crystalline forms or amorphous forms of compound (I) in the manufacture of a medicament for treating or ameliorating a hyperproliferative disease.

In another aspect, the present disclosure is directed to use of the crystalline form as described herein in the manufacture of a medicament for treating or ameliorating a hyperproliferative disease, optionally wherein:

(a) the hyperproliferative disease is cancer; further optionally wherein:

(i) wherein the cancer is ErbB2 positive, and/or

(ii) wherein the cancer is selected from breast, gastric, biliary, colorectal, brain, lung, NSCLC, pancreatic, head and neck, ovarian and uterine cancer; and/or

(b) one or more additional compounds having anti-cancer properties are to be administered in combination.

BRIEF DESCRIPTION OF THE FIGURES

The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings' exemplary embodiments of the invention; however, the invention is not limited to the specific disclosure of the drawings. In the drawings:

Figure 1 is a representative XRPD pattern of Fumarate Type A.

Figure 2 is a representative TGA curve of Fumarate Type A.

Figure 3 is a representative DSC curve of Fumarate Type A.

Figure 4 is a representative ^{1}H NMR spectrum of Fumarate Type A,.

Figure 5 is a representative PLM image of Fumarate Type A.

Figure 6 is a representative XRPD pattern of Fumarate Type B.

Figure 7 is a representative TGA curve of Fumarate Type B.

Figure 8 is a representative DSC curve of Fumarate Type B.

Figure 9 is a representative ^{1}H NMR spectrum of Fumarate Type B.

Figure 10 is a representative XRPD pattern of Fumarate Type C.

Figure 11 is a representative XRPD pattern of Fumarate Type E.

Figure 12 is a representative TGA curve of Fumarate Type E.

Figure 13 is a representative DSC curve of Fumarate Type E.

Figure 14 is a representative XRPD pattern of Freebase Type B.

Figure 15 is a representative TGA curve of Freebase Type B.

Figure 16 is a representative DSC curve of Freebase Type B.

Figure 17 is a representative ^{1}H NMR spectrum of Freebase Type B.

Figure 18 is a representative PLM image of Freebase Type B.

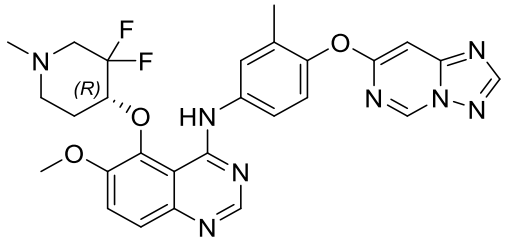
Figure 19 is a representative XRPD pattern of Freebase Type C.

Figure 20 is a representative TGA curve of Freebase Type C.

Figure 21 is a representative DSC curve of Freebase Type C.

Claims

1. A crystalline form of compound (I) represented by the following structural formula:



(I),

wherein the crystalline form is a complex of free base with a pharmaceutically acceptable acid, or the crystalline form is free base.

2. The crystalline form according to claim 1, wherein the complex or free base is a solvate or non-solvate.

3. The crystalline form according to claim 1 or 2, wherein the complex is a salt or a cocrystal or a cocrystal of salt; and/or

wherein the complex has an acid/base molar ratio of 0.5:1 to 3:1, preferably, 0.5:1 to 2.5:1, more preferably, 1:1 to 1.5:1.

4. The crystalline form according to any one of claims 1-3, wherein the pharmaceutically acceptable acid is chosen from a group consisting of hydrochloride, methanesulfonic acid, phosphoric acid, tartaric acid, fumaric acid and adipic acid.

5. The crystalline form according to any one of claims 1-4, wherein the pharmaceutically acceptable acid is fumaric acid.

6. The crystalline form according to claim 5, wherein the crystalline form is:

(i) Fumarate Type A, characterized by a differential scanning calorimeter peak phase transition temperature of about 167.6 °C; and/or

(ii) Fumarate Type A, characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.9 and 11.5, optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 5.8, 6.9, 11.5, 12.1 and 17.7, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 5.8, 6.9, 11.5, 12.1, 17.7, 20.8 and 24.0, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 5.8, 6.9, 11.5, 12.1, 17.7, 18.9, 20.8, 23.1, 23.7, 24.0 and 28.8, further optionally

characterized by substantially the same X-ray powder diffraction pattern as Figure 1.

7. The crystalline form according to claim 5, wherein the crystalline form is:

(i) Fumarate Type B, characterized by a differential scanning calorimeter peak phase

transition temperature of about 91.3 °C and about 166.3 °C; and/or

(ii) Fumarate Type B, characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.6 and 11.4, optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.6, 10.7, 11.4, 12.9, 25.1 and 28.2; further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.6, 10.7, 11.4, 12.9, 15.8, 17.9, 19.7, 25.1 and 28.2; further optionally

characterized by substantially the same X-ray powder diffraction pattern as Figure 6.

8. The crystalline form according to claim 5, wherein the crystalline form is:

(i) Fumarate Type E, characterized by a differential scanning calorimeter peak phase transition temperature of about 134.5 °C and about 166.0 °C; and/or

(ii) Fumarate Type E, characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.7, 11.6 and 28.5, optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.7, 10.9, 11.6, 16.9, 25.2 and 28.5, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.7, 10.9, 11.6, 12.9, 15.3, 16.9, 19.9, 25.2 and 28.5, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 5.5, 6.7, 10.9, 11.6, 12.9, 15.3, 16.9, 18.1, 19.9, 25.2, 27.5 and 28.5, further optionally

characterized by substantially the same X-ray powder diffraction pattern as Figure 11.

9. The crystalline form according to claim 1 or 2, wherein the crystalline form is:

(i) Freebase Type B, characterized by a differential scanning calorimeter peak phase transition temperature of about 169.4 °C; and/or

(ii) Free base Type B, characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 8.0 and 11.5, optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 8.0, 11.5, 16.0, 17.2, 18.8 and 24.3, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 8.0, 11.5, 16.0, 17.2, 18.2, 18.8, 20.3, 21.9 and 24.3, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 8.0, 11.5, 13.1, 16.0, 17.2, 18.2, 18.8, 20.3, 21.2, 21.9, 24.3 and 27.7, further optionally

characterized by substantially the same X-ray powder diffraction pattern as Figure 14.

10. The crystalline form according to claim 1 or 2, wherein the crystalline form is:

(i) Freebase Type F, characterized by a differential scanning calorimeter peak phase transition temperature of about 55.4 °C and about 109.5 °C; and/or

(ii) Freebase Type F, characterized by an X-ray powder diffraction pattern which

comprises at least peaks at 2θ (± 0.2°) of 6.2, 11.6 and 12.6, optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.2, 11.6, 12.6, 14.8, 16.5 and 24.4, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.2, 11.6, 12.6, 14.8, 16.5, 17.6, 19.3, 24.4 and 26.0, further optionally

characterized by an X-ray powder diffraction pattern which comprises at least peaks at 2θ (± 0.2°) of 6.2, 9.3, 11.6, 12.6, 14.8, 16.5, 17.6, 18.7, 19.3, 24.4 and 26.0, further optionally

characterized by substantially the same X-ray powder diffraction pattern as Figure 25.

11. A method for the preparation of the crystalline form according to any one of claims 1-10, comprising:

where the crystalline form is a complex of free base with a pharmaceutically acceptable acid,

a) adding compound (I) and the acid in a solvent,

b) slurrying at a temperature for a time sufficient to initiate precipitation of the complex;

where the crystalline form is free base,

c) adding compound (I) in a solvent; and

d) slurrying at a temperature for a time sufficient to initiate precipitation of the free base;

optionally:

(i) wherein the acid is chosen from a group consisting of hydrochloride, methane sulfonic acid, phosphoric acid, tartaric acid, fumaric acid and adipic acid; and/or

(ii) wherein in step a), where the crystalline form is a complex of free base with a pharmaceutically acceptable acid, the compound (I) and the acid are added in the solvent at an acid/base molar ratio in a range of 0.5:1 to 3:1; preferably, 0.5:1 to 2.5:1; more preferably, 1:1 to 1.5:1; and/or

(iii) wherein the solvent is selected from a group consisting of H_2O, EtOH, EtOAc, n-heptane, ethyl formate, acetone, cyclohexane, isopropyl alcohol, methyl isobutyl ketone, tetrahydrofuran, acetonitrile methyl tert-butyl ether and combination thereof; and/or

(iv) wherein the method further comprises seeding the solvent with a crystalline form of any one of claims 1-10; and/or

(v) wherein the temperature is about 5~50 ℃; and/or

(vi) wherein the time is about 2~7.5 hours.

12. A method for the preparation of Fumarate Type A crystalline form of compound (I) according to claim 6, comprising:

a) dissolving free base of compound (I) in an ester or an alcohol to form a free base solution;

b) dissolving fumaric acid in EtOH to form an acid solution;

c) adding the acid solution into the free base solution dropwise while stirring;

d) adding an alkane dropwise; then optionally seeding the mixture with a Fumarate Type A crystalline form of compound (I);

e) stirring at 0-10 ℃ for 12-24 hours; and

f) isolating a solid via filtration and then vacuum drying the solid at 40-60 °C, optionally:

(i) wherein the ester is selected from a group consisting of ethyl acetate, ethyl formate, methyl acetate and isopropyl acetate, further optionally

wherein the ester is ethyl acetate; or

(ii) wherein the alcohol is selected from a group consisting of methanol, ethanol, n-propanol and isopropanol, further optionally

wherein the alcohol is ethanol; or

(iii) wherein the alkane is selected from a group consisting of n-hexane, n-heptane, n-octane and a mixture thereof, further optionally

wherein the alkane is n-heptane.

13. A method for the preparation of Fumarate Type B crystalline form of compound (I) according to claim 7, comprising:

a) suspending a Fumarate Type A crystalline form of compound (I) in H_2O;

b) magnetically stirring at a speed of about 1000 rpm at about room temperature for about 11 days; and

c) isolating a solid via centrifugation and storing the solid at ambient conditions openly for about 4 days.

14. A method for the preparation of Fumarate Type E crystalline form of compound (I) according to claim 8, comprising:

a) dissolving a Fumarate Type A crystalline form of compound (I) in ethyl formate;

b) evaporating the ethyl formate at about room temperature; and

c) isolating a solid.

15. A method for the preparation of Freebase Type B crystalline form of compound (I) according to claim 9, comprising:

a) suspending amorphous free base of compound (I) in a solvent of methyl isobutyl ketone/Cyclohexane with a volume ratio of about 1:4;

b) magnetically stirring at a speed of about 1000 rpm at about 5 ºC for about 7 days; and

c) isolating a solid via centrifugation.

16. A method for the preparation of Freebase Type F crystalline form of compound (I) according to claim 10, comprising:

a) suspending amorphous free base of compound (I) in a solvent of acetonitrile/n-heptane;

b) magnetically stirring at a speed of about 1000 rpm at about room temperature for about 2 days; and

c) isolating a solid.

17. A pharmaceutical composition comprising the crystalline form according to any one of claims 1-10, and a pharmaceutically acceptable carrier or excipient.

18. The crystalline form according to any one of claims 1-10 for use in treating or ameliorating a hyperproliferative disease, optionally wherein:

(a) the hyperproliferative disease is cancer; further optionally wherein:

(i) wherein the cancer is ErbB2 positive, and/or

(ii) wherein the cancer is selected from breast, gastric, biliary, colorectal, brain, lung, NSCLC, pancreatic, head and neck, ovarian and uterine cancer; and/or

(b) one or more additional compounds having anti-cancer properties are to be administered in combination.

19. Use of the crystalline form according to any one of claims 1-10 in the manufacture of a medicament for treating or ameliorating a hyperproliferative disease, optionally wherein:

(a) the hyperproliferative disease is cancer; further optionally wherein:

(i) wherein the cancer is ErbB2 positive, and/or

(ii) wherein the cancer is selected from breast, gastric, biliary, colorectal, brain, lung, NSCLC, pancreatic, head and neck, ovarian and uterine cancer; and/or

(b) one or more additional compounds having anti-cancer properties are to be administered in combination.