

2-(4-(2-(7,8-DIMETHYL-[1,2,4]TRIAZOLO[1,5-A]PYRIDIN-6-YL)-3-ISOPROPYL-1H-INDOL-5-YL)PIPERIDIN-1-YL)ACETAMIDE AND CRYSTALLINE FORMS THEREOF

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CROSS REFERENCE

This application claims the benefit of U.S. Provisional Application Serial No. 63/598,169 filed November 13, 2023, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

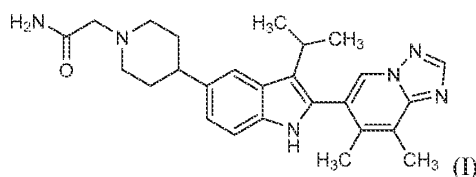
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The present invention generally relates to 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide, free base hemihydrate, and crystalline forms thereof.

BACKGROUND OF THE INVENTION

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The compound, 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide has the structure of Formula (I):



and is referred to herein as "Compound (I)". Compound (I) is disclosed as Example 15 in WO 2018/005586 A1, which is assigned to the present assignee. Compound (I) has the generic name afimetoran.

Compound (I) is an inhibitor of Toll-like receptor 7 and 8 (TLR7/8) and is currently in clinical trials for the treatment of lupus.

In the synthesis of a chemical compound intended for pharmaceutical use, it is necessary to isolate and purify the compound at the completion of the synthetic process and prior to further processing to provide the compound in a pharmaceutical formulation. The isolation and the purification steps, which can be combined or separate consecutive steps, provide the compound as a purified solid with minimal loss of yield during isolation from other components of the reaction mixture and/or during purification to

remove impurities from the isolated compound sample.

In preparing a pharmaceutical composition, a form of the active ingredient is sought that has a balance of desired properties, such as, for example, dissolution rate, solubility, bioavailability, and/or storage stability. For example, a form of the active
5 ingredient is sought having sufficient stability, solubility, and bioavailability to prevent the form converting during manufacture, preparation, and/or storage of the pharmaceutical composition to another form having an undesirable solubility and/or bioavailability profile. Also sought is a form that is stable and has low hygroscopicity at ambient temperature and humidity conditions.

10 It is desirable to isolate the purified compound in a solid form that is physically and chemically stable at a range of storage conditions, such as at different conditions of temperature and humidity.

The Applicants have found a form of Compound (I) that is physically and chemically stable at a range of storage conditions.

15 Further, the Applicants have found a crystalline form of Compound (I) that surprisingly provides Compound (I) in a solid form that is physically and chemically stable at a range of storage conditions.

The present invention is also directed to other important aspects.

20 SUMMARY OF THE INVENTION

The present invention provides Compound (I) as a free base. The present invention also provides Compound (I) as a free base hemihydrate in crystalline Form B and Compound (I) as a free base anhydrate in crystalline Form N, crystalline Form O, and crystalline Form P.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. shows the observed powder x-ray diffraction pattern ($\text{CuK}\alpha$, $\lambda = 1.54178$ Å at $T = 25^\circ\text{C}$) of free base hemihydrate crystalline Form B of Compound (I).

30 FIG. 2 shows a differential scanning calorimetry (DSC) thermogram of free base hemihydrate crystalline Form B, with an endotherm at approximately 275°C .

FIG. 3 shows a thermogravimetric analysis (TGA) thermogram of free base

hemihydrate crystalline Form B.

FIG. 4 shows a moisture-sorption isotherm for free base hemihydrate crystalline Form B at a temperature of 25 °C.

FIG. 5. shows the observed powder x-ray diffraction pattern ($\text{CuK}\alpha$, $\lambda = 1.54178$ Å at T = 25 °C) of free base anhydrate crystalline Form N of Compound (I).

FIG. 6. shows the observed powder x-ray diffraction pattern ($\text{CuK}\alpha$, $\lambda = 1.54178$ Å at T = 25 °C) of free base anhydrate crystalline Form O of Compound (I).

FIG. 7. shows the observed powder x-ray diffraction pattern ($\text{CuK}\alpha$, $\lambda = 1.54178$ Å at T = 25 °C) of free base anhydrate crystalline Form P of Compound (I).

DETAILED DESCRIPTION OF THE INVENTION

The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof.

The names used herein to characterize a specific form, *e.g.*, “Form B” etc., are merely identifiers that are to be interpreted in accordance with the characterization information presented herein and are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics. The name of a specific form should be understood as a mere identifier that should be interpreted according to the characterization information also presented herein.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

All numbers expressing quantities of ingredients, weight percentages, temperatures, and so forth that are preceded by the word “about” are to be understood as only approximations so that slight variations above and below the stated number may be used to achieve substantially the same results as the stated number. Accordingly, unless indicated to the contrary, numerical parameters preceded by the word “about” are

approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

All measurements are subject to experimental error and are within the spirit of the invention.

As used herein, "polymorphs" refer to crystalline forms having the same chemical structure but different spatial arrangements of the molecules and/or ions forming the crystals.

As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

As used herein, "substantially pure," when used in reference to a crystalline form, means a compound having a purity greater than 90 weight %, including greater than 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 weight %, and also including equal to about 100 weight % of Compound (I), based on the weight of the compound. The remaining material comprises other form(s) of the compound, and/or reaction impurities and/or processing impurities arising from its preparation. For example, a crystalline form of Compound (I) may be deemed substantially pure in that it has a purity greater than 90 weight %, as measured by means that are at this time known and generally accepted in the art, where the remaining less than 10 weight % of material comprises amorphous and/or other form(s) of Compound (I) and/or reaction impurities and/or processing impurities.

As used herein, a powder x-ray diffraction (PXRD) pattern "comprising" a number of peaks selected from a specified group of peaks, is intended to include PXRD patterns having additional peaks that are not included in the specified group of peaks. For example, a PXRD pattern comprising four or more, preferably five or more, 2 θ values selected from: A, B, C, D, E, F, G, and H, is intended to include a PXRD pattern having: (a) four or more, preferably five or more, 2 θ values selected from: A, B, C, D, E, F, G, and H; and (b) zero or more peaks that are not one of peaks A, B, C, D, E, F, G, and H.

The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example,

chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, and/or infrared spectroscopy.

As used herein, the unit cell parameter “molecules per unit cell” refers to the number of molecules of Compound (I) in the unit cell.

5 The first aspect of the invention provides Compound (I) as a free base hemihydrate solid form. This solid form has a stoichiometry of 0.5 molecule of water for each molecule of Compound (I).

In one embodiment, the Compound (I), free base hemihydrate form is provided as a crystalline material.

10 In one embodiment, the Compound (I), free base hemihydrate form is provided as a neat crystalline material.

Form B of Compound (I), Free Base Hemihydrate

15 In one embodiment, the Compound (I), free base hemihydrate is provided as a crystalline material comprising Form B. The crystalline Form B of Compound (I), free base hemihydrate is a hemihydrate crystalline form. Crystalline Form B is also referred to herein as “Form B”.

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by unit cell parameters approximately equal to the following:

20 $a = 39.16 \pm 0.10 \text{ \AA}$

$b = 7.50 \pm 0.10 \text{ \AA}$

$c = 16.77 \pm 0.10 \text{ \AA}$

$\alpha = 90.0 \pm 1.0^\circ$

$\beta = 93.2 \pm 1.0^\circ$

25 $\gamma = 90.0 \pm 1.0^\circ$

Space group: *C2/c*

Molecules per unit cell (Z): 8

Unit cell volume = $4920 \pm 20 \text{ \AA}^3$

Calculated density 1.225 g/cm^3

30 wherein the unit cell parameters of Form B of Compound (I), free base hemihydrate are measured at a temperature of about 296 K.

Table 1

Form B of Compound (I), free base hemihydrate

Selected PXRD 2 θ values (CuK α λ =1.5418 Å) measured at room temperature

4.5 $\pm$ 0.2	9.1 $\pm$ 0.2	11.3 $\pm$ 0.2	11.8 $\pm$ 0.2	13.1 $\pm$ 0.2	13.6 $\pm$ 0.2
14.5 $\pm$ 0.2	14.8 $\pm$ 0.2	16.1 $\pm$ 0.2	16.4 $\pm$ 0.2	16.8 $\pm$ 0.2	17.0 $\pm$ 0.2
17.7 $\pm$ 0.2	19.2 $\pm$ 0.2	19.9 $\pm$ 0.2	20.3 $\pm$ 0.2	21.3 $\pm$ 0.2	22.1 $\pm$ 0.2
22.5 $\pm$ 0.2	24.7 $\pm$ 0.2	24.9 $\pm$ 0.2	25.5 $\pm$ 0.2	26.1 $\pm$ 0.2	26.5 $\pm$ 0.2
27.4 $\pm$ 0.2	28.0 $\pm$ 0.2	28.9 $\pm$ 0.2	29.2 $\pm$ 0.2	30.3 $\pm$ 0.2	-

5 In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by a powder x-ray diffraction pattern comprising four or more 2 θ values (CuK α λ =1.5418 Å) selected from: 4.5 $\pm$ 0.2, 11.3 $\pm$ 0.2, 11.8 $\pm$ 0.2, 13.1 $\pm$ 0.2, 13.6 $\pm$ 0.2, 14.5 $\pm$ 0.2, 14.8 $\pm$ 0.2, 16.1 $\pm$ 0.2, 19.9 $\pm$ 0.2, and 21.3 $\pm$ 0.2, wherein the PXRD pattern of Form B is measured at a temperature of about 25 °C.

10 In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by a powder x-ray diffraction pattern comprising five or more 2 θ values (CuK α λ =1.5418 Å) selected from: 4.5 $\pm$ 0.2, 11.3 $\pm$ 0.2, 11.8 $\pm$ 0.2, 13.1 $\pm$ 0.2, 13.6 $\pm$ 0.2, 14.5 $\pm$ 0.2, 14.8 $\pm$ 0.2, 16.1 $\pm$ 0.2, 19.9 $\pm$ 0.2, and 21.3 $\pm$ 0.2, wherein the PXRD pattern of Form B is measured at a temperature of about 25 °C.

15 In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by a powder x-ray diffraction pattern comprising six or more 2 θ values (CuK α λ =1.5418 Å) selected from: 4.5 $\pm$ 0.2, 11.3 $\pm$ 0.2, 11.8 $\pm$ 0.2, 13.1 $\pm$ 0.2, 13.6 $\pm$ 0.2, 14.5 $\pm$ 0.2, 14.8 $\pm$ 0.2, 16.1 $\pm$ 0.2, 19.9 $\pm$ 0.2, and 21.3 $\pm$ 0.2, wherein the PXRD pattern of Form B is measured at a temperature of about 25 °C.

20 In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by an observed powder x-ray diffraction pattern substantially as shown in Figure 1.

25 In one embodiment, crystalline Form B of Compound (I), free base hemihydrate, is characterized by a differential scanning calorimetry (DSC) thermogram substantially as shown in Figure 2.

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by an endotherm in the range of from 273 °C to 277 °C.

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by (i) a powder x-ray diffraction pattern comprising the 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418 \text{ \AA}$) at 16.1 ± 0.2 and 21.3 ± 0.2 , measured at a temperature of about 25°C ; and (ii) a differential scanning calorimetry (DSC) thermogram substantially in accordance with that shown in Figure 2.

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by (i) a powder x-ray diffraction pattern comprising four or more 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418 \text{ \AA}$) selected from: 4.5 ± 0.2 , 11.3 ± 0.2 , 11.8 ± 0.2 , 13.1 ± 0.2 , 13.6 ± 0.2 , 14.5 ± 0.2 , 14.8 ± 0.2 , 16.1 ± 0.2 , 19.9 ± 0.2 , and 21.3 ± 0.2 , wherein the PXRD pattern of Form B is measured at a temperature of about 25°C ; and (ii) a melting point in the range of from 273°C to 275°C .

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate exhibits a thermogravimetric analysis (TGA) thermogram substantially as shown in Figure 3.

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate is characterized by a thermogravimetric analysis (TGA) thermogram having weight loss of about 2.3 to 2.7 weight %, based on the weight of the sample of Form B, upon being heated to a temperature of about 220°C .

In one embodiment, crystalline Form B of Compound (I), free base hemihydrate exhibits a moisture-sorption isotherm substantially as shown in Figure 4. In Figure 4, an approximately 0.3 wt % change between 5 and 95 % relative humidity was observed in for crystalline Form B of Compound (I), free base hemihydrate.

In still yet an even further embodiment, crystalline Form B of Compound (I), free base hemihydrate is substantially pure.

In another embodiment, the crystalline form of Compound (I), free base hemihydrate consists essentially of Form B. The crystalline form of this embodiment may comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the crystalline form, Form B of Compound (I), free base hemihydrate.

One embodiment provides a composition comprising Compound (I), free base hemihydrate, wherein at least 95 wt. %, preferably at least 97 wt. %, and more preferably at least 99 wt. % of said Compound (I), free base hemihydrate is in crystalline Form B.

Form N of Compound (I), Free Base Anhydrate

In one embodiment, the Compound (I), free base is provided as crystalline material comprising Form N. The crystalline Form N of Compound (I), free base is an anhydrate crystalline form. Crystalline Form N is also referred to herein as "Form N".

Table 2

Form N of Compound (I), free base anhydrate

Selected PXRD 2 θ values (CuK α λ =1.5418 Å) measured at room temperature

8.7 $\pm$ 0.2	10.0 $\pm$ 0.2	10.6 $\pm$ 0.2	11.2 $\pm$ 0.2	13.2 $\pm$ 0.2	14.0 $\pm$ 0.2
14.6 $\pm$ 0.2	15.9 $\pm$ 0.2	16.6 $\pm$ 0.2	17.1 $\pm$ 0.2	17.4 $\pm$ 0.2	18.8 $\pm$ 0.2
19.2 $\pm$ 0.2	20.0 $\pm$ 0.2	20.8 $\pm$ 0.2	21.8 $\pm$ 0.2	22.2 $\pm$ 0.2	22.6 $\pm$ 0.2
23.1 $\pm$ 0.2	23.5 $\pm$ 0.2	24.4 $\pm$ 0.2	26.5 $\pm$ 0.2	27.8 $\pm$ 0.2	28.4 $\pm$ 0.2

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In one embodiment, crystalline Form N of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising four or more 2 θ values (CuK α λ =1.5418 Å) selected from: 8.7 $\pm$ 0.2, 10.0 $\pm$ 0.2, 10.6 $\pm$ 0.2, 11.2 $\pm$ 0.2, 13.2 $\pm$ 0.2, 14.0 $\pm$ 0.2, 14.6 $\pm$ 0.2, 15.9 $\pm$ 0.2, 17.1 $\pm$ 0.2, 19.2 $\pm$ 0.2, 20.0 $\pm$ 0.2, 23.1 $\pm$ 0.2, and 24.4 $\pm$ 0.2, wherein the PXRD pattern of Form N is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form N of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising five or more 2 θ values (CuK α λ =1.5418 Å) selected from: 8.7 $\pm$ 0.2, 10.0 $\pm$ 0.2, 10.6 $\pm$ 0.2, 11.2 $\pm$ 0.2, 13.2 $\pm$ 0.2, 14.0 $\pm$ 0.2, 14.6 $\pm$ 0.2, 15.9 $\pm$ 0.2, 17.1 $\pm$ 0.2, 19.2 $\pm$ 0.2, 20.0 $\pm$ 0.2, 23.1 $\pm$ 0.2, and 24.4 $\pm$ 0.2, wherein the PXRD pattern of Form N is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form N of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising six or more 2 θ values (CuK α λ =1.5418 Å) selected from: 8.7 $\pm$ 0.2, 10.0 $\pm$ 0.2, 10.6 $\pm$ 0.2, 11.2 $\pm$ 0.2, 13.2 $\pm$ 0.2, 14.0 $\pm$ 0.2, 14.6 $\pm$ 0.2, 15.9 $\pm$ 0.2, 17.1 $\pm$ 0.2, 19.2 $\pm$ 0.2, 20.0 $\pm$ 0.2, 23.1 $\pm$ 0.2, and 24.4 $\pm$ 0.2, wherein the PXRD pattern of Form N is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form N of Compound (I), free base anhydrate is

characterized by an observed powder x-ray diffraction pattern substantially as shown in Figure 5.

In one embodiment, crystalline Form N of Compound (I), free base anhydrate is substantially pure.

5 In another embodiment, the crystalline form of Compound (I), free base anhydrate consists essentially of Form N. The crystalline form of this embodiment may comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the crystalline form, Form N of Compound (I), free base anhydrate.

10 One embodiment provides a composition comprising Compound (I), free base anhydrate, wherein at least 95 wt. %, preferably at least 97 wt. %, and more preferably at least 99 wt. % of said Compound (I), free base anhydrate is in crystalline Form N.

Form O of Compound (I), Free Base Anhydrate

15 In one embodiment, the Compound (I), free base is provided as a crystalline material comprising Form O. The crystalline Form O of Compound (I), free base is an anhydrate crystalline form. Crystalline Form O is also referred to herein as "Form O".

Table 3

20 Form O of Compound (I), free base anhydrate

Selected PXRD 2 θ values (CuK α λ =1.5418 Å) measured at room temperature

7.0 $\pm$ 0.2	9.3 $\pm$ 0.2	10.4 $\pm$ 0.2	12.9 $\pm$ 0.2	13.3 $\pm$ 0.2	14.1 $\pm$ 0.2
15.0 $\pm$ 0.2	16.0 $\pm$ 0.2	16.6 $\pm$ 0.2	17.0 $\pm$ 0.2	18.4 $\pm$ 0.2	18.7 $\pm$ 0.2
19.8 $\pm$ 0.2	21.0 $\pm$ 0.2	21.7 $\pm$ 0.2	22.2 $\pm$ 0.2	23.4 $\pm$ 0.2	24.9 $\pm$ 0.2
25.4 $\pm$ 0.2	26.1 $\pm$ 0.2	26.8 $\pm$ 0.2	27.4 $\pm$ 0.2	28.4 $\pm$ 0.2	30.2 $\pm$ 0.2

In one embodiment, crystalline Form O of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising four or more 2 θ values (CuK α λ =1.5418 Å) selected from: 7.0 $\pm$ 0.2, 9.3 $\pm$ 0.2, 10.4 $\pm$ 0.2, 13.3 $\pm$ 0.2, 14.1 $\pm$ 0.2, 25 15.0 $\pm$ 0.2, 16.0 $\pm$ 0.2, 16.6 $\pm$ 0.2, 17.0 $\pm$ 0.2, 18.7 $\pm$ 0.2, 21.0 $\pm$ 0.2, 21.7 $\pm$ 0.2, and 22.2 $\pm$ 0.2, wherein the PXRD pattern of Form O is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form O of Compound (I), free base anhydrate is

characterized by a powder x-ray diffraction pattern comprising five or more 2θ values (CuKα λ=1.5418 Å) selected from: 7.0 ± 0.2 , 9.3 ± 0.2 , 10.4 ± 0.2 , 13.3 ± 0.2 , 14.1 ± 0.2 , 15.0 ± 0.2 , 16.0 ± 0.2 , 16.6 ± 0.2 , 17.0 ± 0.2 , 18.7 ± 0.2 , 21.0 ± 0.2 , 21.7 ± 0.2 , and 22.2 ± 0.2 , wherein the PXRD pattern of Form O is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form O of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising six or more 2 θ values (CuK α λ =1.5418 Å) selected from: 7.0 $\pm$ 0.2, 9.3 $\pm$ 0.2, 10.4 $\pm$ 0.2, 13.3 $\pm$ 0.2, 14.1 $\pm$ 0.2, 15.0 $\pm$ 0.2, 16.0 $\pm$ 0.2, 16.6 $\pm$ 0.2, 17.0 $\pm$ 0.2, 18.7 $\pm$ 0.2, 21.0 $\pm$ 0.2, 21.7 $\pm$ 0.2, and 22.2 $\pm$ 0.2, wherein the PXRD pattern of Form O is measured at a temperature of about 25 °C.

10 In one embodiment, crystalline Form O of Compound (I), free base anhydrate is characterized by an observed powder x-ray diffraction pattern substantially as shown in Figure 6.

In one embodiment, crystalline Form O of Compound (I), free base anhydrate is substantially pure.

15 In another embodiment, the crystalline form of Compound (I), free base anhydrate consists essentially of Form O. The crystalline form of this embodiment may comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the crystalline form, Form O of Compound (I), free base anhydrate.

20 One embodiment provides a composition comprising Compound (I), free base anhydrate, wherein at least 95 wt. %, preferably at least 97 wt. %, and more preferably at least 99 wt. % of said Compound (I), free base anhydrate is in crystalline Form O.

Form P of Compound (I), Free Base Anhydrate

25 In one embodiment, the Compound (I), free base is provided as a crystalline material comprising Form P. The crystalline Form P of Compound (I), free base is an anhydrate crystalline form. Crystalline Form P is also referred to herein as "Form P".

Table 4

Form P of Compound (I), free base anhydrate

Selected PXRD 2 θ values (CuK α λ =1.5418 Å) measured at room temperature

6.0 ± 0.2	8.1 ± 0.2	8.8 ± 0.2	9.5 ± 0.2	10.6 ± 0.2	11.4 ± 0.2
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12.1 ± 0.2	12.7 ± 0.2	13.2 ± 0.2	13.9 ± 0.2	14.5 ± 0.2	15.2 ± 0.2
15.6 ± 0.2	15.9 ± 0.2	16.7 ± 0.2	17.2 ± 0.2	17.6 ± 0.2	18.2 ± 0.2
18.5 ± 0.2	19.2 ± 0.2	20.0 ± 0.2	20.3 ± 0.2	20.8 ± 0.2	21.5 ± 0.2
22.2 ± 0.2	22.7 ± 0.2	23.0 ± 0.2	23.8 ± 0.2	24.4 ± 0.2	24.7 ± 0.2
25.3 ± 0.2	25.6 ± 0.2	26.5 ± 0.2	27.0 ± 0.2	27.4 ± 0.2	27.8 ± 0.2
28.6 ± 0.2	29.1 ± 0.2				

In one embodiment, crystalline Form P of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising four or more 2 θ values (CuK α λ =1.5418 Å) selected from: 6.0 ± 0.2, 8.1 ± 0.2, 8.8 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 12.1 ± 0.2, 13.2 ± 0.2, 14.5 ± 0.2, 16.7 ± 0.2, 17.2 ± 0.2, 21.5 ± 0.2, 22.2 ± 0.2, and 23.8 ± 0.2, wherein the PXRD pattern of Form P is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form P of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising five or more 2 θ values (CuK α λ =1.5418 Å) selected from: 6.0 ± 0.2, 8.1 ± 0.2, 8.8 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 12.1 ± 0.2, 13.2 ± 0.2, 14.5 ± 0.2, 16.7 ± 0.2, 17.2 ± 0.2, 21.5 ± 0.2, 22.2 ± 0.2, and 23.8 ± 0.2, wherein the PXRD pattern of crystalline Form P is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form P of Compound (I), free base anhydrate is characterized by a powder x-ray diffraction pattern comprising six or more 2 θ values (CuK α λ =1.5418 Å) selected from: 6.0 ± 0.2, 8.1 ± 0.2, 8.8 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 12.1 ± 0.2, 13.2 ± 0.2, 14.5 ± 0.2, 16.7 ± 0.2, 17.2 ± 0.2, 21.5 ± 0.2, 22.2 ± 0.2, and 23.8 ± 0.2, wherein the PXRD pattern of crystalline Form P is measured at a temperature of about 25 °C.

In one embodiment, crystalline Form P of Compound (I), free base anhydrate is characterized by an observed powder x-ray diffraction pattern substantially as shown in Figure 6.

In one embodiment, crystalline Form P of Compound (I), free base anhydrate is substantially pure.

In another embodiment, the crystalline Form P of Compound (I), free base anhydrate consists essentially of Form P. The crystalline Form P of this embodiment may comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably

at least about 99 wt. %, based on the weight of the crystalline form, Form P of Compound (I), free base anhydrate.

One embodiment provides a composition comprising Compound (I), free base anhydrate, wherein at least 95 wt. %, preferably at least 97 wt. %, and more preferably at least 99 wt. % of said Compound (I), free base anhydrate is in crystalline Form P.

Crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents may be employed, for example, the compound may be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An antisolvent is a solvent in which the compound has low solubility.

In one method to prepare crystals, a compound is suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, which may also contain an additional amount of the compound to afford a heterogeneous mixture of the compound and a solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote

crystallization. Seeding may be employed to control growth of a particular polymorph or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed
5 Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, 1971,26, 369-377. In general, seeds of small size are needed to control effectively the growth of crystals in the batch. Seed of small size may be generated by sieving, milling, or micronizing of large crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change
10 in crystallinity form the desired crystal form (i.e., change to amorphous or to another polymorph).

A cooled crystallization mixture may be filtered under vacuum, and the isolated solids may be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids
15 may be analyzed by a suitable spectroscopic or analytical technique, such as solid-state nuclear magnetic resonance, differential scanning calorimetry, powder x-ray diffraction, or the like, to assure formation of the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight % isolated yield, preferably greater than 90 weight % isolated yield, based on the
20 weight of the compound originally employed in the crystallization procedure. The product may be comilled or passed through a mesh screen to delump the product, if necessary.

Crystalline forms may be prepared directly from the reaction medium of the final process for preparing Compound (I). This may be achieved, for example, by employing
25 in the final process step a solvent or a mixture of solvents from which Compound (I) may be crystallized. Alternatively, crystalline forms may be obtained by distillation or solvent addition techniques. Suitable solvents for this purpose include, for example, the aforementioned nonpolar solvents and polar solvents, including protic polar solvents such as alcohols, and aprotic polar solvents such as ketones.

30 The presence of more than one polymorph in a sample may be determined by techniques such as powder x-ray diffraction (PXRD) or solid-state nuclear magnetic resonance spectroscopy. For example, the presence of extra peaks in the comparison of

an experimentally measured PXRD pattern with a simulated PXRD pattern may indicate more than one polymorph in the sample. The simulated PXRD may be calculated from single crystal x-ray data. see Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns*," Lawrence Radiation Laboratory, Livermore, California,
5 UCRL-7196 (April 1963).

The forms of Compound (I) may be characterized using various techniques, the operation of which are well known to those of ordinary skill in the art. The forms may be characterized and distinguished using single crystal x-ray diffraction, which is based on unit cell measurements of a single crystal at a fixed analytical temperature. A detailed
10 description of unit cells is provided in Stout & Jensen, *X-Ray Structure Determination: A Practical Guide*, Macmillan Co., New York (1968), Chapter 3, which is herein incorporated by reference. Alternatively, another means of characterizing the crystalline structure is by powder x-ray diffraction analysis in which the diffraction profile is compared to a simulated profile representing pure powder material, both run at the same
15 analytical temperature, and measurements for the subject form characterized as a series of 2θ values (usually four or more).

Other means of characterizing the form may be used, such as solid-state nuclear magnetic resonance (ssNMR), differential scanning calorimetry, thermal analysis, and vibrational spectroscopy. These parameters may also be used in combination to
20 characterize the subject form.

UTILITY

The free base hemihydrate of Compound (I) can be used to isolate Compound (I) from other components at the completion of the synthesis process; and/or to purify
25 Compound (I) by one or a series of crystallization steps.

Crystalline Form B of the free base hemihydrate of Compound (I) can be used to isolate Compound (I) from other components at the completion of the synthesis process; and/or to purify Compound (I) by one or a series of crystallization steps. The isolation and the purification steps can be combined or practiced as separate process steps.

30 The free base hemihydrate of Compound (I) can be formulated into a pharmaceutical composition for oral administration.

Crystalline Form B of the free base hemihydrate of Compound (I) can be

formulated into a pharmaceutical composition for oral administration.

The free base hemihydrate of Compound (I) and its Form B are useful as a source of purified Compound (I) in the preparation of salts of Compound (I).

5

EXAMPLES

The invention will now be further described by the following working example(s), which are preferred embodiments of the invention. All temperatures are in degrees Celsius (°C) unless otherwise indicated. These examples are illustrative rather than limiting and it is to be understood that there may be other embodiments that fall within
10 the spirit and scope of the invention as defined by the claims appended hereto.

The synthesis of Compound (I) is disclosed in WO 2018/005586 as Example 15.

Example 1: Preparation of Compound (I), Free Base, Hemihydrate Crystalline Form B

Compound (I) (100 mg) was dissolved in 1 mL DMF at 41 °C. The sample was
15 cooled to room temperature and 0.2 mL water was added to Form B slurry. The slurry was stirred at room temperature for 2 days. The solids in slurry were the free base, hemihydrate crystalline Form B.

Example 2: Preparation of Compound (I), Free Base, Hemihydrate Crystalline Form B

20 Compound (I) (1.15 g) was dissolved in 95:5 THF: water (vol:vol) at room temperature. Next, 1 mL of the solution was transferred to vials. The vials were placed in a vacuum concentrator to evaporate the solvent from each of the vials.

To one vial, 1 mL of 90:10 DCM: MeOH (vol:vol) was added and the slurry was stirred for 13 days. The solids in slurry were the free base, hemihydrate crystalline Form
25 B.

To another vial, 1 mL of 1 mL MIBK was added and the slurry was stirred for 13 days. The solids in slurry were the free base, hemihydrate crystalline Form B.

Example 3: Preparation of Compound (I), Free Base, Anhydrate Crystalline Form N

30 Compound (I) (31 g) was added to 420 mL of EtOH in a volumetric flask. The solution was heated until all solids dissolved and then allowed to cool back down to room temperature. The solids were isolated via vacuum filtration and characterized via PXRD.

Example 4: Preparation of Compound (I), Free Base, Anhydrate Crystalline Form O

A sample of Compound (I), free base, Form N (Example 3) was heated in a pan to 200 °C using a differential scanning calorimeter. The solids were isolated from the pan
5 and analyzed via PXRD.

Example 5: Preparation of Compound (I) Free Base, Anhydrate Crystalline Form P

A sample of Compound (I), free base, Form N (Example 3) was added to 95:5 v:v THF/water at a concentration of 5 mg/mL and stirred in a vial with a stir bar for 1 day.
10 The slurry was then dried via speed vacuum. Next, 1 mL of MeOH was added to the vial to return the concentration to 5 mg/mL. The slurry was stirred at room temperature with a stir bar for 14 days. The solids were isolated using vacuum filtration and dried in a vacuum oven set at 50 °C for 5 days. The solids were analyzed via PXRD.

15 The solid state stability of Compound (I), free base hemihydrate, Form B was studied by storing samples at:

- (i) 5 °C in a closed container;
- (ii) 25 °C / 60% relative humidity (RH) in open container;
- (iii) 40 °C / 75 % relative humidity in an open container; and
- 20 (iv) 50 °C in a closed container.

The physical stability, characterized by DSC, TGA, and PXRD, and the chemical stability, characterized by HPLC, were measured at 2 and 4 weeks.

Table 5

Time point	Condition	% AP	Form
2wk	Initial (5°C)	98.92	Form B
	25°C/60% RH Open	98.97	Form B
	40°C/75% RH Open	98.98	Form B
	40°C/75% RH Closed	98.96	Form B
	50°C	98.91	Form B

	Ambient Light	98.94	Form B
	HIL	98.73	Form B
4wk	25°C/60% RH Open	98.85	Form B
	40°C/75% RH Open	99.08	Form B
	40°C/75% RH Closed	99.14	Form B
	50°C	99.02	Form B
	Ambient Light	99.05	Form B
	High Intensity Light	98.98	Form B

In Table 5, the physical stability analyses (PXRD, DSC and TGA) showed that Form B of was physically stable for at least 4 weeks under all stressed conditions.

In Table 2, the chemical stability analysis by HPLC indicated no significant degradation of Form B of Compound (I), free base hemihydrate for at least 4 weeks under all stressed conditions.

Figure 4 shows the moisture-sorption isotherm for Compound (I), free base hemihydrate crystalline Form B at a temperature of 25 °C. In this measurement, the weight change for Compound (I), free base hemihydrate crystalline Form B was approximately 0.3 wt % change between 5 and 95 % relative humidity, indicating that the crystalline Form B of Compound (I), free base hemihydrate is non-hygroscopic.

Single Crystal Data

Single crystal X-ray data of Form B were collected using a Bruker X8-Proteum diffractometer equipped with APEX II CCD detector and a MICROSTAR microfocus rotating anode X-ray generator of monochromatic Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$). The single crystal was at room temperature (approximately 25 °C) during data collection.

Indexing and processing of the measured intensity data were carried out with the APEX2 program suite (Bruker AXS, Inc., 5465 East Cheryl Parkway, Madison, WI 53711 USA).

The final unit cell parameters were determined using the full data set. The structures were solved by direct methods and refined by full-matrix least-squares

approach using the SHELXTL software package (G. M. Sheldrick, SHELXTL v6.14, Bruker AXS, Madison, WI USA.). Structure refinements involved minimization of the function defined by $\sum w(|F_o| - |F_c|)^2$, where w is an appropriate weighting factor based on errors in the observed intensities, F_o is the structure factor based on measured reflections, and F_c is the structure factor based on calculated reflections. Agreement between the refined crystal structure model and the experimental X-ray diffraction data is assessed by using the residual factors $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $wR = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|]^2$. Difference Fourier maps were examined at all stages of refinement. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Hydrogen atoms were introduced using idealized geometry with isotropic temperature factors and included in structure factor calculations with fixed parameters.

Powder X-ray Diffraction (PXRD)

PXRD data for Form B was collected using a Bruker D8 Discover DaVinci with XYZ Stage. The I μ S X-ray generator was operated at 50 kV and 1 mA with a Cu target (CuK α radiation). Incident beam optics included Montel mirrors with a 0.3 mm collimator. Photons were counted using an Eiger2 R 500K Detector in 2D, 2 θ optimized mode. Sample-to-detector distance was set to 140 mm. The samples were run for 1000 seconds in transmission, snapshot mode with the incident beam at 0° and the detector at 17.5°.

PXRD data for N, O and P were obtained using a Bruker C2 GADDS. The radiation was Cu K α (40 KV, 40 mA). The sample-detector distance was 15 cm. Samples were placed in sealed glass capillaries with diameters of ≤ 1 mm. The capillary was rotated during data collection. Data were collected for approximately $2 \leq 2\theta \leq 32^\circ$ with a sample exposure time of at least 1000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional PXRD pattern with a step size of 0.05 degrees 2θ in the approximate range of 2 to 32 degrees 2θ .

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) experiments were performed using a TA Instruments Discovery DSC 2500. The sample (about 1-5 mg) was weighed in a Tzero aluminum pan. The weight of the sample was recorded accurately to a hundredth of a

milligram before transferring to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and 350 °C at a heating rate of 10 °C/min. DSC plots were generated such that the endothermic peaks pointed down.

5

Thermal Gravimetric Analysis (TGA)

Thermal gravimetric analysis (TGA) experiments were performed using a TA Instruments Discovery TGA 5500. The sample (about 1-10 mg) was placed in a previously cleaned and tarred platinum pan. The weight of the sample was measured accurately and recorded to a thousandth of a milligram by the instrument. The furnace was purged with nitrogen gas at 25 mL/min. Data were collected between room temperature and 400 °C at a heating rate of 10 °C/min.

10

Moisture Sorption Isotherm

Moisture sorption isotherm data were collected on a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was tested at 25 °C from 95% relative humidity (RH) to 5% RH and then back to 95% RH at 5% RH decrements and increments, respectively. Equilibration at each RH was reached when the rate of 0.0010 wt.%/min for 60 minutes was achieved or a maximum of 120 minutes.

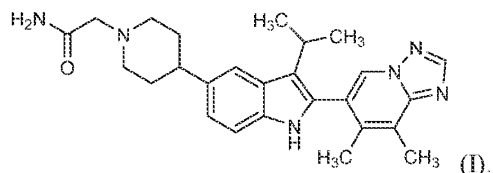
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CLAIMS

What is claimed is:

1. A free base hemihydrate of Compound (I):



5

2. The free base hemihydrate of Compound (I) according to Claim 1, wherein said free base hemihydrate of Compound (I) is crystalline.

- 10 3. The free base hemihydrate of Compound (I) according to Claim 2, wherein said free base hemihydrate of Compound (I) is neat.

4. The free base hemihydrate of Compound (I) according to Claim 2, wherein said free base hemihydrate of Compound (I) is in crystalline Form B.

15

5. The free base hemihydrate of Compound (I) according to Claim 4, wherein said crystalline Form B is characterized by a powder x-ray diffraction pattern (PXRD) comprising four or more 2θ values ($\text{CuK}\alpha \lambda=1.5418 \text{ \AA}$) selected from: 4.5 ± 0.2 , 11.3 ± 0.2 , 11.8 ± 0.2 , 13.1 ± 0.2 , 13.6 ± 0.2 , 14.5 ± 0.2 , 14.8 ± 0.2 , 16.1 ± 0.2 , 19.9 ± 0.2 , and

20

$^{\circ}\text{C}$.

6. The free base hemihydrate of Compound (I) according to Claim 4, wherein said crystalline Form B is characterized by a powder x-ray diffraction pattern (PXRD) comprising five or more 2θ values ($\text{CuK}\alpha \lambda=1.5418 \text{ \AA}$) selected from: 4.5 ± 0.2 , 11.3 ± 0.2 , 11.8 ± 0.2 , 13.1 ± 0.2 , 13.6 ± 0.2 , 14.5 ± 0.2 , 14.8 ± 0.2 , 16.1 ± 0.2 , 19.9 ± 0.2 , and 21.3 ± 0.2 , wherein the PXRD pattern of Form B is measured at a temperature of about 25°C .

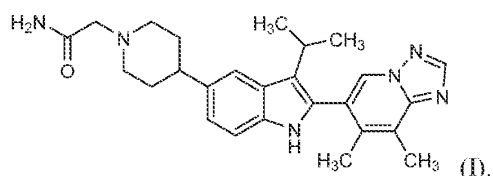
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7. The free base hemihydrate of Compound (I) according to Claim 4, wherein said crystalline Form B is characterized by a powder x-ray diffraction pattern (PXRD) comprising six or more 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) selected from: 4.5 ± 0.2 , 11.3 ± 0.2 , 11.8 ± 0.2 , 13.1 ± 0.2 , 13.6 ± 0.2 , 14.5 ± 0.2 , 14.8 ± 0.2 , 16.1 ± 0.2 , 19.9 ± 0.2 , and
- 5 21.3 ± 0.2 , wherein the PXRD pattern of Form B is measured at a temperature of about 25°C .
8. The free base hemihydrate of Compound (I) according to Claim 4, wherein said crystalline Form B is characterized by:
- 10 (i) a powder x-ray diffraction pattern comprising the 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) at 16.1 ± 0.2 and 21.3 ± 0.2 , measured at a temperature of about 25°C ; and
- (ii) a melting point in the range of from 273°C to 277°C .
9. The free base hemihydrate of Compound (I) according to Claim 4, wherein said
- 15 crystalline Form B is characterized by:
- (i) a powder x-ray diffraction pattern comprising the 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) at 16.1 ± 0.2 and 21.3 ± 0.2 , measured at a temperature of about 25°C ; and
- (ii) a differential scanning calorimetry (DSC) thermogram substantially in accordance with that shown in Figure 2.
- 20
10. The free base hemihydrate of Compound (I) according to Claim 4, wherein said crystalline Form B is characterized by:
- (i) a powder x-ray diffraction pattern comprising the 2θ values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) at 16.1 ± 0.2 and 21.3 ± 0.2 , measured at a temperature of about 25°C ; and
- 25 (ii) a weight loss of 0.2 to 0.4 weight % upon heating from 25°C to 220°C .
11. The free base hemihydrate of Compound (I) according to claim 4, consisting essentially of crystalline Form B.
- 30 12. The free base hemihydrate of Compound (I) according to claim 4, wherein said Form B is in substantially pure form.

13. A composition comprising the free base hemihydrate of Compound (I) according to claim 1.

14. The composition according to claim 13, wherein at least 95 weight % of said free
5 base hemihydrate of Compound (I) is in crystalline Form B.

15. A crystalline free base anhydrate of Compound (I):



10 16. The crystalline free base anhydrate of Compound (I) according to Claim 15, wherein said crystalline free base anhydrate of Compound (I) is in crystalline Form N characterized by a powder x-ray diffraction pattern comprising four or more 20 values (CuK α λ =1.5418 Å) selected from: 8.7 ± 0.2 , 10.0 ± 0.2 , 10.6 ± 0.2 , 11.2 ± 0.2 , 13.2 ± 0.2 , 14.0 ± 0.2 , 14.6 ± 0.2 , 15.9 ± 0.2 , 17.1 ± 0.2 , 19.2 ± 0.2 , 20.0 ± 0.2 , 23.1 ± 0.2 , and
15 24.4 ± 0.2 , wherein the PXRD pattern of crystalline Form N is measured at a temperature of about 25 °C.

17. The crystalline free base anhydrate of Compound (I) according to Claim 15, wherein said crystalline free base anhydrate of Compound (I) is crystalline Form O characterized
20 by a powder x-ray diffraction pattern comprising four or more 20 values (CuK α λ =1.5418 Å) selected from: 7.0 ± 0.2 , 9.3 ± 0.2 , 10.4 ± 0.2 , 13.3 ± 0.2 , 14.1 ± 0.2 , 15.0 ± 0.2 , 16.0 ± 0.2 , 16.6 ± 0.2 , 17.0 ± 0.2 , 18.7 ± 0.2 , 21.0 ± 0.2 , 21.7 ± 0.2 , and 22.2 ± 0.2 , wherein the PXRD pattern of crystalline Form O is measured at a temperature of about 25 °C.

25 18. The crystalline free base anhydrate of Compound (I) according to Claim 15, wherein said crystalline free base anhydrate of Compound (I) is crystalline Form P characterized by a powder x-ray diffraction pattern comprising four or more 20 values (CuK α λ =1.5418 Å) selected from: 6.0 ± 0.2 , 8.1 ± 0.2 , 8.8 ± 0.2 , 9.5 ± 0.2 , 11.4 ± 0.2 , 12.1 ± 0.2 , $13.2 \pm$

0.2, 14.5 ± 0.2 , 16.7 ± 0.2 , 17.2 ± 0.2 , 21.5 ± 0.2 , 22.2 ± 0.2 , and 23.8 ± 0.2 , wherein the PXRD pattern of crystalline Form P is measured at a temperature of about 25 °C.