

**CRYSTALLINE PROLYL HYDROXYLASE DOMAIN-CONTAINING PROTEIN (PHD)
INHIBITOR AND USES THEREOF**

CROSS-REFERENCE

[0001] This patent application claims the benefit of International Application No. PCT/CN2023/091785, filed April 28, 2023; which is incorporated herein by reference in its entirety.

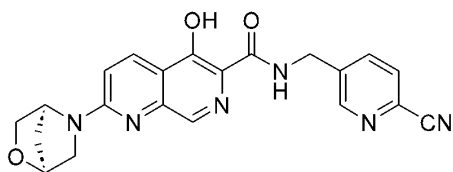
BACKGROUND

[0002] Hypoxia-inducible factor (HIF) mediates gene expression in response to changes in cellular oxygen concentration. HIF is a heterodimer having an oxygen-regulated subunit (HIF- α) and a constitutively expressed subunit (HIF- β). HIF prolyl hydroxylase, which is also known as prolyl hydroxylase domain-containing protein (PHD), exists as three isoforms in humans (PHD1, PHD2, and PHD3). PHDs act as oxygen sensors modulating the hypoxia-inducible factor ("HIF") degradation pathway. Briefly, PHDs are responsible for hydroxylation of HIF α , a subunit of HIF, which initiates the pathway that eventually results in the degradation of HIF α by the proteasome. There are three subtypes of PHDs, including PHD1, PHD2 and PHD3. Inhibition of PHDs has been indicated as a promising therapy for the HIF α related disease, such as anemia.

[0003] Inhibitors of PHDs coordinate erythropoiesis by inducing both renal and hepatic erythropoietin ("EPO") synthesis, which stimulates the production of red blood cells in the bone marrow, and by regulating the metabolism of iron, an indispensable component of functional red blood cells. Inhibitors of PHDs could also suppress the production of hepatic hepcidin, which has negative effects on iron mobilization. It is also speculated that inhibitors of PHDs might upregulate the expression several iron metabolism gene, such as DMT1 and DCYTB. Because of the central role HIF prolyl hydrolase plays in cellular oxygen sensing, inhibitors of PHD may be useful in treating cardiovascular disorders, metabolic disorders, hematological disorders, pulmonary disorders, kidney disorders, liver disorders, wound healing disorders, and cancer, among others.

SUMMARY

[0004] Disclosed herein is a solid state form of 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide:



(Compound 1) or a pharmaceutically acceptable salt thereof.

[0005] In some embodiments, the solid state form is a crystalline form.

[0006] In some embodiments, the solid state form is crystalline Compound 1 as a freebase.

[0007] In some embodiments, the solid state form is crystalline Compound 1 freebase Type A.

[0008] In some embodiments, the solid state form is crystalline Compound 1 as a salt.

[0009] In some embodiments, the solid state form is crystalline Compound 1 HCl salt Type A, Compound 1 HCl salt Type B, or Compound 1 Tosylate salt Type A.

[0010] Also disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a crystalline form disclosed herein and a pharmaceutically acceptable excipient.

[0011] Also disclosed herein is a method of treating a disease or disorder in a subject, the method comprising administering to the subject a crystalline form disclosed herein or a pharmaceutical composition disclosed herein, wherein the disease or disorder is anemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The features of the invention are set forth with particularity in the appended claims. A better understanding of the features of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0013] **FIG. 1** shows the X-Ray Powder Diffraction (XRPD) pattern of Compound 1 Freebase Type A.

[0014] **FIG. 2** shows the Differential Scanning Calorimetry (DSC) thermogram and the Thermogravimetric Analysis (TGA) thermogram of Compound 1 Freebase Type A.

[0015] **FIG. 3** shows the X-Ray Powder Diffraction (XRPD) pattern of Compound 1 HCl salt Type A.

[0016] **FIG. 4** shows the Differential Scanning Calorimetry (DSC) thermogram and the Thermogravimetric Analysis (TGA) thermogram of Compound 1 HCl salt Type A.

[0017] **FIG. 5** shows the X-Ray Powder Diffraction (XRPD) pattern of Compound 1 HCl salt Type B.

[0018] **FIG. 6** shows the Differential Scanning Calorimetry (DSC) thermogram and the Thermogravimetric Analysis (TGA) thermogram of Compound 1 HCl salt Type B.

[0019] **FIG. 7** shows the X-Ray Powder Diffraction (XRPD) pattern of Compound 1 Tosylate salt Type A.

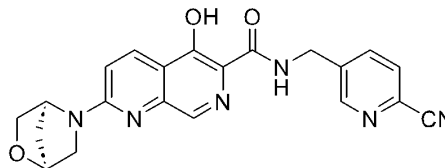
[0020] **FIG. 8** shows the Differential Scanning Calorimetry (DSC) thermogram and the Thermogravimetric Analysis (TGA) thermogram of Compound 1 Tosylate salt Type A.

DETAILED DESCRIPTION

[0021] While small molecule inhibitors are often initially evaluated for their activity when dissolved in solution, solid state characteristics such as polymorphism are also important. Polymorphic forms of a drug substance can have different physical properties, including melting point, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process or manufacture a drug substance and the drug product. Moreover, differences in these properties can and often lead to different pharmacokinetics profiles for different polymorphic forms of a drug. Therefore, polymorphism is often an important factor under regulatory review of the ‘sameness’ of drug products from various manufacturers.

Compound 1

[0022] Compound 1 is 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((6-cyanopyridin-3-

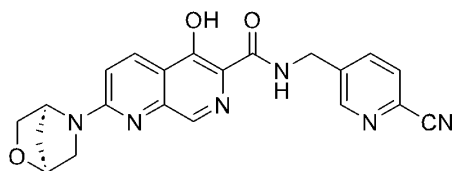


yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide:

(Compound 1). In some embodiments, Compound 1 is in the form of a freebase. In some embodiments, Compound 1 is in the form of a pharmaceutically acceptable salt. In some embodiments, Compound 1 is in the form of an HCl salt. In some embodiments, Compound 1 is in the form of a Tosylate salt.

Solid State Form of Compound 1

[0023] In one aspect, provided herein is a solid state form of 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-



carboxamide:

(Compound 1) or a pharmaceutically

acceptable salt thereof.

[0024] In some embodiments, the solid state form is a crystalline form.

[0025] In some embodiments, the solid state form is crystalline Compound 1 freebase. In some embodiments, the solid state form is crystalline Compound 1 freebase Type A.

[0026] In some embodiments, the solid state form is Compound 1 HCl salt. In some embodiments, the solid state form is crystalline Compound 1 HCl salt. In some embodiments, the solid state form is crystalline Compound 1 HCl salt Type A. In some embodiments, the solid state form is crystalline Compound 1 HCl salt Type B.

[0027] In some embodiments, the solid state form is Compound 1 Tosylate salt. In some embodiments, the solid state form is crystalline Compound 1 Tosylate salt. In some embodiments, the solid state form is crystalline Compound 1 Tosylate salt Type A.

Compound 1 Freebase Type A

[0028] Disclosed herein is Compound 1 freebase Type A. In some embodiments, the crystalline form is Compound 1 freebase characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 1** as measured using Cu K α radiation;
- (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;

- (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 2**;
- (d) a Differential Scanning Calorimetry (DSC) thermogram with an endothermic peak having a peak temperature at about 215°C;
- (e) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 2**; or
- (f) combinations thereof.

[0029] In some embodiments, the crystalline form is Compound 1 freebase characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
- (b) a Differential Scanning Calorimetry (DSC) thermogram with an endothermic peak having a peak temperature at about 215°C; or
- (c) combinations thereof.

[0030] In some embodiments, the crystalline form is Compound 1 freebase characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 1** as measured using Cu K α radiation;
- (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
- (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 2**;
- (d) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 2**; or
- (e) combinations thereof.

[0031] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 1** as measured using Cu K α radiation.

[0032] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks found in Table 1 as measured using Cu K α radiation.

[0033] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0034] In some embodiments of Compound 1 freebase, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $14.2 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, and $22.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0044] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least eight peaks selected from $8.5 \pm 0.2^\circ 2\theta$, $14.2 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, $18.0 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, $20.3 \pm 0.2^\circ 2\theta$, $22.3 \pm 0.2^\circ 2\theta$, $22.8 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, $26.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0045] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least nine peaks selected from $8.5 \pm 0.2^\circ 2\theta$, $14.2 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, $18.0 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, $20.3 \pm 0.2^\circ 2\theta$, $22.3 \pm 0.2^\circ 2\theta$, $22.8 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, $26.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0046] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least ten peaks selected from $8.5 \pm 0.2^\circ 2\theta$, $14.2 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, $18.0 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, $20.3 \pm 0.2^\circ 2\theta$, $22.3 \pm 0.2^\circ 2\theta$, $22.8 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, $26.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0047] In some embodiments of Compound 1 freebase, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least 11 peaks selected from $8.5 \pm 0.2^\circ 2\theta$, $14.2 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, $18.0 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, $20.3 \pm 0.2^\circ 2\theta$, $22.3 \pm 0.2^\circ 2\theta$, $22.8 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, $26.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0048] In some embodiments of Compound 1 freebase, the Differential Scanning Calorimetry (DSC) thermogram is substantially the same as shown in **FIG. 2**.

[0049] In some embodiments of Compound 1 freebase, the Differential Scanning Calorimetry (DSC) thermogram has an endothermic peak having a peak temperature at about 215°C.

[0050] In some embodiments of Compound 1 freebase, the Thermogravimetric Thermal Analysis (TGA) thermogram is substantially the same as shown in **FIG. 2**.

[0051] In some embodiments of Compound 1 freebase, the crystalline form is an anhydrate.

[0052] In some embodiments of Compound 1 freebase, the crystalline form is stable.

[0053] In some embodiments of Compound 1 freebase, the crystalline form is chemically stable.

[0054] In some embodiments of Compound 1 freebase, the crystalline form is thermodynamically stable.

Table 1 XRPD peaks table of Compound 1 freebase Type A

Index	Angle	Rel. Intensity
1	8.5	21.80%
2	11.8	4.00%
3	12.1	1.00%
4	14.1	17.00%
5	14.2	32.50%
6	14.5	2.50%
7	14.9	2.30%
8	15.8	4.40%
9	16.2	21.50%
10	18.0	12.50%
11	18.6	68.60%
12	19.3	1.80%
13	20.0	7.40%
14	20.3	100.00%
15	20.7	1.00%
16	22.3	17.70%
17	22.8	16.30%

Index	Angle	Rel. Intensity
18	23.0	6.10%
19	23.4	7.50%
20	23.9	12.40%
21	24.5	3.10%
22	25.2	4.20%
23	25.9	16.80%
24	26.1	8.80%
25	26.9	14.20%
26	27.4	2.50%
27	28.0	7.00%
28	28.1	13.10%
29	28.5	0.90%
30	30.1	2.60%
31	30.6	10.20%
32	31.0	2.00%
33	31.8	1.20%
34	31.9	1.50%
35	32.4	4.40%
36	33.9	1.90%
37	34.4	3.20%
38	36.2	3.60%
39	37.6	1.50%
40	37.9	3.00%
41	39.2	1.10%
42	39.7	2.10%

Compound 1 HCl Salt Type A

[0055] Disclosed herein is Compound 1 HCl salt Type A. In some embodiments, the crystalline form is Compound 1 HCl salt characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 3** as measured using Cu K α radiation;
- (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $7.9 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, and $15.9 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
- (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 4**;
- (d) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 4**; or
- (e) combinations thereof.

[0056] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 3** as measured using Cu K α radiation.

[0057] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks found in Table 2 as measured using Cu K α radiation.

[0058] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $7.9 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, and $15.9 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0059] In some embodiments of Compound 1 HCl salt, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $9.0 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0060] In some embodiments of Compound 1 HCl salt, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $21.0 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0061] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0062] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least two peaks selected from $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0063] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least three peaks selected from $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0064] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least four peaks selected from $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0065] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least five peaks selected from $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0066] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least six peaks selected from $7.9 \pm 0.2^\circ 2\theta$, $9.0 \pm 0.2^\circ 2\theta$, $10.8 \pm 0.2^\circ 2\theta$, $13.1 \pm 0.2^\circ 2\theta$, $15.9 \pm 0.2^\circ 2\theta$, $21.0 \pm 0.2^\circ 2\theta$, and $24.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0067] In some embodiments of Compound 1 HCl salt, the Differential Scanning Calorimetry (DSC) thermogram is substantially the same as shown in **FIG. 4**.

[0068] In some embodiments of Compound 1 HCl salt, the Thermogravimetric Thermal Analysis (TGA) thermogram is substantially the same as shown in **FIG. 4**.

Table 2: XRPD peaks table of Compound 1 HCl salt Type A

Index	Angle	Rel. Intensity
1	6.0	12.60%
2	7.9	100.00%
3	9.0	46.50%
4	10.8	22.70%
5	13.1	34.00%
6	13.8	23.10%
7	15.9	40.30%

8	21.0	24.40%
9	24.6	43.80%
10	25.7	16.20%
11	27.1	17.10%
12	32.5	16.30%

Compound 1 HCl Salt Type B

[0069] Disclosed herein is Compound 1 HCl salt Type B. In some embodiments, the crystalline form is Compound 1 HCl salt characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 5** as measured using Cu K α radiation;
- (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $4.8 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, and $27.2 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
- (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 6**;
- (d) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 6**; or
- (e) combinations thereof.

[0070] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 5** as measured using Cu K α radiation.

[0071] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks found in Table 3 as measured using Cu K α radiation.

[0072] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $4.8 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, and $27.2 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0073] In some embodiments of Compound 1 HCl salt, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $16.8 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0074] In some embodiments of Compound 1 HCl salt, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $13.7 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, and $19.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0075] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0076] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least two peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$

20, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0077] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least three peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0078] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least four peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0079] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least five peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0080] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least six peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0081] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least seven peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0082] In some embodiments of Compound 1 HCl salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with at least eight peaks selected from $4.8 \pm 0.2^\circ 2\theta$, $13.7 \pm 0.2^\circ 2\theta$, $16.8 \pm 0.2^\circ 2\theta$, $17.5 \pm 0.2^\circ 2\theta$, $19.3 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, $22.2 \pm 0.2^\circ 2\theta$, $27.2 \pm 0.2^\circ 2\theta$, and $27.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0083] In some embodiments of Compound 1 HCl salt, the Differential Scanning Calorimetry (DSC) thermogram is substantially the same as shown in **FIG. 6**.

[0084] In some embodiments of Compound 1 HCl salt, the Thermogravimetric Thermal Analysis (TGA) thermogram is substantially the same as shown in **FIG. 6**.

Table 3 XRPD peaks table of Compound 1 HCl salt Type B

Index	Angle	Rel. Intensity
1	4.8	74.90%
2	7.9	6.60%
3	9.6	13.30%
4	13.7	13.90%
5	14.4	9.70%
6	15.6	5.50%
7	16.8	52.30%

Index	Angle	Rel. Intensity
8	17.5	30.80%
9	18.2	6.50%
10	19.3	15.20%
11	20.0	71.50%
12	20.6	4.60%
13	21.3	9.40%
14	22.2	34.10%
15	23.6	10.50%
16	24.3	15.00%
17	27.2	100.00%
18	27.7	83.40%
19	30.2	20.40%
20	31.0	9.70%
21	33.5	9.60%
22	35.5	5.80%
23	37.4	6.40%
24	38.2	4.20%

Compound 1 Tosylate Salt Type A

[0085] Disclosed herein is Compound 1 Tosylate salt Type A. In some embodiments, the crystalline form is Compound 1 Tosylate salt characterized as having at least one of the following properties:

- (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 7** as measured using Cu K α radiation;
- (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $5.1 \pm 0.2^\circ 2\theta$, $16.9 \pm 0.2^\circ 2\theta$, and $20.2 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
- (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 8**;
- (d) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 8**; or
- (e) combinations thereof.

[0086] In some embodiments of Compound 1 Tosylate salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 7** as measured using Cu K α radiation.

[0087] In some embodiments of Compound 1 Tosylate salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks found in Table 4 as measured using Cu K α radiation.

[0088] In some embodiments of Compound 1 Tosylate salt, the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $4.8 \pm 0.2^\circ 2\theta$, $20.0 \pm 0.2^\circ 2\theta$, and $27.2 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[0089] In some embodiments of Compound 1 Tosylate salt, the X-ray powder diffraction (XRPD) pattern further comprises peaks at $16.0 \pm 0.2^\circ 2\theta$, $20.8 \pm 0.2^\circ 2\theta$, and $23.7 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

$0.2^\circ 2\theta$, $19.1 \pm 0.2^\circ 2\theta$, $20.2 \pm 0.2^\circ 2\theta$, $20.8 \pm 0.2^\circ 2\theta$, $21.6 \pm 0.2^\circ 2\theta$, $23.7 \pm 0.2^\circ 2\theta$, $25.6 \pm 0.2^\circ 2\theta$, and $26.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

[00101] In some embodiments of Compound 1 Tosylate salt, the Differential Scanning Calorimetry (DSC) thermogram is substantially the same as shown in **FIG. 8**.

[00102] In some embodiments of Compound 1 Tosylate salt, the Thermogravimetric Thermal Analysis (TGA) thermogram is substantially the same as shown in **FIG. 8**.

[00103] In some embodiments of Compound 1 Tosylate salt, the ratio of Compound 1 to p-toluenesulfonic acid is about 1:1.02.

Table 4 XRPD peaks table of Compound 1 Tosylate salt Type A

Index	Angle	Rel. Intensity
1	5.1	100.00%
2	8.8	8.40%
3	12.4	15.90%
4	14.2	1.80%
5	15.3	4.10%
6	16.0	24.10%
7	16.9	57.90%
8	17.4	7.20%
9	17.8	7.00%
10	19.1	17.20%
11	20.2	50.30%
12	20.4	16.80%
13	20.8	51.10%
14	21.2	4.20%
15	21.6	36.50%
16	22.0	29.20%
17	22.8	3.50%
18	23.7	21.30%
19	24.8	3.50%
20	25.2	13.80%
21	25.6	25.50%
22	25.8	19.30%
23	26.3	20.50%
24	26.6	16.90%
25	27.9	7.30%
26	29.4	2.80%
27	30.0	4.10%
28	30.4	6.70%
29	30.8	8.70%
30	31.3	1.70%
31	32.5	5.20%
32	33.7	4.80%
33	34.7	2.60%
34	35.4	4.30%
35	39.1	3.00%

Method of Treatment

[00104] Disclosed herein is a method of treating a disease or disorder in a subject, the method

comprising administering to the subject a crystalline form disclosed herein, wherein the disease or disorder is anemia.

Anemia

[00105] Anemia is a frequent and serious complication of chronic kidney diseases with a relative deficiency in EPO production and a decrease in iron availability for hemoglobin (“Hb”) synthesis. According to Informa, in 2020, there were 168 million prevalent cases of anemia resulted from chronic kidney diseases around the world. It is estimated that the number will rise to 182 million in 2027, according to the same source.

[00106] Currently, anemia resulting from chronic kidney diseases is managed by iron supplementation and, in more severe cases, by administration of supraphysiologic doses of erythropoiesis stimulating agents (“ESAs”) in combination with adjuvant iron therapy. High doses of ESAs increase the risk of serious adverse events, including myocardial infarction, congestive heart failure, stroke, and death. Several inhibitors of PHDs have been launched and may serve as effective treatments for patients with anemia resulted from chronic kidney disease. However, the cardiovascular side effects caused by erythropoietin induction and potential off-target toxicities may raise safety concerns for long-term treatment. New therapies are needed to address both impaired EPO production and functional iron deficiency.

Dosing

[00107] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient’s health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00108] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder, or condition. Such an amount is defined to be a “prophylactically effective amount or dose.” In this use, the precise amounts also depend on the patient’s state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient’s health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of or risk factor for the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00109] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00110] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

Routes of Administration

[00111] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00112] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00113] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, and topical routes of administration.

[00114] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional

manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00115] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

[00116] The pharmaceutical compositions described herein are administered to a subject by appropriate administration routes, including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00117] Pharmaceutical compositions including compounds described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes.

[00118] Pharmaceutical compositions for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as

sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00119] Pharmaceutical compositions that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00120] Pharmaceutical compositions for parental use are formulated as infusions or injections. In some embodiments, the pharmaceutical composition suitable for injection or infusion includes sterile aqueous solutions, or dispersions, or sterile powders comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the pharmaceutical composition comprises a liquid carrier. In some embodiments, the liquid carrier is a solvent or liquid dispersion medium comprising, for example, water, saline, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and any combinations thereof. In some embodiments, the pharmaceutical compositions further comprise a preservative to prevent growth of microorganisms.

Definitions

[00121] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00122] The term “acceptable” with respect to a formulation, composition, or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00123] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[00124] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in

disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00125] The terms “enhance” or “enhancing,” as used herein, means to increase, or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00126] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00127] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[00128] The term “about” means within a statistically meaningful range of a value, such as a stated concentration range, time frame, molecular weight, particle size, temperature, or pH. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, and even more typically within 3% of the indicated value or range. Sometimes, such a range can be within the experimental error typical of standard methods used for the measurement and/or determination of a given value or range. The allowable variation encompassed by the term “about” will depend upon the particular system under study, and can be readily appreciated by one of ordinary skill in the art. Whenever a range is recited within this application, every whole number integer within the range is also contemplated as an embodiment of the disclosure. In the context of the disclosure, when used or whether or not used the word, such as “about,” it means that within a given value or range of 10%, appropriately within 5%, especially within 1%.

[00129] If multiple diffraction patterns are available, then assessments of particle statistics (PS) and/or preferred orientation (PO) are possible. Consistency of relative intensity among XRPD patterns from multiple diffractometers indicates good orientation statistics. Alternatively, the observed XRPD pattern may be compared with a calculated XRPD pattern based upon a single crystal structure, if available. Two-dimensional scattering patterns using area detectors can also be used to evaluate PS/PO. If the effects of both PS and PO are determined to be negligible, then the XRPD pattern is representative of the powder average intensity for the sample and prominent peaks may be identified as “Representative Peaks.” In general, the more data collected to determine Representative Peaks, the more confident one can be of the classification of those peaks.

[00130] “Characteristic peaks,” to the extent they exist, are a subset of representative peaks and are used to differentiate one crystalline polymorph from another crystalline polymorph (polymorphs being crystalline forms having the same chemical composition). Characteristic peaks are determined by evaluating which representative peaks, if any, are present in one crystalline polymorph of a compound against all other known crystalline polymorphs of that compound to within $\pm 0.2^\circ 2\theta$. Not all crystalline polymorphs of a compound necessarily have at least one characteristic peak.

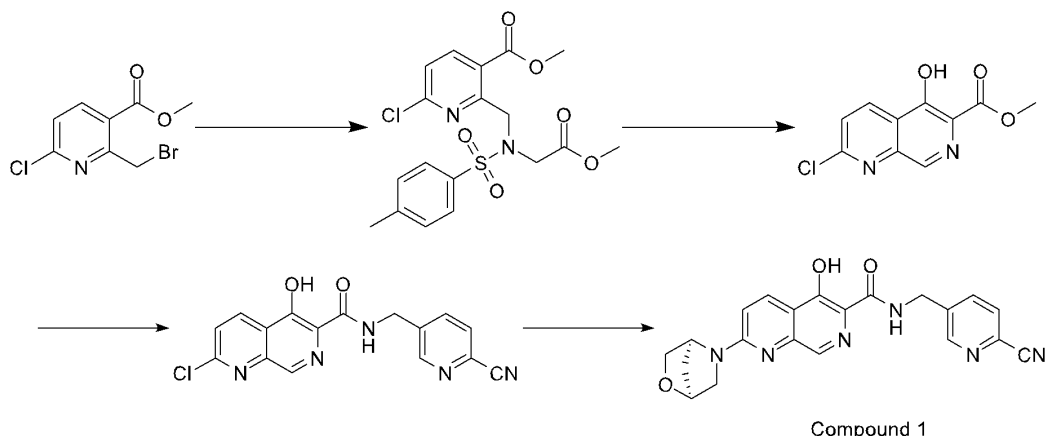
[00131] The term “preferred orientation” as used herein refers to an extreme case of non-random distribution of the crystallites of a solid state form. In XRPD, the ideal sample is homogenous and the crystallites are randomly distributed in the bulk solid. In a truly random sample, each possible reflection from a given set of planes will have an equal number of crystallites contributing to it. However, when the solid state form is in a preferred orientation this is not the case. Accordingly, comparing the intensity between a randomly oriented diffraction pattern and a preferred oriented diffraction pattern can look entirely different. Quantitative analysis depending on intensity ratios are greatly distorted by preferred orientation. Careful sample preparation is important for decreasing the incidence of a preferred orientation.

[00132] The term “substantially the same,” as used herein to reference a figure is intended to mean that the figure is considered representative of the type and kind of characteristic data that is obtained by a skilled artisan in view of deviations acceptable in the art. Such deviations may be caused by factors related to sample size, sample preparation, particular instrument used, operation conditions, and other experimental condition variations known in the art. For example, one skilled in the art can appreciate that the endotherm onset and peak temperatures as measured by differential scanning calorimetry (DSC) may vary significantly from experiment to experiment. For example, one skilled in the art can readily identify whether two X-ray diffraction patterns or two DSC thermograms are substantially the same. In some embodiments, when characteristic peaks of two X-ray diffraction patterns do not vary more than $\pm 0.2^\circ 2\theta$, it is deemed that the X-ray diffraction patterns are substantially the same.

[00133] As used herein, salts of Compound 1 include compounds where the corresponding acid is in an ionized, non-ionized, associated, or unassociated form. In some embodiments, the corresponding acid is in an ionized and/or associated forms. In some embodiments, the corresponding acid is in a nonionized and/or unassociated forms. Salts of Compound 1 also include mono-acid, di-acid, etc. forms of the salts.

EXAMPLES

[00134] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Preparation of Compound 1

[00135] To a solution of methyl 2-(bromomethyl)-6-chloronicotinate (5 g, 18.9 mmol) and methyl 2-(p-tolylsulfonylamino)acetate (4.6 g, 18.9 mmol) in DMF (50 mL) was added K_2CO_3 (5.02 g, 47.4 mmol) and NaI (0.28 g, 1.86 mmol). The mixture was stirred at 50°C for 12 h under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with H_2O (80 mL $\times$ 3). The organic layer was washed with brine (80 mL $\times$ 3), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatograph to afford methyl 6-chloro-2-(((N-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)nicotinate (6 g, crude) as a yellow solid.

[00136] To a solution of methyl 6-chloro-2-(((N-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)nicotinate (6 g, 14 mmol) in DMSO (60 mL) was added K_2CO_3 (11.6 g, 84.3 mmol). The mixture was stirred at 50°C for 4 h under N_2 atmosphere. The mixture was diluted with H_2O (60 mL) and the aqueous was adjusted pH to 6 with 1 M HCl. The precipitated solid was filtered and dried to afford methyl 2-chloro-5-hydroxy-1,7-naphthyridine-6-carboxylate (1.5 g, 45% yield) as an off-white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.86 (s, 1H), 8.72 (d, J = 0.9 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H).

[00137] To a solution of methyl 2-chloro-5-hydroxy-1,7-naphthyridine-6-carboxylate (1 g, 4.19 mmol) in MeOH (30 mL) were added 5-(aminomethyl)pyridine-2-carbonitrile (0.84 g, 6.29 mmol), TEA (2.91 mL, 20.95 mmol), and the reaction was stirred at 75°C overnight. The reaction mixture was filtered through normal funnel and the filter cake was washed with 10 mL MeOH, dried in vacuum to afford 2-chloro-N-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide (1.1 g, 3.24 mmol, 77% yield) as a yellow solid.

[00138] To a solution of 2-chloro-N-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide (8 g, 23.55 mmol, 1.0 eq) in DMSO (80 mL) were added (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (4.7 g, 36.66 mmol, 1.5 eq) and TEA (13 mL, 93.53 mmol, 4.0 eq) and the reaction was stirred at 100 °C for 1 hr. The reaction mixture was cooled and poured into water (160 mL). The mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with sat. NaCl solution (80 mL $\times$ 3), dried over Na_2SO_4 , and concentrated. A large amount of

yellow solid precipitated out when the volume of solution was concentrated to about 40 mL. The mixture was filtered and the filter cake was washed with EA (40 mL), and dried to afford Compound 1. LCMS: Retention time: 1.021 min, (M+H) = 403.2. ¹H NMR: (400 MHz, DMSO-*d*₆) δ 13.35 (s, 1H), 9.75 (t, *J* = 6.3 Hz, 1H), 8.76 (s, 1H), 8.42 (s, 1H), 8.25 (d, 1H), 8.02-8.00 (m, 2H), 7.19-6.98 (m, 1H), 5.19-5.17 (m, 1H), 4.75 (s, 1H), 4.63 (d, *J* = 6.4 Hz, 2H), 3.85 (d, *J* = 6.6 Hz, 1H), 3.74-3.72 (m, 1H), 3.62-3.60 (m, 1H), 3.31-3.30 (m, 1H), 2.01-1.92 (m, 2H).

Example 2: PHD2 Enzymatic Assay Procedure

[00139] Compound DMSO stock preparation: Compound 1 was reconstituted into 20mM stock by DMSO.

Compound storage: Compound 1 in DMSO was stored at RT in a desiccator for short-term storage (up to 3 months).

[00140] Working stock preparation:

- Reference Roxadustat (FG-4592) was 3-fold serial diluted from 400 μM for 10 doses in DMSO.
- The compounds were 3-fold serial diluted from 400 μM for 10 doses in DMSO.
- Prepared 200× positive control (400 μM, FG-4592) and 200× vehicle control (100% DMSO).
- Centrifuged compound plates at 1000rpm for 1min.

[00141] Compound screening:

- Transferred 40 nL compound dilutions into each well of assay plates using Echo 655;
- Sealed the assay plate and centrifuge compound plates at 1000rpm for 1min.
- Prepared and add 4 μL of the 2x PHD2 enzyme working solution to individual well of the assay plate.
- Sealed the assay plate and centrifuge compound plates at 1000rpm for 1min. Incubate plate at RT for 30min.
- Prepared and add 4 μL 2x PHD2 substrate working solution to each well of the assay plate.
- Prepared and added 4 μL 4x stop solution to the each well of the assay plate.
- Prepared 4x detection solution with AlphaScreen Streptavidin Donor beads, AlphaScreen Protein A Acceptor beads and Hydroxy-HIF-1α (Pro564) (D43B5) XP® Rabbit mAb.
- Added 4 μL 4x detection solution to the each well of the assay plate. repeat at step d.
- Read Alphascreen signal on Envision HTS plate reader.

[00142] Data analysis

ALPHASCREEN signal (ALP_{compd}) is calculated for each well

%Inhibition is calculated as follow:

$$\%Inhibition = \left[1 - \frac{ALP_{compound} - \overline{ALP}_{positive}}{\overline{ALP}_{vehicle} - \overline{ALP}_{positive}} \right] \times 100$$

$\overline{ALP}_{positive}$: The average ALP for the positive controls across the plate.

$\overline{ALP}_{\text{vehicle}}$: The average ALP for the negative controls across the plate.

Calculate IC_{50} and Plot effect-dose curve of compounds:

Calculated IC_{50} by fitting %inhibition values and log of compound concentrations to nonlinear regression (dose response – variable slope) with Graphpad 8.0.

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log}IC_{50} - X) * \text{HillSlope}))}$$

X: log of Inhibitor concentration; Y: % Inhibition.

Example 3: EPO Elisa Assay

[00143] The compounds powder were dissolved in 100% DMSO. The compounds stock solution were kept in nitrogen cabinet.

Experimental Methods

[00144] Cell seeding: Added 100 μ L cell suspension contain 20k Hep3B cell per well.

Preparation of compound concentration gradient: Compound 1 at top dose of 100 μ M, 3-fold dilution, 8 doses, singlet or duplicate. Prepare a solution of 200x the final concentration in a 96-well plate, dilute the compound by 200/3x with cell culture medium, and then pipette 50 μ L to wells. Add 50 μ L of culture medium containing DMSO to the minimum control well to make the final concentration contain 5% DMSO, and add 50 μ L of the highest concentration of reference compound to the maximum control well, and incubate at 37 $^{\circ}$ C for 24h.

- Washed the reaction plate twice with 400 μ L of 1x Wash Buffer per well.
- Added 100 μ L of the diluted standard (including standard blank control) to the appropriate wells.
- Added 50 μ L of sample and 50 μ L of Sample Diluent to the sample well.
- Added 50 μ L 1x Biotin Conjugated Antibody to all wells and incubate for 1 hour at room temperature.
- Washed the reaction plate 6 times with 400 μ L 1x Wash Buffer per well.
- Added 100 μ L 1x Streptavidin-HRP to each well. Incubate at room temperature for 15 minutes.
- Washed the reaction plate 6 times with 400 μ L 1x Wash Buffer per well.
- Added 100 μ L TMB Substrate Solution to each well. Incubate at room temperature for 10 minutes.
- Added 100 μ L Stop Solution to each well.
- Read OD450 with EnSight.

Data Analysis

[00145] Using GraphPad Prism 5.

$$\% \text{Act.} = (\text{Compound signal} - \text{Min signal}) / (\text{Max signal} - \text{Min signal}) * 100.$$

[00146] Max signal was obtained from the maximum control wells.

Min signal was obtained from the minimum control wells.

[00147] Take the log value of the concentration as the X-axis, and the percentage inhibition rate on the Y-axis. Use the analysis software GraphPad Prism 5 log(inhibitor) vs. response -Variable slope to fit the dose-response curve to obtain the EC₅₀ value of each compound.

[00148] The data from examples 2 and 3 are shown below.

Ex.	PHD2	HEP3B EPO assay EC50
Compound 1	A	B

PHD2 (nM): 0<A≤5; 5<B≤20; 20<C≤100; 100<D≤1,000; 1,000<E<100,000

HEP3B EPO assay (EC₅₀, nM): 0<A≤2,500; 2,500<B≤5,000; 5,000<C≤7500; 7,500<D≤10,000; 10,000<E≤100,000

Example 4: Preparation of Compound 1 Freebase Type A

[00149] Approximate 30 mg of the Compound 1 was equilibrated in 0.5 mL of ethanol, methylethylketone, acetone, ethyl acetate, acetonitrile, or dichloromethane at 25°C for 11 days with a stirring bar on a magnetic stirring plate at a rate of 500 rpm. The solid precipitate was collected for XRPD, DSC, TGA and ¹H-NMR.

[00150] The XRPD pattern of Compound 1 freebase Type A is shown in FIG. 1. Major peaks and their related intensities in the XRPD pattern are shown in Table 1. Compound 1 freebase Type A is an anhydrate.

[00151] DSC and TGA results shown in FIG. 2 indicates Compound 1 freebase Type A has an onset of endothermal event at around 215°C.

Example 5: Alternative preparation of Compound 1 Freebase Type A

[00152] Approximate 30mg of the Compound 1 was equilibrated in 0.45-1.0mL of acetone, acetonitrile, dichloromethane, tetrahydrofuran, or isopropanol under a temperature cycle between 5°C to 50°C at a heating/cooling rate of 0.1°C /min for about 10 cycles. The equilibration was executed with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. Residual solids were collected by centrifugation at 14,000 rpm and investigated by XRPD. The XRPD pattern of solid was same as that in Table 1 and confirmed to be Compound 1 Freebase Type A.

Example 6: Alternative preparation of Compound 1 Freebase Type A

[00153] Approximate 30 mg of the Compound 1 was equilibrated in 0.45-1.0mL of Acetone, acetonitrile, tetrahydrofuran, dichloromethane, or isopropanol) at 50°C. The system was cooled to 5°C at the rate of 0.1°C/min. The equilibration was executed with a stirring bar on a magnetic stirring plate at a rate of 400 rpm. Residual solids were collected by centrifugation at 14,000 rpm. The solid precipitate was collected for XRPD test. The XRPD pattern of solid was same as that in Table 1 and confirmed to be Compound 1 Freebase Type A.

Example 7: Alternative preparation of Compound 1 Freebase Type A

[00154] Approximate 30mg of the Compound 1 was weighed into 2-ml vials, and then 1ml tetrahydrofuran, Dimethylformamide, or 1,4-Dioxane were added, stirring with a stirring bar on a magnetic stirring plate at a rate of 500 rpm for 30 min at 50°C, and then filtered. A certain amount of n-heptane was added stepwise until a large amount of solids precipitated out. All the samples were kept stirring at 25°C at 500 rpm/min. Residual solids were collected by centrifugation at 14,000 rpm and investigated by XRPD. The XRPD pattern of solid was same as that in Table 1 and confirmed to be Compound 1 Freebase Type A.

Example 8: Alternative preparation of Compound 1 Freebase Type A

[00155] About 30 mg of the Compound 1 was weighed into a 2.0-mL glass vial and then 1.0 mL tetrahydrofuran or dichloromethane were added to get a clear solution. The vial was then covered with aluminum foil with pinhole and placed in the fume hood until the liquid totally evaporated. Or the vial was blow dried with nitrogen until the liquid totally evaporated. Then the obtained solids from system were characterized by XRPD. The XRPD pattern of solid was same as that in Table 1 and confirmed to be Compound 1 Freebase Type A.

Example 9: Preparation of Compound 1 HCl salt Type A

[00156] Approximate 25 mg of Compound 1 Freebase Type A were weighed in 2mL glass vials and then 300 µL of methylethylketone was added. The vials were placed on the hot-plate and stirred with the speed of 300 r/min at 50°C. Hydrochloric acid of 1.1 equivalent was diluted in methylethylketone and slowly charged into the solution of compound 1. After stirring for 2 hours, the systems were cooled to 25°C and kept stirring at 25°C for 4 days. The obtained suspensions were centrifuged (8000 r/min, 10 mins) and residual solids were vacuum dried 30°C. The solids were characterized for XRPD, DSC, and TGA.

[00157] The XRPD pattern of Compound 1 HCl salt Type A is shown in **FIG. 3**. Major peaks and their related intensities in the XRPD pattern are shown in Table 2. DSC and TGA results are shown in **FIG. 4**.

Example 10: Preparation of Compound 1 HCl salt Type B

[00158] Approximate 25 mg of Compound 1 Freebase Type A were weighed in 2mL glass vials and then 300 µL of ethyl acetate were added. The vials were placed on the hot-plate and stirred with the speed of 300 r/min at 50°C. Hydrochloric acid of 1.1 equivalent was diluted in ethyl acetate, and slowly added into the solution of compound 1. After stirring for 2 hours, the systems were cooled to 25°C and kept stirring at 25°C for 4 days. The obtained suspensions were centrifuged (8000 r/min, 10 mins) and residual solids were vacuum dried 30°C. The solids were characterized for XRPD, DSC, TGA, and ¹H-NMR.

[00159] The XRPD pattern of Compound 1 HCl salt Type B is shown in **FIG. 5**. Major peaks and their related intensities in the XRPD pattern are shown in Table 3. DSC and TGA results are shown in **FIG. 6**.

Example 11: Preparation of Compound 1 Tosylate salt Type A

[00160] Approximate 25 mg of Compound 1 Freebase Type A were weighed in 2mL glass vials and then 300 μ L of methylethylketone were added. The vials were placed on the hot-plate and stirred with the speed of 300 r/min at 50 $^{\circ}$ C. P-toluenesulfonic acid of 1.1 equivalent was pre-dissolved in methylethylketone, and slowly added into the solution of compound 1. After stirring for 2 hours, the systems were cooled to 25 $^{\circ}$ C and kept stirring at 25 $^{\circ}$ C for 4 days. The obtained suspensions were centrifuged (8000 r/min, 10 mins) and residual solids were vacuum dried 30 $^{\circ}$ C. The solids were characterized for XRPD, DSC, TGA, and 1 H-NMR.

[00161] The XRPD pattern of Compound 1 Tosylate salt Type A is shown in **FIG. 7**. Major peaks and their related intensities in the XRPD pattern are shown in Table 4. DSC and TGA results are shown in **FIG. 8**. 1 H-NMR shows the ratio of Compound 1: p-toluenesulfonic acid is about 1:1.02.

Analytical methods**Differential Scanning Calorimetry (DSC)**

[00162] Accurate amount of sample (0.5 ~ 1.5 mg) was added into a standard aluminum TA-Instrument sample pan/Tzero aluminum pan. Closed the sample pan with the standard lid / Tzero lid of pinhole and recorded the DSC curve on a TA-Instruments Q2000/Discovery DSC 2500 equipped with a RCS cooling unit.

Nitrogen flow	50 mL/min
Initial temperature	RT
Heating rate	10 $^{\circ}$ C/min
Final temperature	250 $^{\circ}$ C

X-ray Powder Diffractometer (XRPD)

X-ray geometry	Reflection
Detector	LYNXEYE_XE_T (1D mode)
Radiation	Cu/K-Alpha1 ($\lambda=1.5406\text{\AA}$)
X-ray generator power	40kV, 40mA
Open angle	2.5 $^{\circ}$ (max)
Primary beam path slits	Twin_Primary motorized slit: 20.0mm by sample length; Primary Soller slit: 2.5 $^{\circ}$
Secondary beam path slits	Secondary Soller slit: 2.5 $^{\circ}$
Scan mode	Continuous scan
Scan type	Locked coupled

Step size	0.02°
Time per step	0.3 second per step
Scan range	2° to 40°
Sample rotation speed	15 rpm
Sample holder	Flat monocrystalline silicon C79298A3244B249 (sample loading: 10-20mg)

Thermal Gravimetric Analysis (TGA)

[00163] Approximately 2-10 mg sample was put on an open Aluminum pan/ a sealed Aluminum pan. Details of TGA (Discovery TGA 5500 or TGA Q5000) method used in the tests are mentioned below:

Purge Flow	N2
Balance (Protective Gas)	10 mL/min
Sample (Reacting Gas)	25 mL/min
Start temperature	RT (below 35℃)
Heating rate	10 ℃/min
Final temperature	300℃ or abort next segment if weight < 80% (w/w) (The weight loss of the compound is no more than 20% (w/w))

High Performance Liquid Chromatography (HPLC)_Related substance

Instrument	Agilent 1260		
Columns	Waters XSelect CHS C18 (3.5μm, 4.6*150mm, PDS-HPLC-442)		
Column temperature	40℃		
Mobile phase A	0.05% TFA in water (v/v)		
Mobile phase B	0.05% TFA in ACN (v/v)		
Flow rate	1.0 mL/min		
Gradient profile	Time (mins)	A%	B%
	0.00	95	5
	10.00	70	30
	20.00	5	95
	22.00	5	95
	22.10	95	5
	30.00	95	5

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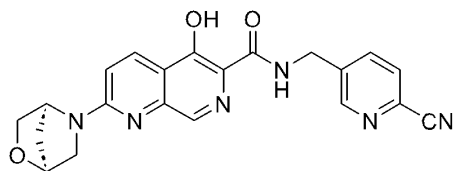
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Run Time	30 min
Injection volume	5 µL (0.4 mg/mL)
Dilution	0.05% TFA in ACN /water (1/1, v/v)

CLAIMS

WHAT IS CLAIMED IS:

1. A solid state form of 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-((6-cyanopyridin-3-yl)methyl)-5-hydroxy-1,7-naphthyridine-6-carboxamide:



(Compound 1) or a pharmaceutically acceptable salt thereof.

2. The solid state form of claim 1, wherein the solid state form is a crystalline form.
3. The solid state form of claim 1 or 2, wherein the solid state form is crystalline Compound 1 as a freebase.
4. The solid state form of claim 3, wherein the solid state form is crystalline Compound 1 Freebase Type A.
5. The solid state form of claim 1 or 2, wherein the solid state form is crystalline Compound 1 as a salt.
6. The solid state form of claim 5, wherein the solid state form is crystalline Compound 1 HCl salt Type A, Compound 1 HCl salt Type B, or Compound 1 Tosylate salt Type A.
7. The crystalline form of claim 2, wherein the crystalline form is Compound 1 Freebase characterized as having at least one of the following properties:
 - (a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 1** as measured using Cu K α radiation;
 - (b) an X-Ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation;
 - (c) a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **FIG. 2**;
 - (d) a Thermogravimetric Thermal Analysis (TGA) thermogram substantially the same as shown in **FIG. 2**; or
 - (e) combinations thereof.
8. The crystalline form of claim 7, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **FIG. 1** as measured using Cu K α radiation.
9. The crystalline form of claim 7 or 8, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks found in Table 1 as measured using Cu K α radiation.
10. The crystalline form of any one of claims 7-9, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, and $20.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.

11. The crystalline form of any one of claims 7-10, wherein the X-ray powder diffraction (XRPD) pattern further comprises peaks at $14.2 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, and $22.3 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.
12. The crystalline form of any one of claims 7-11, wherein the X-ray powder diffraction (XRPD) pattern further comprises peaks at $22.8 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, and $26.9 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.
13. The crystalline form of any one of claims 7-12, wherein the X-ray powder diffraction (XRPD) pattern further comprises peaks at $18.0 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.
14. The crystalline form of any one of claims 7-9, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with peaks at $8.5 \pm 0.2^\circ 2\theta$, $14.2 \pm 0.2^\circ 2\theta$, $16.2 \pm 0.2^\circ 2\theta$, $18.0 \pm 0.2^\circ 2\theta$, $18.6 \pm 0.2^\circ 2\theta$, $20.3 \pm 0.2^\circ 2\theta$, $22.3 \pm 0.2^\circ 2\theta$, $22.8 \pm 0.2^\circ 2\theta$, $23.9 \pm 0.2^\circ 2\theta$, $25.9 \pm 0.2^\circ 2\theta$, $26.9 \pm 0.2^\circ 2\theta$, $28.1 \pm 0.2^\circ 2\theta$, and $30.6 \pm 0.2^\circ 2\theta$ as measured using Cu K α radiation.
15. The crystalline form of any one of claims 7-14, wherein the crystalline form is an anhydrate.
16. A pharmaceutical composition comprising a therapeutically effective amount of a crystalline form of any one of claims 2-15 and a pharmaceutically acceptable excipient.
17. A method of treating a disease or disorder in a subject, the method comprising administering to the subject a crystalline form of any one of claims 2-15, or a pharmaceutical composition of claim 16, wherein the disease or disorder is anemia.