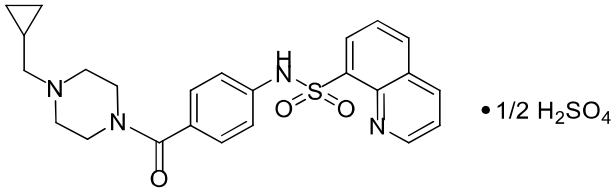
SUMMARY

[0004a] In one aspect, the present disclosure refers to a crystalline form of a compound having the formula:



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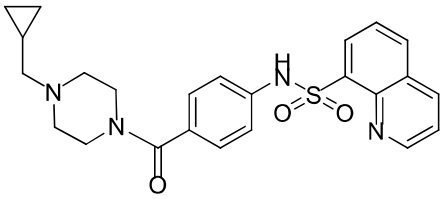
[0004b] In another aspect, the present disclosure refers to a crystalline free base of a compound having the formula:



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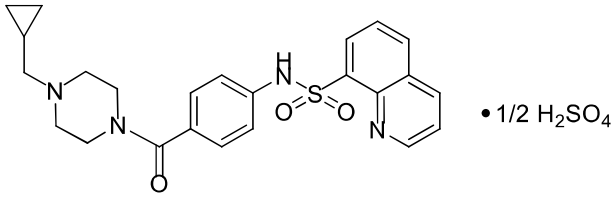
[0004c] In another aspect, the present disclosure refers to an amorphous Form of a hemisulfate salt of a compound having the formula:



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[0004d] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the crystalline Form A, B, C, D, E, F, G, H, I, J, or crystalline free base disclosed herein, or the amorphous Form disclosed herein; and a pharmaceutically acceptable carrier.

[0004e] In a further aspect, the present disclosure refers to a tablet composition comprising the crystalline Form A, B, C, D, E, F, G, H, I, J, or crystalline free base disclosed herein, or the amorphous Form disclosed herein; and a pharmaceutically acceptable carrier.

[0004f] In another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating Pyruvate Kinase Deficiency (PKD) in a subject in need thereof.

[0004g] In yet another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating sickle cell disease (SCD) in a subject in need thereof.

[0004h] In a further aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating thalassemia (such as beta-thalassemia, non-transfusion-dependent thalassemia, and transfusion-dependent thalassemia) in a subject in need thereof.

[0004i] In another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating hemolytic anemia in a subject in need thereof.

[0004j] In yet another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease selected from hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof.

[0004k] In a further aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for regulating 2,3-diphosphoglycerate levels in blood in a subject in need thereof.

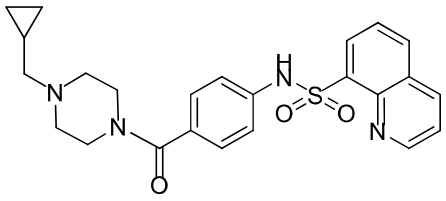
[0004l] In another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for activating wild-type or mutant PKR in red blood cells in a subject in need thereof.

[0004m] In yet another aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the

manufacture of a medicament for increasing the amount of hemoglobin in a subject in need thereof.

[0004n] In a further aspect, the present disclosure refers to a use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for evaluating the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in a subject in need thereof.

[0004o] In another aspect, the present disclosure refers to a method of forming crystalline Form A disclosed herein, the method comprising reacting a compound of Formula **1**:



(**1**)

with H_2SO_4 in an alcoholic solution.

[0004p] In yet another aspect, the present disclosure refers to a composition for use in treating Pyruvate Kinase Deficiency (PKD) in a subject in need thereof; or

for use in treating sickle cell disease (SCD) in a subject in need thereof; or

for use in treating thalassemia (such as beta-thalassemia, non-transfusion-dependent thalassemia, and transfusion-dependent thalassemia) in a subject in need thereof; or

for use in treating hemolytic anemia in a subject in need thereof; or

for use in treating a disease selected from hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof; or

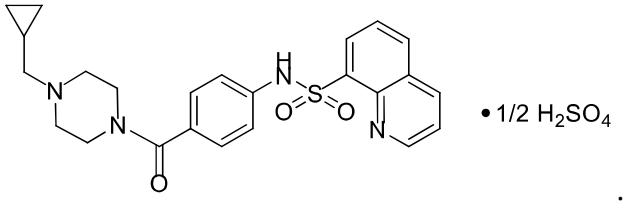
for use in regulating 2,3-diphosphoglycerate levels in blood in a subject in need thereof; or

for use in activating wild-type or mutant PKR in red blood cells in a subject in need thereof; or

for use in increasing the amount of hemoglobin in a subject in need thereof evaluating the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in a subject in need thereof;

wherein the composition comprises the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base disclosed herein, or the amorphous Form disclosed herein, or the pharmaceutical composition disclosed herein.

[0005] Provided herein are amorphous and crystalline hemisulfate salt forms of a compound having the formula.



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[0006] Also provided herein are pharmaceutical compositions comprising the amorphous and crystalline hemisulfate salt forms, methods for their manufacture, and uses thereof for treating conditions associated with pyruvate kinase such as e.g., PKD.

BRIEF DESCRIPTION OF THE FIGURES

[0007] **FIG. 1** depicts an X-ray powder diffraction pattern (XRPD) for crystalline hemisulfate salt Form A.

[0008] **FIG. 2** depicts the combined thermogravimetric analysis (TGA) thermogram and differential scanning calorimetry (DSC) thermogram for crystalline hemisulfate salt Form A.

[0009] **FIG. 3** depicts the differential scanning calorimetry (DSC) thermogram for crystalline hemisulfate salt Form A

[0010] **FIG. 4** depicts the dynamic vapor sorption (DVS) isotherm for crystalline hemisulfate salt Form A.

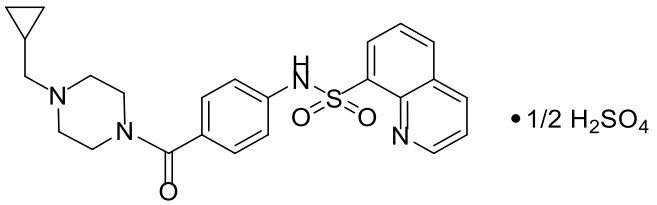
[0011] **FIG. 5 (i)** depicts X-ray powder diffraction pattern (XRPD) overlay for crystalline hemisulfate salt Form A and after exposure to 11%, 48%, and 75% relative humidity and 40 °C for two weeks. The XRPD remained unchanged aftger two-week test under these three humidity conditions. FIG. 5 (ii) depicts XRPD overlay for crystalline hemisulfate salt Form A and after exposure to phosphorus pentoxide (P_2O_5) granules at room temperature and 50°C for one week, as well as ambient temperature in a vial for 24hrs. It was observed that there was no change in XRPD pattern at room temperature after one week, but some peaks were slightly shifted at 50°C. However, these peaks shifted back to original positions after exposure to ambient for 24 hrs, indicating these changes were reversible.

[0012] **FIG. 6** depicts an X-ray powder diffraction pattern (XRPD) for crystalline hemisulfate salt Form B obtained in MeOH:EtOH (3:7) .

[0013] **FIG. 7(i)** depicts the combined thermogravimetric analysis (TGA) thermogram and differential scanning calorimetry (DSC) thermogram for crystalline hemisulfate salt Form

Listing of Claims:

1. A crystalline form of a compound having the formula:



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2. The crystalline form of Claim 1, wherein the compound is a solvate.

3. The crystalline form of Claim 2, wherein the compound is a hydrate.

4. The crystalline form of Claim 3, wherein the compound is a sesquihydrate.

5. The crystalline form of Claim 1, wherein the compound is anhydrous.

6. The crystalline form of Claim 2, wherein the compound is an ethanol solvate.

7. The crystalline form of Claim 4, wherein the crystalline form is crystalline Form A characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 9.9°, 15.8°, and 22.6°.

8. The crystalline Form A of Claim 7, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 9.9°, 15.8°, and 22.6°; and at least one, at least two, or at least three additional x-ray powder diffraction peak at 2Θ angles (± 0.2°) selected from 15.0°, 17.1°, 21.3°, and 21.9°.

9. The crystalline Form A of Claim 8, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 9.9°, 11.4°, 15.0°, 15.3°, 15.8°, 17.1°, 17.7°, 21.3°, 21.9°, 22.6°, and 23.5°.

10. The crystalline Form A of Claim 9, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 4.9°, 9.9°, 11.0°, 11.4°, 11.7°, 12.3°, 12.8°, 13.6°, 13.9°, 14.2°, 15.0°, 15.3°, 15.8°, 17.1°, 17.4°, 17.7°, 18.8°, 19.1°, 19.8°, 21.3°, 21.9°, 22.6°, 23.0°, 23.2°, 23.5°, 23.8°, 24.1°, 24.5°, 25.3°, 25.6°, 26.1°, 27.1°, 28.1°, and 29.8°.

11. The crystalline form of Claim 6, wherein the crystalline form is crystalline Form B characterized by at least three, at least four, at least five, or at least six x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 9.9°, 10.6°, 12.7°, 15.7°, 16.9°, 22.0°, and 22.5°.

12. The crystalline form of Claim 1, wherein the crystalline form is crystalline Form C characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 6.9°, 10.4°, and 12.0°.

13. The crystalline form of Claim 5, wherein the crystalline form is Crystalline Form D characterized by at least three, at least four, at least five, or at least six x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 5.8°, 10.0°, 10.2°, 19.3°, 22.9°, 23.3°, and 25.2° .

14. The crystalline form of Claim 1, wherein the crystalline form is Crystalline Form E characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 4.6°, 9.0°, 13.5°, and 22.5°.

15. The crystalline form of Claim 1, wherein the crystalline form is Crystalline Form F characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 5.0°, 9.9°, and 14.7°.

16. The crystalline form of Claim 1, wherein the crystalline form is Crystalline Form G characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 4.7°, 9.4°, and 14.1°.

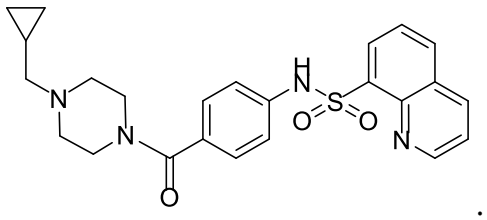
17. The crystalline form of Claim 1, wherein the crystalline form is Crystalline Form H is characterized by at least three, at least four, at least five, or at least six x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 4.6°, 7.4°, 9.2°, 11.1°, 13.5°, 14.9°, and 22.3° .

18. The crystalline form of Claim 6, wherein the crystalline form is Crystalline Form I characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 6.7°, 9.5°, and 19.7°.

19. The crystalline Form I of Claim 17, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) 6.7°, 9.5°, and 19.7°; and at least one, at least two, or at least three additional x-ray powder diffraction peak at 2Θ angles (± 0.2°) selected from 9.9°, 12.6°, 15.8°, 21.9°, and 22.3°.

20. The crystalline form of Claim 1, wherein the crystalline form is Crystalline Form J characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 12.4°, 13.2°, 14.6°, 20.4°, and 23.7°.

21. A crystalline free base of a compound having the formula:



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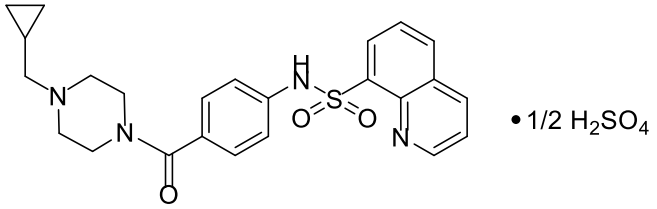
22. The crystalline free base of Claim 21, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2Θ angles (± 0.2°) selected from 6.9°, 13.5°, 19.8°, and 20.3°.

23. The crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 22, wherein the compound is at least 60% a single crystalline form, at least 70% a single crystalline form, at least 80% a single crystalline form, at least 90% a single crystalline form, at least 95% a single crystalline form, or at least 99% a single crystalline form by weight.

24. The crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 23, wherein the compound form is substantially free of amorphous forms of Formula (I).

25. An amorphous Form of a hemisulfate salt of a compound having the formula:



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26. The amorphous Form of Claim 25, wherein the compound is substantially free of crystalline forms of Formula (I).

27. A pharmaceutical composition comprising the crystalline Form A, B, C, D, E, F, G, H, I, J, or crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26; and a pharmaceutically acceptable carrier.

28. A tablet composition comprising the crystalline Form A, B, C, D, E, F, G, H, I, J, or crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26; and a pharmaceutically acceptable carrier.

29. The composition of Claim 27 or tablet composition of Claim 28, wherein the carrier is selected from one or more of microcrystalline cellulose, mannitol, Croscarmellose Sodium, and Sodium Stearyl Fumarate.

30. The tablet composition of Claim 28 or Claim 29, wherein the composition comprises about 5.7 to about 5.9 mg, about 23.4 to about 23.6 mg, or about 58.7 to about 58.9 mg crystalline Form A; 62% w/w (±2%) microcrystalline cellulose; 23% w/w (±2%) mannitol, 3% w/w (±2%) croscarmellose sodium, and 2% w/w (±2%) stearyl fumarate.

31. The composition of any one of Claims 28 to 30, wherein the crystalline Form is Form A.

32. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for treating Pyruvate Kinase Deficiency (PKD) in a subject in need thereof.

33. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for treating sickle cell disease (SCD) in a subject in need thereof.

34. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for treating thalassemia (such as beta-thalassemia, non-transfusion-dependent thalassemia, and transfusion-dependent thalassemia) in a subject in need thereof.

35. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for treating hemolytic anemia in a subject in need thereof.

36. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for treating a disease selected from hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof.

37. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for regulating 2,3-diphosphoglycerate levels in blood in a subject in need thereof.

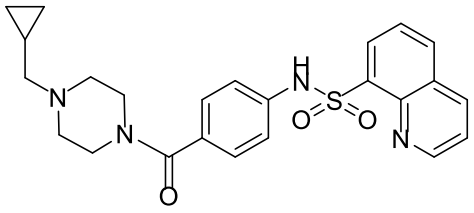
38. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for activating wild-type or mutant PKR in red blood cells in a subject in need thereof.

39. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for increasing the amount of hemoglobin in a subject in need thereof.

40. Use of the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31, in the manufacture of a medicament for evaluating the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in a subject in need thereof.

41. The use of any one of claims 32 to 40, wherein the crystalline form is Form A.

42. A method of forming crystalline Form A of any one of Claims 7-10, 23, and 24, the method comprising reacting a compound of Formula **1**:



(**1**)

with H_2SO_4 in an alcoholic solution.

43. A composition for use in treating Pyruvate Kinase Deficiency (PKD) in a subject in need thereof; or

for use in treating sickle cell disease (SCD) in a subject in need thereof; or

for use in treating thalassemia (such as beta-thalassemia, non-transfusion-dependent thalassemia, and transfusion-dependent thalassemia) in a subject in need thereof; or

for use in treating hemolytic anemia in a subject in need thereof; or

for use in treating a disease selected from hereditary spherocytosis, hereditary elliptocytosis, abetalipoproteinemia, Bassen-Kornzweig syndrome, and paroxysmal nocturnal hemoglobinuria in a subject in need thereof; or

for use in regulating 2,3-diphosphoglycerate levels in blood in a subject in need thereof; or

for use in activating wild-type or mutant PKR in red blood cells in a subject in need thereof; or

for use in increasing the amount of hemoglobin in a subject in need thereof evaluating the level of 2,3-diphosphoglycerate (2,3-DPG), the level of adenosine triphosphate (ATP), or the activity of PKR in a subject in need thereof;

wherein the composition comprises the crystalline Form A, B, C, D, E, F, G, H, I, J, or the crystalline free base of any one of Claims 1 to 24, or the amorphous Form of Claim 25 or 26, or the pharmaceutical composition of any one of Claims 27 to 31.