SUMMARY

[0005] The present disclosure fulfills these needs and others by providing crystalline forms of Compound A, salts, and solvates. The present disclosure also provides an amorphous form of Compound A. The present disclosure also provides pharmaceutical compositions comprising amorphous or one or more crystalline forms of Compound A. The disclosure also provides processes for making the amorphous and crystalline solid forms and methods for using them to treat, and prevent HIF-associated disorders including conditions involving anemia, ischemia, and hypoxia.

[0005a] In one aspect, there is provided a pharmaceutical composition comprising crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (Compound A Form A), wherein at least about 85% of Compound A is in Form A.

[0006] Thus, one example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (Compound A Form A) characterized by an X-ray powder diffractogram comprising the following peaks: 8.5, 16.2, and 27.4 °2θ ± 0.2 °2θ.

[0007] Another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid hemihydrate (Compound A Form B) characterized by an X-ray powder diffractogram comprising the following peaks: 4.2, 8.3, and 16.6 °2θ ± 0.2 °2θ.

[0008] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid hexafluoropropan-2-ol solvate (Compound A Form C) characterized by an X-ray powder diffractogram comprising the following peaks: 4.5, 13.7, and 16.4 °2θ ± 0.2 °2θ.

[0009] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid DMSO:water solvate (Compound A Form D) characterized by an X-ray powder diffractogram comprising the following peaks: 8.4, 8.5, and 16.8 °2θ ± 0.2 °2θ.

[0010] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid sodium salt (Compound A sodium salt) characterized by an X-ray powder diffractogram comprising the following peaks: 5.3, 16.0, and 21.6 °2θ ± 0.2 °2θ.

[0011] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid L-arginine salt (Compound A L-arginine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 20.8, 21.8, and 25.4 °2θ ± 0.2 °2θ.

[0012] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid L-lysine salt (Compound A L-lysine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 19.8, 20.7, and 21.2 °2θ ± 0.2 °2θ.

[0013] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid ethanolamine salt (Compound A ethanolamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 21.8, 22.7, and 27.1 °2θ ± 0.2 °2θ.

[0014] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid diethanolamine salt (Compound A diethanolamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 16.9, 23.7, and 25.0 °2θ ± 0.2 °2θ.

[0015] Yet another example provided is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid tromethamine salt (Compound A tromethamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 10.1, 14.2, and 21.1 °2θ ± 0.2 °2θ.

[0016] Yet another example provided is amorphous [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (amorphous Compound A).

[0017] Yet another example provided is substantially amorphous [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid potassium salt (Compound A potassium salt).

[0018] Still another example provided is directed to a pharmaceutical composition comprising a crystalline or amorphous form of Compound A, or a salt thereof, and a pharmaceutically acceptable excipient.

[0019] Additionally, the disclosure provides in one example a method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF). The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0020] Also provided is a method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO), comprising administering to a patient in need thereof, a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0021] Also provided is a method for treating, pretreating, or delaying onset or progression of anemia, comprising administering to a patient in need thereof, a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0022] Also provided is a method of inhibiting the activity of a HIF hydroxylase enzyme, the method comprising bringing into contact the HIF hydroxylase enzyme and a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt,

Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0022a] In another aspect, there is provided use of a pharmaceutical composition as provided herein in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

[0022b] In another aspect, there is provided use of a pharmaceutical composition as provided herein in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO).

[0022c] In another aspect, there is provided use of a pharmaceutical composition as provided herein in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1** is an X-ray powder diffraction pattern of Compound A Form A.

[0024] **FIG. 2** is a differential scanning calorimetry (DSC) curve of Compound A Form A.

[0025] **FIG. 3** is an X-ray powder diffraction pattern of Compound A Form B (bottom) plotted with an X-ray powder diffraction pattern of Compound A Form A (top).

[0026] **FIG. 4** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A Form B.

[0027] **FIG. 5** is an X-ray powder diffraction pattern of Compound A Form C (bottom) plotted with an X-ray powder diffraction pattern of Compound A Form A (top).

[0028] **FIG. 6** is a differential scanning calorimetry (DSC) curve (top) and a thermogravimetric analysis (TGA) (bottom) of Compound A Form C.

[0029] **FIG. 7** is an X-ray powder diffraction pattern of Compound A Form D.

[0030] **FIG. 8** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A Form D.

[0031] **FIG. 9** is an X-ray powder diffraction pattern of Compound A sodium salt as isolated (bottom) and at 40 °C/75% RH (top).

[0032] **FIG. 10** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A sodium salt.

[0033] **FIG. 11** is an X-ray powder diffraction pattern of Compound A L-arginine salt as isolated (bottom) and at 40 °C/75% RH (top).

[0034] **FIG. 12** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A L-arginine salt.

[0035] **FIG. 13** is an X-ray powder diffraction pattern of Compound A L-lysine salt as isolated (bottom) and at 40 °C/75% RH (top).

What is claimed is:

1. A pharmaceutical composition comprising crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (Compound A Form A), wherein at least about 85% of Compound A is in Form A.

2. The pharmaceutical composition of claim 1, wherein at least about 90% of Compound A is in Form A.

3. The pharmaceutical composition of claim 1, wherein at least about 95% of Compound A is in Form A.

4. The pharmaceutical composition of claim 1, wherein at least about 99% of Compound A is in Form A.

5. The pharmaceutical composition of claim 1, wherein at least about 99.5% of Compound A is in Form A.

6. The pharmaceutical composition of claim 1, wherein at least about 99.9% of Compound A is in Form A.

7. The pharmaceutical composition of claim 1, wherein at least about 99.99% of Compound A is in Form A.

8. The pharmaceutical composition of claim 1, wherein the Compound A Form A is characterized by a differential scanning calorimetry (DSC) curve that comprise an endotherm at about 223°C.

9. The pharmaceutical composition of claim 8, wherein the DSC curve is substantially as shown in Figure 2.

10. The pharmaceutical composition of claim 1, wherein the Compound A Form A is characterized by an X-ray powder diffractogram comprising the following peaks: at 8.5, 12.8, 16.2, 21.6, 22.9 and 27.4 °2θ ± 0.2 °2θ.

11. The pharmaceutical composition of claim 1, wherein the diffractogram is substantially as shown in Figure 1.

12. The pharmaceutical composition of claim 1, for use in therapy.

13. Use of a pharmaceutical composition of claim 1 in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

14. The use of claim 13, wherein the condition mediated at least in part by HIF is tissue damage associated with ischemia or hypoxia.

15. The use of claim 14, wherein the ischemia is associated with an acute event selected from the group consisting of myocardial infarction, pulmonary embolism, intestinal infarction, chronic kidney failure, ischemic stroke, and renal ischemic-reperfusion injury.

16. The use of claim 14, wherein the ischemia is associated with a chronic event selected from the group consisting of cardiac cirrhosis, transient ischemic attack, macular degeneration, peripheral artery disease, and congestive heart failure.

17. Use of a pharmaceutical composition of claim 1 in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO).

18. Use of a pharmaceutical composition of claim 1 in the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.

19. The use of claim 13, 17 or 18, wherein the compound used in the pharmaceutical composition is Compound A Form A.

20. The use of claim 13, 17 or 18, wherein at least about 85% of the compound used in the pharmaceutical composition is Compound A Form A.

21. The use of claim 13, 17 or 18, wherein at least about 90% of the compound used in the pharmaceutical composition is Compound A Form A.

22. The use of claim 13, 1 7 or 18, wherein at least about 95% of the compound used in the pharmaceutical composition is Compound A Form A.

23. The use of claim 13, 17 or 18, wherein at least about 99% of the compound used in the pharmaceutical composition is Compound A Form A.

24. The use of claim 13, 17 or 18, wherein at least about 99.5% of the compound used in the pharmaceutical composition is Compound A Form A.

25. The use of claim 13, 17 or 18, wherein at least about 99.9% of the compound used in the pharmaceutical composition is Compound A Form A.

26. The method of claim 13, 17 or 18, wherein at least about 99.99% of the compound used in the pharmaceutical composition is Compound A Form A.