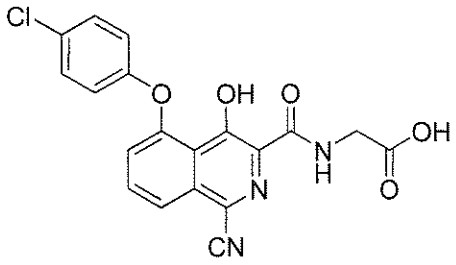
favorable physicochemical properties. Therefore provided herein, are crystalline forms of Compound A, which can be manufactured as a drug product, and can be used to treat, and prevent HIF-associated disorders including conditions involving anemia, ischemia, and hypoxia.

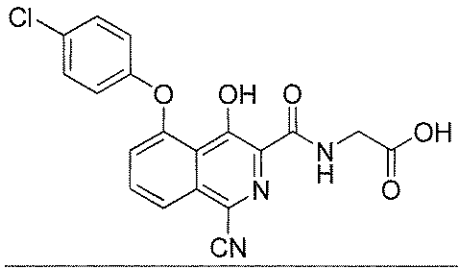
SUMMARY

[0005] The present disclosure relates to crystalline forms of Compound A and methods for preparing crystalline forms.

[0005a] In an aspect, there is provided a crystalline form of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) having the following structure:

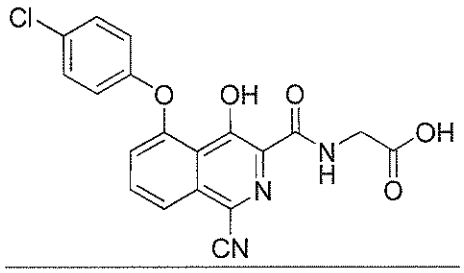


[0005b] In another aspect, there is provided a crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) having the following structure:



(Compound A, Form 2).

[0005c] In a further aspect, there is provided a pharmaceutical composition comprising one or more crystalline forms as defined above of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) having the following structure:



and at least one pharmaceutically acceptable excipient.

[0005d] In a further aspect, there is provided the use of a composition as defined above in the manufacture of a medicament for treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by hypoxia inducible factor (HIF).

[0005e] In another aspect, there is provided the use of a composition as defined above in the manufacture of a medicament for treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by erythropoietin (EPO).

[0005f] In yet a further aspect, there is provided the use of a composition as defined above, in the manufacture of a medicament for treating, pretreating, or delaying onset of anemia.

[0005g] In a further aspect, there is provided a process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprising:

a) heating a mixture comprising a salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) optionally in the presence of a base;

b) cooling the mixture;

c) adding an acid to the mixture; and

d) isolating Form 1 of Compound A.

[0005h] In another aspect, there is provided a process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprising:

a) heating a mixture comprising ethyl 1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carboxylate, glycine and sodium methoxide in methanol;

b) cooling the mixture;

c) adding hydrochloric acid to the mixture; and

d) isolating Form 1 of Compound A.

[0005i] In yet another aspect, there is provided a process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A), comprising heating Compound A in a suitable solvent, cooling the mixture, and isolating Form 1 of Compound A.

[0005j] In another aspect, there is provided a process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprising:

a) heating a mixture comprising a salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A);

b) adding an acid to the mixture and continuing heating;

c) cooling the mixture; and

d) isolating Form 2 of Compound A.

[0005k] In a further aspect, there is provided a process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprising:

a) heating a mixture comprising the sodium salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) in water to about 80-85 °C;

b) adding acetic acid to the mixture and continuing heating at about 80-85 °C;

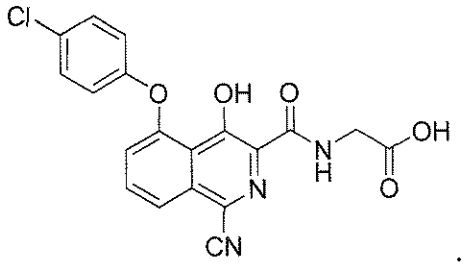
c) cooling the mixture; and

d) isolating Form 2 of Compound A.

[0005l] In a further aspect, there is provided a process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A), comprising heating Compound A in a suitable solvent, and isolating Form 2 of Compound A.

[0005m] In yet another aspect, there is provided a process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A), comprising heating Form 1 of Compound A.

[0006] One ~~aspect~~ embodiment of the present disclosure is directed to a crystalline form of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) having the following structure:



[0007] In one embodiment is provided crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A). In one embodiment, Compound A, Form 1 is characterized by having an X-ray powder diffractogram (XRPD) comprising at least one peak selected from 7.7, 11.2, 13.8, 14.7, 15.3, 15.8, 18.3, 21.1, and 22.2 °2θ ± 0.2 °2θ, as determined on a diffractogram using Cu-Kα radiation. In one embodiment, Form 1 is characterized by having an X-ray powder diffractogram comprising a peak at 18.3 ± 0.2 °2θ. In another embodiment, the diffractogram of Form 1 further comprises a peak at 11.2 ± 0.2 °2θ. In another embodiment, the diffractogram of Form 1 further comprises peaks at 7.7, 13.8, 21.1 and 22.2 °2θ ± 0.2 °2θ. In another embodiment, the diffractogram of Compound A, Form 1, is substantially as shown in Figure 1.

[0008] In one embodiment, Compound A, Form 1 is characterized by a differential scanning calorimetry (DSC) curve that comprises an endotherm at about 251 °C. In another embodiment, the DSC curve of Form 1 further comprises an exotherm at about 210 °C. In another embodiment, the DSC curve of Compound A, Form 1 is substantially as shown in Figure 2.

curve comprising an endotherm at about 249 °C. In another embodiment, the diffractogram of Compound A, Form 2, is substantially as shown in Figure 3; and the DSC curve of Compound A, Form 2 is substantially as shown in Figure 4.

[0013] In another embodimentaspect, the present disclosure is directed to a process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A). In one embodiment, the process comprises:

a) heating a mixture comprising a salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) optionally in the presence of a base;

b) cooling the mixture; and

c) adding an acid to the mixture.

[0014] In one embodiment, the process further comprises isolating Form 1 of Compound A.

[0015] In certain embodiments, the process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprises:

a) heating a mixture comprising ethyl 1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carboxylate, glycine and sodium methoxide in methanol;

b) cooling the mixture; and

c) adding hydrochloric acid to the mixture.

[0016] In one embodiment, the process further comprises isolating Form 1 of Compound A.

[0017] In one embodiment, the process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprises heating Compound A in a suitable solvent. In one embodiment, the process further comprises isolating Form 1 of Compound A.

[0018] In another embodimentaspect, the present disclosure is directed to a process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A). In one embodiment, the process comprises:

a) heating a mixture comprising a salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A);

b) adding an acid to the mixture and continuing heating; and

c) cooling the mixture.

[0019] In one embodiment, the process further comprises isolating Form 2 of Compound A.

[0020] In certain embodiments, the process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprises:

a) heating a mixture comprising the sodium salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) in water to about 80-85 °C;

b) adding acetic acid to the mixture and continuing heating at about 80-85 °C; and

c) cooling the mixture.

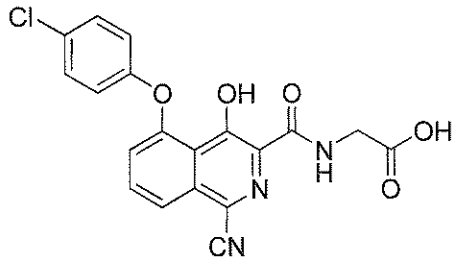
[0021] In one embodiment, the process further comprises isolating Form 2 of Compound A.

[0022] In one embodiment, the process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprises heating Compound A in a suitable solvent. In one embodiment, the process further comprises isolating Form 2 of Compound A.

[0023] In one embodiment, the process for making crystalline Form 2 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A), comprises heating Form 1 of Compound A.

[0024] In one embodiment, the process further comprises isolating Form 2 of Compound A.

[0025] In another embodimentaspect, the present disclosure is directed to a pharmaceutical composition comprising one or more crystalline forms of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) having the following structure:



and at least one pharmaceutically acceptable excipient.

[0026] In one embodiment, the pharmaceutical composition comprises Compound A, Form 1, and at least one pharmaceutically acceptable excipient. In another embodiment,

the pharmaceutical composition comprises Compound A, at least 90% of which is present as Form 1, and at least one pharmaceutically acceptable excipient. In yet another embodiment, the pharmaceutical composition comprises Compound A, at least 95%, 98%, 99%, 99.5%, 99.8%, 99.9%, 99.95%, 99.98% or 99.99% of which is present as Form 1, and at least one pharmaceutically acceptable excipient. In another embodiment, the pharmaceutical composition comprises Compound A, at least 90% to 99.99% of which is present as Form 1, and at least one pharmaceutically acceptable excipient.

[0027] In one embodiment, the pharmaceutical composition comprises Compound A, Form 2, and at least one pharmaceutically acceptable excipient. In another embodiment, the pharmaceutical composition comprises Compound A, at least 90% of which is present as Form 2, and at least one pharmaceutically acceptable excipient. In yet another embodiment, the pharmaceutical composition comprises Compound A, at least 95%, 98%, 99%, 99.5%, 99.8%, 99.9%, 99.95%, 99.98% or 99.99% of which is present as Form 2, and at least one pharmaceutically acceptable excipient. In another embodiment, the pharmaceutical composition comprises Compound A, at least 90% to 99.99% of which is present as Form 2, and at least one pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises Compound A, no more than 10%, 5%, 2%, 1%, 0.5%, 0.2%, 0.1%, 0.05%, 0.02% or 0.01% of which is present as Form 1, and at least one pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises Compound A, no more than 0.1% to10% of which is present as Form 1, and at least one pharmaceutically acceptable excipient.

[0028] In one embodiment, the pharmaceutical composition further comprises an additional therapeutic agent selected from the group consisting of vitamin B12, folic acid, ferrous sulfate, recombinant human erythropoietin, and an erythropoiesis stimulating agent (ESA). In another embodiment, the pharmaceutical composition is formulated for oral delivery. In another embodiment, the pharmaceutical composition is formulated as a tablet or a capsule.

[0029] In another embodimentaspect, the present disclosure is directed to a method of treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by hypoxia inducible factor (HIF), the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising one or more crystalline forms of Compound A. In one embodiment, the condition associated with or mediated at least in part by HIF is tissue damage associated with ischemia or hypoxia. In another embodiment, the ischemia is associated with an ischemic event selected from the

group consisting of myocardial infarction, pulmonary embolism, intestinal infarction, chronic kidney failure, ischemic stroke, renal ischemic-reperfusion injury, cardiac cirrhosis, transient ischemic attack, macular degeneration, peripheral artery disease, and congestive heart failure. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 1. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 2.

[0030] In another embodimentaspect, the present disclosure is directed to a method of treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by erythropoietin (EPO), the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising one or more crystalline forms of Compound A. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 1. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 2.

[0031] In another embodimentaspect, the present disclosure is directed to a method of treating, pretreating, or delaying onset of anemia, the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising one or more crystalline forms of Compound A. In one embodiment, the anemia is associated with a chronic disease or a condition selected from the group consisting of diabetes, cancer, ulcers, kidney disease, immunosuppressive disease, infection, and inflammation. In another embodiment, the anemia is associated with a procedure or treatment selected from the group consisting of radiation therapy, chemotherapy, dialysis, and surgery. In another embodiment, the anemia is associated with blood loss caused by bleeding disorders, trauma, injury, surgery, etc. In yet another embodiment, the anemia is associated with abnormal hemoglobin, abnormal erythrocytes, or defects in iron transport, processing, or utilization. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 1. In one embodiment of this method, the pharmaceutical composition comprises Compound A, Form 2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **Figure 1** is an XRPD pattern of crystalline Form 1, Compound A.

[0033] **Figure 2** is a DSC pattern of crystalline Form 1, Compound A.

[0034] **Figure 3** is an XRPD pattern of crystalline Form 2, Compound A.

30. The pharmaceutical composition of claim 21, wherein at least 99.9% of the crystalline form is Compound A, Form 2.

31. The pharmaceutical composition of claim 21, wherein at least 99.99% of the crystalline form is Compound A, Form 2.

32. The pharmaceutical composition of claim 21, wherein no more than 10% of the crystalline form is Compound A, Form 1.

33. The pharmaceutical composition of claim 21, wherein no more than 1% of the crystalline form is Compound A, Form 1.

34. The pharmaceutical composition of claim 21, wherein no more than 0.1% of the crystalline form is Compound A, Form 1.

35. The pharmaceutical composition of claim 21, wherein no more than 0.01% of the crystalline form is Compound A, Form 1.

36. The pharmaceutical composition of claim 21, wherein the composition is formulated for oral delivery.

37. The pharmaceutical composition of claim 21, wherein the composition is formulated as a tablet or a capsule.

38. Use of a composition of claim 21 in the manufacture of a medicament for~~A method of~~ treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by hypoxia inducible factor (HIF)~~, the method comprising administering to a patient a therapeutically effective amount of a composition of claim 21~~.

39. Use of a composition of claim 21 in the manufacture of a medicament for~~A method of~~ treating, pretreating, or delaying onset of a condition associated with or mediated at least in part by erythropoietin (EPO)~~, the method comprising administering to a patient a therapeutically effective amount of a composition of claim 21~~.

40. Use of a composition of claim 21, in the manufacture of a medicament ~~A method of~~for treating, pretreating, or delaying onset of anemia~~, the method comprising administering to a patient a therapeutically effective amount of a composition of claim 21~~.

41. A process for making crystalline Form 1 of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) comprising:

a) heating a mixture comprising a salt of {[1-cyano-5-(4-chlorophenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-acetic acid (Compound A) optionally in the presence of a base;