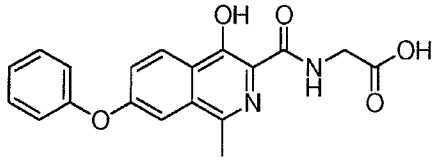
WHAT IS CLAIMED IS

1. A crystalline polymorph of the compound of Formula I,



Formula I .

2. The polymorph of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0° and 25.9°.

3. The polymorph of Claim 2, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å and 3.4Å.

4. The polymorph of Claim 2, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0°, 17.6°, 22.6°, 25.9° and 26.9°.

5. The polymorph of Claim 4, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å, 5.1Å, 3.9Å, 3.4Å and 3.3 Å.

6. The polymorph of Claim 2, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0°, 14.8°, 17.6°, 22.6°, 24.0°, 25.9° and 26.9°.

7. The polymorph of Claim 6, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å, 6.0Å, 5.1Å, 3.9Å, 3.7Å, 3.4Å and 3.3Å.

8. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 1.

9. The polymorph of any one of Claims 2-8, characterized by a melting point of 174-177 °C.

10. The polymorph of any one of Claims 2-9, characterized by a purity of ≥85%.

11. The polymorph of Claim 10, characterized by a purity of ≥95%.

12. The polymorph of Claim 11, characterized by a purity of ≥99%.

13. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray

powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 14.5° and 26.6°.

14. The polymorph of Claim 13, characterized by the X-ray powder diffraction pattern having characteristic peak, expressed in terms of the interplanar distance, at 10.8Å, 6.1Å and 3.4Å.

15. The polymorph of Claim 13, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 13.3°, 14.5°, 21.2° and 26.6°.

16. The polymorph of Claim 15, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 10.8Å, 6.7Å, 6.1Å, 4.2Å and 3.4Å.

17. The polymorph of Claim 13, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 9.6°, 13.3°, 14.5°, 21.2°, 22.8°, 25.4° and 26.6.

18. The polymorph of Claim 17, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 10.8Å, 9.3Å, 6.7Å, 6.1Å, 4.2Å, 3.9Å, 3.5Å and 3.4Å.

19. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 2.

20. The polymorph of any one of Claims 13-19, characterized by a melting point of 209-212 °C.

21. The polymorph of any one of Claims 13-20, characterized by a purity of ≥85%.

22. The polymorph of Claim 21, characterized by a purity of ≥95%.

23. The polymorph of Claim 22, characterized by a purity of ≥99%.

24. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 17.8° and 26.2°.

25. The polymorph of Claim 24, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 5.0Å and 3.4Å.

26. The polymorph of Claim 24, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 17.8°, 22.0°, 26.2° and

26.9°.

27. The polymorph of Claim 26, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 5.0Å, 4.0Å, 3.4Å and 3.3Å.

28. The polymorph of Claim 24, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 12.1°, 15.6°, 17.8°, 22.0°, 26.2°, 26.9° and 28.9°.

29. The polymorph of Claim 28, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 7.3Å, 5.7Å, 5.0Å, 4.0Å, 3.4Å, 3.3Å and 3.1Å.

30. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 3.

31. The polymorph of any one Claims 24-30, characterized by a melting point of 198-200 °C.

32. The polymorph of any one of Claims 24-31, characterized by a purity of ≥85%.

33. The polymorph of Claim 32, characterized by a purity of ≥95%.

34. The polymorph of Claim 33, characterized by a purity of ≥99%.

35. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 12.4°, 20.3° and 26.6°.

36. The polymorph of Claim 35, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 7.1Å, 4.4Å and 3.4Å.

37. The polymorph of Claim 35, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 11.3°, 12.4°, 20.3°, 21.4° and 26.6°.

38. The polymorph of Claim 37, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 7.9Å, 7.1Å, 4.4Å, 4.1Å and 3.4Å.

39. The polymorph of Claim 35, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 11.3°, 12.4°, 15.0°, 17.9°,

20.3°, 21.4°, 24.8° and 26.6°.

40. The polymorph of Claim 39, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 7.9Å, 7.1Å, 5.9Å, 5.0Å, 4.4Å, 4.1Å, 3.6Å and 3.4Å.

41. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 4.

42. The polymorph of any one of Claims 35-41, characterized by a melting point of 204-207 °C.

43. The polymorph of any one of Claims 35-42, characterized by a purity of ≥85%.

44. The polymorph of Claim 43, characterized by a purity of ≥95%.

45. The polymorph of Claim 44, characterized by a purity of ≥99%.

46. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 11.1° and 24.1°.

47. The polymorph of Claim 46, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å、8.0Å and 3.7Å.

48. The polymorph of Claim 46, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 11.1°, 17.7°, 24.1° and 26.9°.

49. The polymorph of Claim 48, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å, 8.0Å, 5.0Å, 3.7Å and 3.3Å.

50. The polymorph of Claim 46, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 8.8°, 11.1°, 11.9°, 14.9°, 17.7°, 24.1° and 26.9°.

51. The polymorph of Claim 50, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å, 10.0Å, 8.0Å, 7.4Å, 6.0Å, 5.0Å, 3.7Å and 3.3Å.

52. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 5.

53. The polymorph of any one of Claims 46-52, characterized by a melting point of 190-193 °C.

54. The polymorph of any one of Claims 46-53, characterized by a purity of ≥85%.

55. The polymorph of Claim 54, characterized by a purity of ≥95%.

56. The polymorph of Claim 55, characterized by a purity of ≥99%.

57. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 22.2° and 26.9°.

58. The polymorph of Claim 57, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 4.0Å and 3.3Å.

59. The polymorph of Claim 57, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 10.6°, 18.8°、22.2° and 26.9°.

60. The polymorph of Claim 59, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 8.4Å, 4.7Å, 4.0Å and 3.3Å.

61. The polymorph of Claim 57, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 9.4°, 10.6°, 16.5°, 18.8°, 21.3°, 22.2° and 26.9°.

62. The polymorph of Claim 61, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 9.4Å, 8.4Å, 5.4Å, 4.7Å, 4.2Å, 4.0Å and 3.3Å.

63. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 6.

64. The polymorph of any one of Claims 57-63, characterized by a melting point of 200-203 °C.

65. The polymorph of any one of Claims 57-64, characterized by a purity of ≥85%.

66. The polymorph of Claim 65, characterized by a purity of ≥95%.

67. The polymorph of Claim 66, characterized by a purity of ≥99%.

68. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray

powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 11.7° and 21.1°.

69. The polymorph of Claim 68, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 7.5Å and 4.2Å.

70. The polymorph of Claim 68, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 11.7°, 15.1°、21.1° and 25.8°.

71. The polymorph of Claim 70, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 7.5Å, 5.9Å, 4.2Å and 3.5Å.

72. The polymorph of Claim 68, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 7.5°, 11.7°, 15.1°, 19.3°, 21.1°, 22.6° and 25.8°.

73. The polymorph of Claim 72, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 11.8Å, 7.5Å, 5.9Å, 4.6Å, 4.2Å, 3.9Å and 3.5Å.

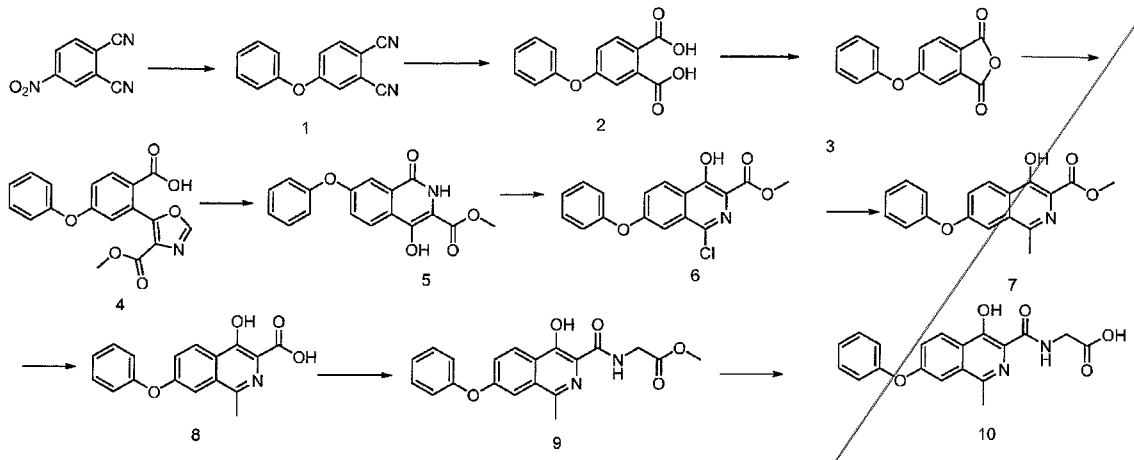
74. The polymorph of the compound of Formula I of Claim 1, characterized by the X-ray powder diffraction pattern shown as in Figure 7.

75. The polymorph of any one of Claims 68-74, characterized by a purity of ≥85%.

76. The polymorph of Claim 75, characterized by a purity of ≥95%.

77. The polymorph of Claim 76, characterized by a purity of ≥99%.

78. A method of preparing the compound of Formula I comprising the steps of:



(a) Synthesis of Compound 1

In inert gas, 4-nitro-o-phthalonitrile, phenol, K_2CO_3 and DMSO were added into a flask, stirred and reacted at room temperature for 45-50 hrs., then heated to 55°C - 65°C and reacted for 1.5-2.5 hr. After cooled down, precipitated, filtered to obtain Compound 1;

(b) Synthesis of Compound 2

Compound 1 dissolved in CH_3OH was added into a 40-60% of NaOH and heated to reflux till the reaction was complete. Concentrated HCl was then added to adjust the pH value to 2.5 - 3.5. The precipitate was filtered and dried to obtain Compound 2;

(c) Synthesis of Compound 3

Compound 2 was dissolved in glacial acetic acid and acetic anhydride and heated to reflux till the reaction was complete. The solvent was removed on a rotary evaporator to obtain Compound 3;

(d) Synthesis of Compound 4

Compounds 3 and methyl isocyanoacetate dissolved in THF were added in DBU (1,8-Diazabicycloundec-7-ene) drop-wise at room temperature and stirred for 0.5-1.5 hrs. at room temperature. Aftere washed with ethyl acetate under alkaline conditions to remove the impurities, the pH value of the aqueous phase was adjusted to 2.5 - 3.5 with diluted HCl.Extracted with ethyl acetate and washed with water, followed by drying with anhydrous Na_2SO_4 and filtered, the resulting extract was distilled on a rotary evaporator to obtain Compound 4;

(e) Synthesis of Compound 5

Compound 4 in CH_3OH was added in concentrated HCl, then heated to 55°C - 65°C and reacted for 3.5-4.5 hrs. The resulted precipitation was filtered and purified by chromatography to obtain Compound 5;

(f) Synthesis of Compound 6

Compound 5 was heated to 65°C - 75°C in $POCl_3$ and reacted for 2.5-3.5 hrs., then cooled down and poured into ice. After $POCl_3$ was completely decomposed, the resulting precipitate was filtered and washed with water, to reach Compound 6;

(g) Synthesis of Compound 7

In inert gas, Compound 6, dioxane, $Pd[P(C_6H_5)_3]_4$, K_2CO_3 and trimethyl borane were mixed and heated to reflux and stir for 2.5-3.5 hrs., then stirred at room temperature for 45-50 hrs. After concentration, the resulting mixture was extracted with ethyl acetate, washed with water, dried and filtered, then distilled on a rotary evaporator, followed by further purification through chromatography, to obtain Compound 7;

(h) Synthesis of Compound 8

Compound 7 was added into a mixture of ethanol and 1.5-2.5N of NaOH and refluxed for 1-2 hrs. After removing the impurities by filtration, the resulting mixture was distilled to remove ethanol on a rotary evaporator. The resulting pale yellow precipitate was then filtered,washed with water, and dried to obtain compound 8;

(i) Synthesis of Compound 9

Compound 8, glycine methyl ester hydrochloride and PyBOP were added into dichloromethane, and then added triethylamine and bis(isopropyl)ethylamine, stirred at room temperature for 2.5-3.5 hrs. After filtration, the organic phase was washed with water, dried and filtered, followed by a rotary evaporation, and further purification by a silica gel column, to obtain Compound 9;

(j) Synthesis of Compound 10, the compound of Formula I

Compound 9 in THF was added in 0.5-1.5N of NaOH and stirred for 0.5-1.5 hrs. at room temperature. After removing THF by a rotary evaporation, the pH value of the residue was adjusted to about 3 by diluted HCl, washed further by ethyl acetate, filtered and dried, to obtain Compound 10 , the compound of Formula I.

79. A method of preparing the crystalline polymorph of any one of Claims 1-12, comprising the steps of dissolving the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of methanol/methyl tertbutyl ether at room temperature, followed by spontaneous precipitation, and recovering the resulted crystalline polymorph.

80. A method of preparing the crystalline polymorph of any one of Claims 1 or 13-23, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of H_2O/acetonitrile (3:1), H_2O/ethanol at room temperature or at 50 °C, or in methanol/H_2O at room temperature for at least 48 hrs, and recovering the resulted crystalline polymorph.

81. A method of preparing the crystalline polymorph of any one of Claims 1 or 24-34, comprising the steps of dissolving the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of methanol/acetonitrile at room temperature, followed by a spontaneous precipitation, and recovering the resulted crystalline polymorph.

82. A method of preparing the crystalline polymorph of any one of Claims 1 or 24-34, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in H_2O, CH_2Cl_2, Isopropyl Acetate, EtOAc, or the mixed solvent of Isopropyl Acetate/heptane at 50 °C for at least 48 hrs, and recovering the resulted crystalline polymorph.

83. A method of preparing the crystalline polymorph of any one of Claims 1 or 35-45, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in methyl tertbutyl ether, the mixed solvent of Isopropyl Acetate/heptane or ethyl acetate/heptane at room temperature for at least 48 hrs, and recovering the resulted crystalline polymorph.

84. A method of preparing the crystalline polymorph of any one of Claims 1 or 35-45, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of ethyl acetate/heptane at 50 °C for at least 48 hrs. , and recovering the resulted crystalline polymorph.

85. A method of preparing the crystalline polymorph of any one of Claims 1 or 46-56, comprising the steps of: slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of methyl tertbutyl ether/heptane at 50 °C for at least 48 hrs.; or adding water as anti-solvent into the methanol solution of the compound of Formula I as prepared in the method of Claim 78, and recovering the resulted crystalline polymorph.

86. A method of preparing the crystalline polymorph of any one of Claims 1 or 57-67, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of acetonitrile/H_2O (1:1) or THF/H_2O at room temperature

for at least 48 hrs, and recovering the resulted crystalline polymorph.

87. A method of preparing the crystalline polymorph of any one of Claims 1 or 57-67, comprising the steps of dissolving the compound of Formula I as prepared in the method of Claim 78 in the mixed solvent of methanol/ethyl acetate at room temperature, followed by a spontaneous precipitation using a crystalline form as prepared in Claim 83 or 84 as crystallization seed, and recovering the resulted crystalline polymorph.

88. A method of preparing the crystalline polymorph of any one of Claims 1 or 68-77, comprising the steps of heating the crystalline polymorph as prepared in Claim 85 to about 180 °C, and recovering the resulted crystalline polymorph.

89. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline polymorph of any one of Claims 1-77, and a pharmaceutically acceptable excipient, adjuvant or carrier.

90. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline polymorph of any one of Claims 1-77, in combination with at least one of additional active ingredient.

91. The pharmaceutical composition of any one of Claims 89 or 90, wherein the composition is used in an oral administration.

92. The pharmaceutical composition of Claim 91, wherein the composition is used in tablets or capsules.

93. The pharmaceutical composition of any one of Claims 89-92, wherein the composition comprises 1 wt%-99 wt% of the crystalline polymorph of any one of Claims 1-77.

94. The pharmaceutical composition of Claim 93, wherein the composition comprises 1 wt%-70 wt% of the crystalline polymorph of any one of Claims 1-77.

95. The pharmaceutical composition of Claim 94, wherein the composition comprises 10 wt%-30 wt% of the crystalline polymorph of any one of Claims 1-77.

96. Use of a crystalline polymorph of any one of Claims 1-77 in manufacturing a medicament for modulating HIF level or HIF activity.

97. Use of a crystalline polymorph of any one of Claims 1-77 in manufacturing a medicament for the treatment of a disease, a disorder, or a condition associated with HIF level or HIF activity.

98. Use of a crystalline polymorph of any one of Claims 1-77 in manufacturing a medicament for the treatment of ischemia, anemia, or a disease, a disorder or a condition associated with ischemia or anemia.

99. Use of a crystalline polymorph of any one of Claims 1-77 in manufacturing a medicament for the treatment of a disease, a disorder, or a condition selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer or an inflammatory disorder, or a combination of two or more thereof, in a subject.

100. A method of modulating HIF levels or activity in a subject by administering to the subject a crystalline polymorph of any one of Claims 1-77.

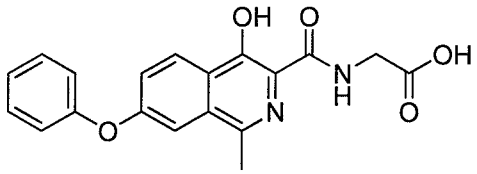
101. A method for treating a disease, a disorder, or a condition associated with HIF level or HIF activity in a subject by administering to the subject a crystalline polymorph of any one of Claims 1-77.

102. A method for treating ischemia, anemia, or a disease, a disorder or a condition associated with ischemia or anemia in a subject by administering to the subject a crystalline polymorph of any one of Claims 1-77.

103. A method for treating a disease, a disorder, or a condition selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer or an inflammatory disorder, or a combination of two or more thereof, in a subject by administering to the subject a crystalline polymorph of any one of Claims 1-77.

WHAT IS CLAIMED IS

1. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0° and 25.9°.

2. The polymorph of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å and 3.4Å.

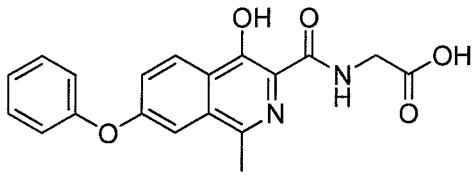
3. The polymorph of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0°, 17.6°, 22.6°, 25.9° and 26.9°.

4. The polymorph of Claim 3, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å, 5.1Å, 3.9Å, 3.4Å and 3.3 Å.

5. The polymorph of Claim 1, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 5.9°, 11.0°, 14.8°, 17.6°, 22.6°, 24.0°, 25.9° and 26.9°.

6. The polymorph of Claim 5, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.9Å, 8.0Å, 6.0Å, 5.1Å, 3.9Å, 3.7Å, 3.4Å and 3.3Å.

7. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 1.

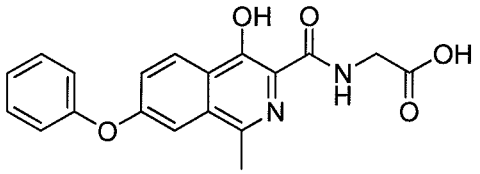
8. The polymorph of any one of Claims 1-7, characterized by a melting point of 174-177 °C.

9. The polymorph of any one of Claims 1-8, characterized by a purity of ≥85%.

10. The polymorph of Claim 9, characterized by a purity of ≥95%.

11. The polymorph of Claim 10, characterized by a purity of ≥99%.

12. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 14.5° and 26.6°.

13. The polymorph of Claim 12, characterized by the X-ray powder diffraction pattern having characteristic peak, expressed in terms of the interplanar distance, at 10.8Å, 6.1Å and 3.4Å.

14. The polymorph of Claim 12, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 13.3°, 14.5°, 21.2° and 26.6°.

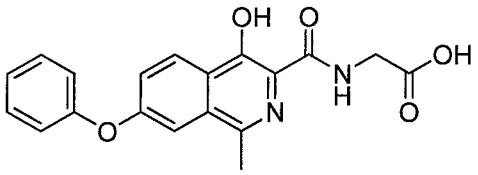
15. The polymorph of Claim 14, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 10.8Å, 6.7Å, 6.1Å, 4.2Å and 3.4Å.

16. The polymorph of Claim 12, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 8.2°, 9.6°, 13.3°, 14.5°,

21.2°, 22.8°, 25.4° and 26.6.

17. The polymorph of Claim 16, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 10.8Å, 9.3Å, 6.7Å, 6.1Å, 4.2Å, 3.9Å, 3.5Å and 3.4Å.

18. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 2.

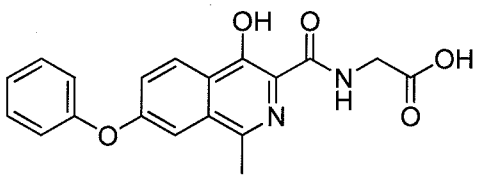
19. The polymorph of any one of Claims 12-18, characterized by a melting point of 209-212 °C.

20. The polymorph of any one of Claims 12-19, characterized by a purity of ≥85%.

21. The polymorph of Claim 20, characterized by a purity of ≥95%.

22. The polymorph of Claim 21, characterized by a purity of ≥99%.

23. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 17.8° and 26.2°.

24. The polymorph of Claim 23, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 5.0Å and 3.4Å.

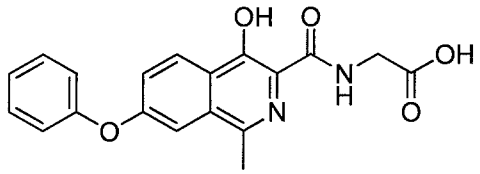
25. The polymorph of Claim 23, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 17.8°, 22.0°, 26.2° and 26.9°.

26. The polymorph of Claim 25, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 5.0Å, 4.0Å, 3.4Å and 3.3Å.

27. The polymorph of Claim 23, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.2°, 12.1°, 15.6°, 17.8°, 22.0°, 26.2°, 26.9° and 28.9°.

28. The polymorph of Claim 27, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.3Å, 7.3Å, 5.7Å, 5.0Å, 4.0Å, 3.4Å, 3.3Å and 3.1Å.

29. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 3.

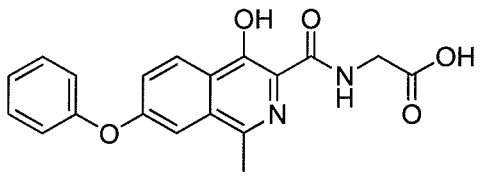
30. The polymorph of any one Claims 23-29, characterized by a melting point of 198-200 °C.

31. The polymorph of any one of Claims 23-30, characterized by a purity of ≥85%.

32. The polymorph of Claim 31, characterized by a purity of ≥95%.

33. The polymorph of Claim 32, characterized by a purity of ≥99%.

34. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 12.4°, 20.3° and 26.6°.

35. The polymorph of Claim 34, characterized by the X-ray powder diffraction pattern

having characteristic peaks, expressed in terms of the interplanar distance, at 7.1Å, 4.4Å and 3.4Å.

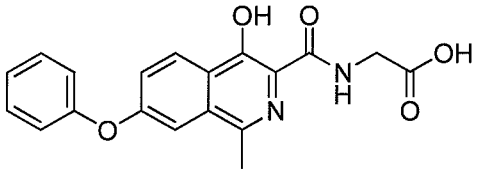
36. The polymorph of Claim 34, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 11.3°, 12.4°, 20.3°, 21.4° and 26.6°.

37. The polymorph of Claim 36, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 7.9Å, 7.1Å, 4.4Å, 4.1Å and 3.4Å.

38. The polymorph of Claim 34, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 11.3°, 12.4°, 15.0°, 17.9°, 20.3°, 21.4°, 24.8° and 26.6°.

39. The polymorph of Claim 38, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 7.9Å, 7.1Å, 5.9Å, 5.0Å, 4.4Å, 4.1Å, 3.6Å and 3.4Å.

40. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 4.

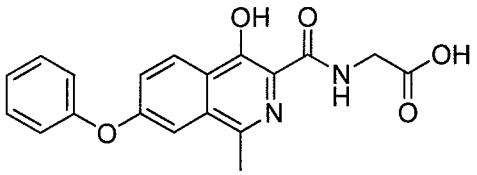
41. The polymorph of any one of Claims 34-40, characterized by a melting point of 204-207 °C.

42. The polymorph of any one of Claims 34-41, characterized by a purity of ≥85%.

43. The polymorph of Claim 42, characterized by a purity of ≥95%.

44. The polymorph of Claim 43, characterized by a purity of ≥99%.

45. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 11.1° and 24.1°.

46. The polymorph of Claim 45, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å、8.0Å and 3.7Å.

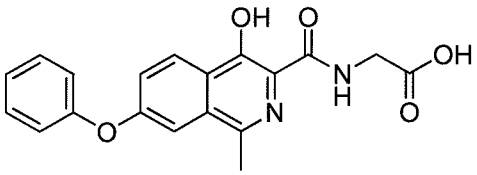
47. The polymorph of Claim 45, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 11.1°, 17.7°, 24.1° and 26.9°.

48. The polymorph of Claim 47, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å, 8.0Å, 5.0Å, 3.7Å and 3.3Å.

49. The polymorph of Claim 45, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.0°, 8.8°, 11.1°, 11.9°, 14.9°, 17.7°, 24.1° and 26.9°.

50. The polymorph of Claim 49, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 14.8Å, 10.0Å, 8.0Å, 7.4Å, 6.0Å, 5.0Å, 3.7Å and 3.3Å.

51. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 5.

52. The polymorph of any one of Claims 45-51, characterized by a melting point of

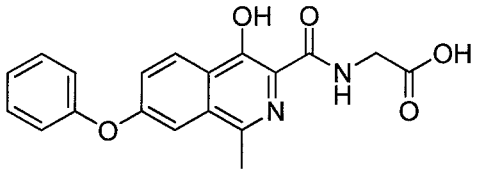
190-193 °C.

53. The polymorph of any one of Claims 45-52, characterized by a purity of ≥85%.

54. The polymorph of Claim 53, characterized by a purity of ≥95%.

55. The polymorph of Claim 54, characterized by a purity of ≥99%.

56. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 22.2° and 26.9°.

57. The polymorph of Claim 56, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 4.0Å and 3.3Å.

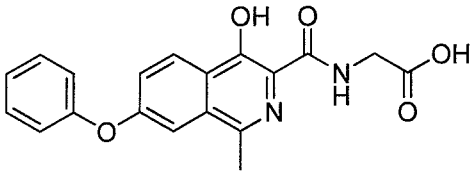
58. The polymorph of Claim 56, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 10.6°, 18.8°、22.2° and 26.9°.

59. The polymorph of Claim 58, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 8.4Å, 4.7Å, 4.0Å and 3.3Å.

60. The polymorph of Claim 56, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 7.1°, 9.4°, 10.6°, 16.5°, 18.8°, 21.3°, 22.2° and 26.9°.

61. The polymorph of Claim 60, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.4Å, 9.4Å, 8.4Å, 5.4Å, 4.7Å, 4.2Å, 4.0Å and 3.3Å.

62. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern shown as in Figure 6.

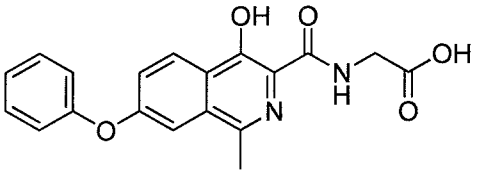
63. The polymorph of any one of Claims 56-62, characterized by a melting point of 200-203 °C.

64. The polymorph of any one of Claims 56-63, characterized by a purity of ≥85%.

65. The polymorph of Claim 64, characterized by a purity of ≥95%.

66. The polymorph of Claim 65, characterized by a purity of ≥99%.

67. A crystalline polymorph of the compound of Formula **I**,



Formula I

characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 11.7° and 21.1°.

68. The polymorph of Claim 67, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 7.5Å and 4.2Å.

69. The polymorph of Claim 67, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 11.7°, 15.1°、21.1° and 25.8°.

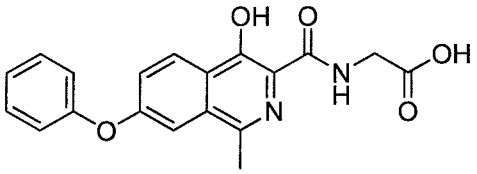
70. The polymorph of Claim 69, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 7.5Å, 5.9Å, 4.2Å and 3.5Å.

71. The polymorph of Claim 67, characterized by the X-ray powder diffraction pattern having characteristic peaks at diffraction angles 2θ of approximately 6.9°, 7.5°, 11.7°, 15.1°,

19.3°, 21.1°, 22.6° and 25.8°.

72. The polymorph of Claim 71, characterized by the X-ray powder diffraction pattern having characteristic peaks, expressed in terms of the interplanar distance, at 12.8Å, 11.8Å, 7.5Å, 5.9Å, 4.6Å, 4.2Å, 3.9Å and 3.5Å.

73. A crystalline polymorph of the compound of Formula **I**,



Formula I

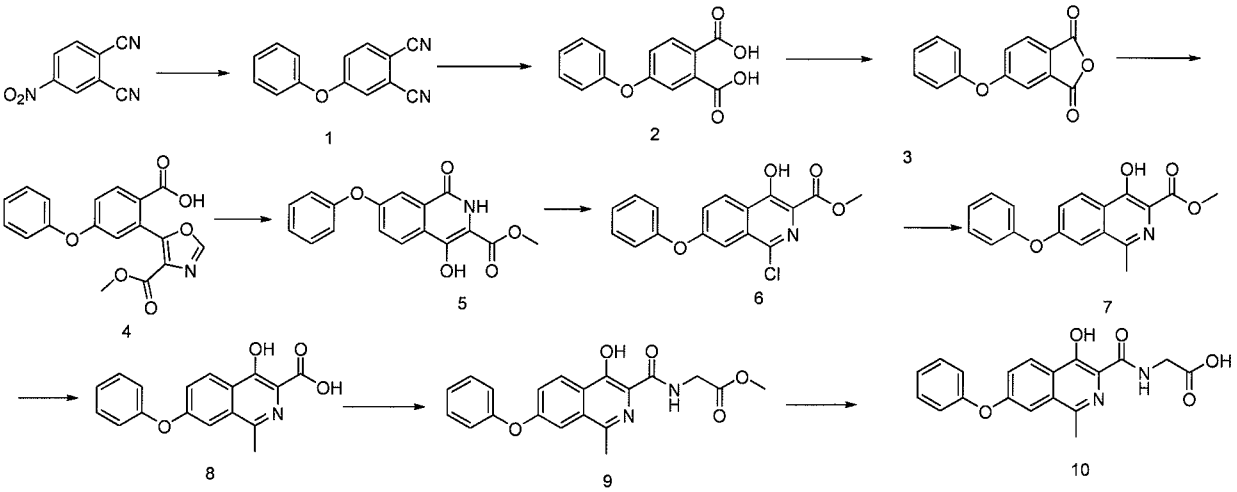
characterized by the X-ray powder diffraction pattern shown as in Figure 7.

74. The polymorph of any one of Claims 67-73, characterized by a purity of ≥85%.

75. The polymorph of Claim 74, characterized by a purity of ≥95%.

76. The polymorph of Claim 75, characterized by a purity of ≥99%.

77. A method of preparing the compound of Formula I comprising the steps of:



(a) Synthesis of Compound 1

In inert gas, 4-nitro-o-phthalonitrile, phenol, K_2CO_3 and DMSO were added into a flask, stirred and reacted at room temperature for 45-50 hrs., then heated to 55°C - 65°C and reacted for 1.5-2.5 hr. After cooled down, precipitated, filtered to obtain Compound **1**;

(b) Synthesis of Compound 2

Compound **1** dissolved in CH_3OH was added into a 40-60% of NaOH and heated to reflux till the reaction was complete. Concentrated HCl was then added to adjust the pH value to 2.5 - 3.5. The precipitate was filtered and dried to obtain Compound **2**;

(c) Synthesis of Compound 3

Compound **2 was dissolved** in glacial acetic acid and acetic anhydride and heated to reflux till the reaction was complete. The solvent was removed on a rotary evaporator to obtain Compound **3**;

(d) Synthesis of Compound 4

Compounds **3** and methyl isocyanoacetate dissolved in THF were added in DBU (1,8-Diazabicycloundec-7-ene) drop-wise at room temperature and stirred for 0.5-1.5 hrs. at room temperature. Aftere washed with ethyl acetate under alkaline conditions to remove the impurities, the pH value of the aqueous phase was adjusted to 2.5 - 3.5 with diluted HCl.Extracted with ethyl acetate and washed with water, followed by drying with anhydrous Na_2SO_4 and filtered, the resulting extract was distilled on a rotary evaporator to obtain Compound **4**;

(e) Synthesis of Compound 5

Compound 4 in CH_3OH was added in concentrated HCl, then heated to 55°C - 65°C and reacted for 3.5-4.5 hrs. The resulted precipitation was filtered and purified by chromatography to obtain Compound **5**;

(f) Synthesis of Compound 6

Compound **5** was heated to 65°C - 75°C in $POCl_3$ and reacted for 2.5-3.5 hrs., then cooled down and poured into ice. After $POCl_3$ was completely decomposed, the resulting precipitate was filtered and washed with water, to reach Compound **6**;

(g) Synthesis of Compound 7

In inert gas, Compound **6**, dioxane, $Pd[P(C_6H_5)_3]_4$, K_2CO_3 and trimethyl borane were mixed and heated to reflux and stir for 2.5-3.5 hrs., then stirred at room temperature for 45-50 hrs. After concentration, the resulting mixture was extracted with ethyl acetate, washed with water, dried and filtered, then distilled on a rotary evaporator, followed by further purification

through chromatography, to obtain Compound **7**;

(h) Synthesis of Compound 8

Compound **7** was added into a mixture of ethanol and 1.5-2.5N of NaOH and refluxed for 1-2 hrs. After removing the impurities by filtration, the resulting mixture was distilled to remove ethanol on a rotary evaporator. The resulting pale yellow precipitate was then filtered,washed with water, and dried to obtain compound **8**;

(i) Synthesis of Compound 9

Compound **8**, glycine methyl ester hydrochloride and PyBOP were added into dichloromethane, and then added triethylamine and bis(isopropyl)ethylamine, stirred at room temperature for 2.5-3.5 hrs. After filtration, the organic phase was washed with water, dried and filtered, followed by a rotary evaporation, and further purification by a silica gel column, to obtain Compound **9**;

(j) Synthesis of Compound 10, the compound of Formula I

Compound **9** in THF was added in 0.5-1.5N of NaOH and stirred for 0.5-1.5 hrs. at room temperature. After removing THF by a rotary evaporation, the pH value of the residue was adjusted to about 3 by diluted HCl, washed further by ethyl acetate, filtered and dried, to obtain Compound **10** , the compound of Formula I.

78. A method of preparing the crystalline polymorph of any one of Claims 1-11, comprising the steps of dissolving the compound of Formula **I** as prepared in the method of Claim 77 in the mixed solvent of methanol/methyl tertbutyl ether at room temperature, followed by spontaneous precipitation, and recovering the resulted crystalline polymorph.

79. A method of preparing the crystalline polymorph of any one of Claims 12-22, comprising the steps of slurrying excess amount of the compound of Formula **I** as prepared in the method of Claim 77 in the mixed solvent of H_2O/acetonitrile (3:1), H_2O/ethanol at room temperature or at 50 °C, or in methanol/H_2O at room temperature for at least 48 hrs, and recovering the resulted crystalline polymorph.

80. A method of preparing the crystalline polymorph of any one of Claims 23-33, comprising the steps of dissolving the compound of Formula **I** as prepared in the method of Claim 77 in the mixed solvent of methanol/acetonitrile at room temperature, followed by a

spontaneous precipitation, and recovering the resulted crystalline polymorph.

81. A method of preparing the crystalline polymorph of any one of Claims 23-33, comprising the steps of slurrying excess amount of the compound of Formula **I** as prepared in the method of Claim 77 in H_2O, CH_2Cl_2, Isopropyl Acetate, EtOAc, or the mixed solvent of Isopropyl Acetate/heptane at 50 °C for at least 48 hrs, and recovering the resulted crystalline polymorph.

82. A method of preparing the crystalline polymorph of any one of Claims 34-44, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 77 in methyl tertbutyl ether, the mixed solvent of Isopropyl Acetate/heptane or ethyl acetate/heptane at room temperature for at least 48 hrs, and recovering the resulted crystalline polymorph.

83. A method of preparing the crystalline polymorph of any one of Claims 34-44, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 77 in the mixed solvent of ethyl acetate/heptane at 50 °C for at least 48 hrs. , and recovering the resulted crystalline polymorph.

84. A method of preparing the crystalline polymorph of any one of Claims 45-55, comprising the steps of: slurrying excess amount of the compound of Formula I as prepared in the method of Claim 77 in the mixed solvent of methyl tertbutyl ether/heptane at 50 °C for at least 48 hrs.; or adding water as anti-solvent into the methanol solution of the compound of Formula I as prepared in the method of Claim 77, and recovering the resulted crystalline polymorph.

85. A method of preparing the crystalline polymorph of any one of Claims 56-66, comprising the steps of slurrying excess amount of the compound of Formula I as prepared in the method of Claim 77 in the mixed solvent of acetonitrile/H_2O (1:1) or THF/H_2O at room temperature for at least 48 hrs, and recovering the resulted crystalline polymorph.

86. A method of preparing the crystalline polymorph of any one of Claims 56-66, comprising the steps of dissolving the compound of Formula I as prepared in the method of Claim 77 in the mixed solvent of methanol/ethyl acetate at room temperature, followed by a spontaneous precipitation using a crystalline form as prepared in Claim 82 or 83 as

crystallization seed, and recovering the resulted crystalline polymorph.

87. A method of preparing the crystalline polymorph of any one of Claims 67-76, comprising the steps of heating the crystalline polymorph as prepared in Claim 84 to about 180 °C, and recovering the resulted crystalline polymorph.

88. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline polymorph of any one of Claims 1-76, and a pharmaceutically acceptable excipient, adjuvant or carrier.

89. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline polymorph of any one of Claims 1-76, in combination with at least one of additional active ingredient.

90. The pharmaceutical composition of any one of Claims 88 or 89, wherein the composition is used in an oral administration.

91. The pharmaceutical composition of Claim 90, wherein the composition is used in tablets or capsules.

92. The pharmaceutical composition of any one of Claims 88-91, wherein the composition comprises 1 wt%-99 wt% of the crystalline polymorph of any one of Claims 1-76.

93. The pharmaceutical composition of Claim 92, wherein the composition comprises 1 wt%-70 wt% of the crystalline polymorph of any one of Claims 1-76.

94. The pharmaceutical composition of Claim 93, wherein the composition comprises 10 wt%-30 wt% of the crystalline polymorph of any one of Claims 1-76.

95. Use of a crystalline polymorph of any one of Claims 1-76 in manufacturing a medicament for modulating HIF level or HIF activity.

96. Use of a crystalline polymorph of any one of Claims 1-76 in manufacturing a medicament for the treatment of a disease, a disorder, or a condition associated with HIF level or **HIF** activity.

97. Use of a crystalline polymorph of any one of Claims 1-76 in manufacturing a medicament for the treatment of ischemia, anemia, or a disease, a disorder or a condition associated with ischemia or anemia.

98. Use of a crystalline polymorph of any one of Claims 1-76 in manufacturing a medicament for the treatment of a disease, a disorder, or a condition selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer or an inflammatory disorder, or a combination of two or more thereof, in a subject.