ylamino)butanoic acid with different chemical and physical stabilities, and compositions and uses of the same.

BRIEF SUMMARY

[0016a] In an aspect of the present disclosure, there is provided a crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof.

[0016b] In another aspect of the present disclosure, there is provided a method of preparing the crystalline form disclosed herein, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and phosphoric acid in a solvent.

[0016c] In a further aspect of the present disclosure, there is provided a method of preparing the crystalline form disclosed herein, comprising converting (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid zwitterion (ZI) to the crystalline form.

[0016d] In another aspect of the present disclosure, there is provided a method of preparing the crystalline form disclosed herein, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and fumaric acid in a solvent.

[0016e] In a further aspect of the present disclosure, there is provided a method of preparing the crystalline form disclosed herein, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and 1,5-naphthalenedisulfonic acid in a solvent.

[0016f] In another aspect of the present disclosure, there is provided a method of preparing the crystalline form disclosed herein, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and phosphoric acid in a solvent comprising isopropyl alcohol.

[0016g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the crystalline form disclosed herein, and a pharmaceutically acceptable carrier or excipient.

[0016h] In another aspect of the present disclosure, there is provided a kit comprising the crystalline form disclosed herein.

[0016i] In a further aspect of the present disclosure, there is provided a use of a crystalline form disclosed herein, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof.

[0016j] In another aspect of the present disclosure, there is provided a crystalline form disclosed herein, for use in inhibiting $\alpha_V\beta_6$ integrin in an individual.

[0016k] In a further aspect of the present disclosure, there is provided a crystalline form disclosed herein, for use in inhibiting TGFβ activation in a cell.

[0016l] In another aspect of the present disclosure, there is provided a crystalline form disclosed herein for use in inhibiting an $\alpha_V\beta_6$ integrin, wherein the crystalline form is to be contacted with the $\alpha_V\beta_6$ integrin in an amount effective to inhibit the $\alpha_V\beta_6$ integrin.

[0016m] In a further aspect of the present disclosure, there is provided a use of a crystalline form disclosed herein, in the manufacture of a medicament for modulating the activity of at least one integrin in an individual in need thereof, wherein the crystalline form is effective to modulate the activity of the at least one integrin in the individual, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin.

[0016n] In another aspect of the present disclosure, there is provided a crystalline form **DISCLOSED HEREIN**, for use in therapy.

[0017] In one example, provided herein is a crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof, as detailed herein.

[0018] In another example, provided herein is a method of preparing a crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof, as detailed herein.

[0019] In another example, provided herein is a composition comprising a crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof, as detailed herein.

[0020] In another example, provided herein is a kit comprising a crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof, as detailed herein.

[0021] In another example, provided herein is a method of treating a fibrotic disease in an individual (such as a human) in need thereof comprising administering to the individual a therapeutically effective amount of a crystalline form or a composition disclosed herein. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC).

[0022] In another example, provided is a method of delaying the onset and/or development of a fibrotic disease in an individual (such as a human) who is at risk for developing a fibrotic disease comprising administering to the individual a therapeutically effective amount of a crystalline form or a composition disclosed herein. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or PBC. In some examples, the individual at risk of developing a fibrotic disease has or is suspected of having NAFLD, NASH,

CLAIMS

1. A crystalline form of a salt of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid or a solvate thereof.

2. The crystalline form of claim 1, wherein the crystalline form is a crystalline form of a phosphate salt of the (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid.

3. The crystalline form of claim 2, wherein the crystalline form is characterized as having an X-ray powder diffraction (XRPD) pattern comprising:

    a. peaks at angles 2-theta of about 4.31, about 6.76, about 18.89, about 21.29, and about 23.16 degrees,

    b. peaks at angles 2-theta of about 4.31, about 6.76, about 11.25, about 12.75, about 18.89, about 20.38, about 21.29, about 23.16, about 23.97, and about 24.68 degrees, or

    c. peaks at angles 2-theta of about 4.31, about 6.76, about 8.55, about 10.04, about 11.25, about 12.75, about 13.76, about 17.20, about 18.02, about 18.89, about 20.38, about 21.29, about 23.16, about 23.97, about 24.68, about 25.50, about 26.18, about 29.88, and about 33.49 degrees.

4. The crystalline form of claims 2 or 3, wherein the crystalline form is characterized as having an XRPD pattern comprising peaks at angles 2-theta of about 4.31 and about 6.76 degrees.

5. The crystalline form of any one of claims 2-4, wherein the crystalline form is characterized as having an XRPD pattern comprising a peak at an angle 2-theta of about 4.31 degrees.
6. The crystalline form of any one of claims 2-5, wherein the crystalline form is characterized as having an XRPD pattern substantially as shown in FIG. 1A.

7. The crystalline form of any one of claims 2-6, wherein the crystalline form is characterized as having a DSC graph substantially as shown in FIG. 1B, FIG. 1C, FIG. 1D, or FIG. 1E.

8. The crystalline form of any one of claims 2-7, wherein the crystalline form is characterized as having:
    a. endotherm peaks at about 88.3 °C, about 136.3 °C, and/or about 197.6 °C, as determined by DSC;
    b. endotherm peaks at about 86.1 °C, about 140.8 °C, and/or about 197.0 °C, as determined by DSC;
    c. endotherm peaks at about 77.3 °C, 132.2 °C, and/or about 197.0 °C, as determined by DSC; or
    d. endotherm peaks at about 95.2 °C, about 134.1 °C, and/or about 200.9 °C, as determined by DSC.
9. The crystalline form of any one of claims 2-8, wherein the crystalline form is characterized as having a TGA graph substantially as shown in FIG. 1B, FIG. 1C, FIG. 1D, or FIG. 1E.

10. The crystalline form of any one of claims 2-9, wherein the crystalline form is characterized as showing:
    a. a weight loss of about 5.21% after heating from about 26.5 °C about 150.0 °C, as determined by TGA,
    b. a weight loss of about 5.04% after heating from about 27.0 °C to about 110.0 °C, as determined by TGA,

c. a weight loss of about 10.32% after heating from about 30.0 °C to about 150.0 °C, as determined by TGA, or

d. a weight loss of about 7.37% after heating from about 27.0 °C to about 150.0 °C, as determined by TGA.

11. The crystalline form of any one of claims 2-10, wherein the crystalline form is characterized as having DVS graph substantially as shown in FIG. 1F.

12. The crystalline form of any one of claims 2-11, wherein the crystalline form is a hydrate of the phosphate salt.

13. The crystalline form of any one of claims 2-12, wherein the crystalline form is the phosphate salt and has a water content of about 3% by weight.

14. The crystalline form of claim 1, wherein the crystalline form is a crystalline form of the fumarate salt.

15. The crystalline form of claim 14, wherein the crystalline form is characterized as having an XRPD pattern comprising:

a. peaks at angles 2-theta of about 8.47, about 10.51, about 13.98, about 23.70, and about 24.43 degrees,

b. peaks at angles 2-theta of about 8.47, about 9.37, about 10.51, about 13.98, about 16.20, about 17.26, about 23.70, about 24.01, about 24.43, and about 25.59 degrees, or

c. peaks at angles 2-theta of about 6.87, about 8.47, about 9.37, about 10.51, about 12.20, about 12.63, about 13.34, about 13.98, about 16.20, about 17.26, about 18.11, about 18.72, about 19.42, about 20.46, about 21.87, about 22.15, about 23.70, about 24.01, about 24.43, and about 25.59 degrees.

16. The crystalline form of claims 14 or 15, wherein the crystalline form is characterized as having an XRPD pattern comprising peaks at angles 2-theta of about 8.47 and about 9.37 degrees.

17. The crystalline form of any one of claims 14-16, wherein the crystalline form is characterized as having an XRPD pattern comprising a peak at an angle 2-theta of about 8.47 degrees.

18. The crystalline form of any one of claims 14-17, wherein the crystalline form is characterized as having an XRPD pattern substantially as shown in FIG. 2A.

19. The crystalline form of any one of claims 14-18, wherein the crystalline form is characterized as having a DSC graph substantially as shown in FIG. 2B.

20. The crystalline form of any one of claims 14-19, wherein the crystalline form is characterized as having an endotherm peak at about 95.4 °C, as determined by DSC.

21. The crystalline form of any one of claims 14-20, wherein the crystalline form is characterized as having a TGA graph substantially as shown in FIG. 2B.

22. The crystalline form of any one of claims 14-21, wherein the crystalline form is characterized as showing a weight loss of about 13.02 % after heating from about 26.0 °C to about 125.0 °C, as determined by TGA.

23. The crystalline form of claim 1, wherein the crystalline form is a crystalline form of the 1,5-naphthalenedisulfonate salt.

24. The crystalline form of claim 23, wherein the crystalline form is characterized as having an XRPD pattern comprising:

    a. peaks at angles 2-theta of about 15.87 and about 23.85 degrees,

b. peaks at angles 2-theta of about 12.58, about 15.87, about 16.77, about 23.85, and about 31.95 degrees, or

c. peaks at angles 2-theta of about 3.17, about 12.58, about 15.87, about 16.77, about 18.78, about 23.85, about 25.30, about 27.34, about 29.61, about 31.95, about 38.05, and about 38.63 degrees.

25. The crystalline form of claims 23 or 24, wherein the crystalline form is characterized as having an XRPD pattern comprising peaks at angles 2-theta of about 12.58 and about 15.87 degrees.

26. The crystalline form of any one of claims 23-25, wherein the crystalline form is characterized as having an XRPD pattern comprising a peak at an angle 2-theta of about 12.58 degrees.

27. The crystalline form of any one of claims 23-26, wherein the crystalline form is characterized as having an XRPD pattern substantially as shown in FIG. 3A.

28. The crystalline form of any one of claims 23-27, wherein the crystalline form is characterized as having a DSC graph substantially as shown in FIG. 3B.

29. The crystalline form of any one of claims 23-28, wherein the crystalline form is characterized as having an endotherm peak at about 103.4 °C, as determined by DSC.

30. The crystalline form of any one of claims 23-29, wherein the crystalline form is characterized as having a TGA graph substantially as shown in FIG. 3B.

31. The crystalline form of any one of claims 23-30, wherein the crystalline form is characterized as showing a weight loss of about 11.11% after heating from about 23.0 °C to about 150.0 °C, as determined by TGA.

32. The crystalline form of claim 1, wherein the crystalline form is a crystalline form of a mixed solvate of isopropyl alcohol and water of the phosphate salt.

33. The crystalline form of claim 32, wherein the crystalline form is characterized as having an XRPD pattern comprising peaks at angles 2-theta of about 4.14, about 20.02, about 21.57, about 6.64, and about 25.22 degrees, or an XRPD pattern substantially as shown in FIG. 4.

34. The crystalline form of claims 32 or 33, wherein the crystalline form is characterized as having an XRPD pattern comprising peaks at angles 2-theta of about 4.14 and about 6.64 degrees.

35. The crystalline form of any one of claims 32-34, wherein the crystalline form is characterized as having an XRPD pattern comprising a peak at an angle 2-theta of about 4.14 degrees.

36. The crystalline form of any one of claims 1-31, wherein the crystalline form has a water content of less than about 0.5% by weight.

37. The crystalline form of any one of claims 1-31 or claim 36, wherein the crystalline form is anhydrous.

38. The crystalline form of any one of claims 1-35, wherein the crystalline form has a water content of less than about 0.5% by weight.

39. The crystalline form of any one of claims 1-35, wherein the crystalline form has a water content in % by weight of one of about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 5, 5.5, 6, 6.5, 7, 7.5 8, 8.5, 9, 9.5, or 10, or a range between any two of the preceding values.

40. A method of preparing the crystalline form of any one of claims 2-13, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and phosphoric acid in a solvent.

41. The method of claim 40, wherein the solvent comprises an alcohol.

42. The method of claim 41, wherein the solvent comprises ethanol.

43. The method of any one of claims 39-41, wherein the method is conducted at room temperature.

44. The method of any one of claims 39-41, further comprising subjecting the mixture to one or more temperature cycles.

45. A method of preparing the crystalline form of any one of claims 2-13, comprising converting (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid zwitterion (ZI) to the crystalline form.

46. The method of claim 45, wherein converting (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid ZI to the crystalline form comprises mixing the (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid ZI and phosphoric acid in a solvent.

47. The method of claim 46, wherein the solvent comprises an alcohol.

48. The method of claim 46 or 47, wherein the solvent comprises a mixture of methanol and ethanol.

49. The method of claim 48, wherein the ratio of methanol to ethanol is about 1:4 (v/v).

50. The method of any one of claims 45-49, further comprising converting a hydrochloride salt of benzyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoate to the (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid ZI.

51. The method of claim 50, wherein the hydrochloride salt is a dihydrochloride salt.

52. A method of preparing the crystalline form of any one of claims 14-22, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and fumaric acid in a solvent.

53. The method of claim 52, wherein the solvent comprises a ketone, water, or a mixture thereof.

54. The method of claim 53, wherein the solvent comprises a mixture of acetone and water.

55. The method of claim 54, wherein the ratio of acetone to water is about 19:1 (v/v).

56. The method of any one of claims 52-55, further comprising subjecting the mixture to one or more temperature cycles.

57. A method of preparing the crystalline form of any one of claims 23-31, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and 1,5-naphthalenedisulfonic acid in a solvent.

58. The method of claim 57, wherein the solvent comprises an acetate.

59. The method of claim 58, wherein the solvent comprises ethyl acetate.

60. The method of any one of claims 57-59, wherein the method is conducted at room temperature.

61. A method of preparing the crystalline form of any one of claims 32-35, comprising preparing a mixture of (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid and phosphoric acid in a solvent comprising isopropyl alcohol.

62. The method of claim 61, wherein at least one of the solvent and an ambient atmosphere comprises water effective to incorporate the water into the crystalline form of claim 24 or 25.

63. The method of claim 62, wherein the solvent comprises methanol.

64. The method of any one of claims 61-63, wherein the method is conducted at room temperature.

65. The method of any one of claims 39-64, wherein the method comprises preparing the crystalline form at a water content of less than about 0.5% by weight.

66. The method of any one of claims 39-64, wherein the method comprises preparing the crystalline form having a water content in % by weight of one of about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 5, 5.5, 6, 6.5, 7, 7.5 8, 8.5, 9, 9.5, or 10, or a range between any two of the preceding values.

67. The method of claim 66, wherein the method comprises a humidification step effective to prepare the crystalline form having a water content in % by weight of one of about 1, 1.5,

2, 2.5, 3, 3.5, 4, 4.5 5, 5.5, 6, 6.5, 7, 7.5 8, 8.5, 9, 9.5, or 10, or a range between any two of the preceding values.

68. A pharmaceutical composition comprising the crystalline form of any one of claims 1-38, and a pharmaceutically acceptable carrier or excipient.

69. A kit comprising the crystalline form of any one of claims 1-38.

70. The kit of claim 69, further comprising instructions for the treatment of a fibrotic disease.

71. Use of a crystalline form of any one of claims 1-38, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof.

72. The use of claim 71, wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

73. The use of claim 72, wherein the fibrotic disease is liver fibrosis, cardiac fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

74. A crystalline form of any one of claims 1-38, for use in inhibiting $\alpha_v\beta_6$ integrin in an individual.

75. A crystalline form of any one of claims 1-38, for use in inhibiting TGFβ activation in a cell.

76. The crystalline form of any one of claims 1-38 for use in inhibiting an $\alpha_v\beta_6$ integrin, wherein the crystalline form is to be contacted with the $\alpha_v\beta_6$ integrin in an amount effective to inhibit the $\alpha_v\beta_6$ integrin.

77. Use of a crystalline form of any one of claims 1-38, in the manufacture of a medicament for modulating the activity of at least one integrin in an individual in need thereof, wherein the crystalline form is effective to modulate the activity of the at least one integrin in the individual, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin.

78. The use of claim 78, wherein the crystalline form inhibits the activity of one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the individual.

79. The use of claim 78 or claim 79, wherein the individual has or is at risk of a fibrotic disease selected from the group consisting of: idiopathic pulmonary fibrosis (IPF), interstitial lung disease, radiation-induced pulmonary fibrosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic liver disease induced fibrosis, Alport syndrome, primary sclerosing cholangitis (PSC), primary biliary cholangitis, biliary atresia, systemic sclerosis associated interstitial lung disease, scleroderma, diabetic nephropathy, diabetic kidney disease, focal segmental glomerulosclerosis, chronic kidney disease, and Crohn's Disease; and

wherein the crystalline form inhibits the activity of one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the individual, thereby treating the fibrotic disease in the individual.

80. The use of claim 78 or claim 79, wherein the individual is in need of treatment for NASH, the crystalline form is to be administered to the individual, and the amount of the crystalline form is effective to inhibit the activity of at least $\alpha_V\beta_1$ integrin, thereby treating the individual for NASH.

81. The use of claim 78 or claim 79, the individual being in need of treatment for IPF, the crystalline form is to be administered to the individual, and the amount of the crystalline form is effective to inhibit the activity of at least $\alpha_V\beta_6$ integrin, thereby treating the individual for IPF.

82. The use of claim 78 or claim 79, the individual being in need of treatment for PSC, the crystalline form is to be administered to the individual, and the amount of the crystalline form is to inhibit the activity of at least one of $\alpha_v\beta_6$ integrin and $\alpha_v\beta_1$ integrin, thereby treating the individual for PSC.

83. A crystalline form of any one of claims 1-38, for use in therapy.